ABSTRACT

By inducing a steady state of ^{133}Xe exchange across the lung and measuring the ^{133}Xe concentration in individual lung regions, we were able to measure steady state regional ventilation/perfusion ratios ($\dot{V}_A/\dot{Q}$). This technique was combined with independent assessments of regional ventilation and blood flow, and a variety of subjects studied. Erect normal subjects showed an apex-to-base gradient in $\dot{V}_A/\dot{Q}$ which, though sizable, did not explain all $\dot{V}_A/\dot{Q}$ variation reported in such lungs. Seated post-pneumonectomy patients were examined; the increased flow through the remaining lung decreased, apex-to-base differences in perfusion and $\dot{V}_A/\dot{Q}$, but ventilation distribution was unchanged. Lung regions affected by pulmonary emboli demonstrated high $\dot{V}_A/\dot{Q}$ and reduced perfusion but again ventilation distribution was not altered. In patients with bronchiectasis ^{133}Xe studies agreed well with bronchograms, but regional function appeared to depend more on the presence than the morphological severity of the lesion. Asymptomatic asthmatics commonly showed regions with depressed ventilation and $\dot{V}_A/\dot{Q}$; however, regional malfunction was not apparent unless overall expiratory flow rates were distinctly abnormal. In contrast, patients with chronic bronchitis often showed impairment of regional gas exchange in the absence of major deficits of overall function. These patients also showed evidence for subregional inhomogenieties of function, a feature which dominated the findings in patients with emphysema.

Short title:

Regional Pulmonary Gas Exchange

STEADY STATE REGIONAL GAS EXCHANGE IN HEALTH AND DISEASE STUDIED WITH ^{133}Xe

by

N.R. Anthonisen

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the Degree of Doctor of Experimental Medicine.

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PREFACE

The results presented in this thesis represent the first exploration of steady state gas exchanging function of individual lung regions. Regional measurements had been made previously and extrapolated to the steady state, but such extrapolations present theoretical and practical difficulties. Because the results are unique, they have given new insights into regional gas exchange and its determinants, both in health and disease

We hope it is apparent that this work could not have been done by one person; the experimental work took more than two years to complete and another two years were required to analyze the data. Necessarily, many people were involved in these studies at one time or another. The following paragraphs list these people and their specific contributions; the importance of these contributions is self explanatory.

This work was done in the ^{133}Xe laboratory of the Royal Victoria Hospital, which was supported both financially and spiritually by Dr. D. V. Bates. Dr. Bates consulted and advised on each phase of these studies.

The ^{133}Xe laboratory was shared with Dr. J. Milic-Emili, whose cooperation and advice were of particular importance in initiating the author into the mysteries of the ^{133}Xe technique.

Full time assistants in the ^{133}Xe laboratory were Mrs. M. B. Dolovich and Mr. W.R. D. Ross. All data acquisition was instrumented and supervised by them. Mrs. Dolovich helped with theoretical aspects of the method, and Mr. Ross built much of the special equipment and conducted experiments on Compton scatter.

Drs. Harry Bass, Thomas Heckscher, and P.C. Robertson worked directly with the author at various times during these studies. Dr. Bass helped with all studies of abnormal subjects, with special emphasis on those involving patients with pulmonary embolism and bronchiectasis. Dr. Heckscher

participated in all studies of abnormals except for those invovlving patients with bronchitis; he was particularly interested in the asthmatics and helped with many of the theoretical aspects of this work. Dr. Robertson did critical experiments involving Compton scatter.

All the cardiac outputs measured during these studies were performed by Dr. Antonio Oriol and Miss Judy Doman.

Dr. J. A. M. Henderson selected most of the bronchiectatic patients and analyzed their bronchograms.

Measurements of the mean effective half life of ^{133}Xe in the body were carried out by Mr. Hyman Tannenbaum while a second year medical student at McGill.

A large number of senior clinicians at the Royal Victoria Hospital helped to supply patient material for these studies. Of special importance were Dr. D. D. Monro, who permitted study of his patients after pneumonectomy, Dr. Bram Rose, who recruited all the asthmatics we studied, and Dr. R. E. G. Place, who supplied the patients with bronchitis.

Plain films of the chest were evaluated by Dr. R. G. Fraser.

Figures and diagrams were drawn by Mr. Lionel Bartlett and by HMC R. Culberson, USN.

The manuscript was typed and edited by Mrs. Jeannine Quinn.

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TABLE 1. SYMBOLS USED FREQUENTLY IN THIS THESIS

Standard symbols of respiratory physiology

V - gas volume (liters, L) $\dot{V}$ - gas flow (L/min)

Q - blood volume (L) $\dot{Q}$ - blood flow (L/min)

F - fractional concentration of gas in gas (cc/100cc)

C - concentration of gas in blood (cc/100cc)

P - partial pressure of gas in gas or blood

Subscripts are used with the above to connote:

1) the particular gas referred to, O_2, CO_2, etc; when no specific gas is noted the reference is either general or to ^{133}Xe.

2) the physiological status of the gas or blood.

I - inspired a- arterial

E - expired v - venous

A - alveolar $\bar{v}$ - mixed venous (pulmonary artery)

thus: $\dot{V}_A$ is alveolar ventilation

P_{aCO_2} is the partial pressure of CO_2 in arterial blood

$\dot{V}_{O2}$ - O_2 uptake (L/min) $\dot{V}_{CO2}$ - CO_2 output (L/min)

R - $\dot{V}_{CO_2}/\dot{V}_{O2}$ - respiratory quotient

D - difference in the partial pressures of a gas in alveolar gas and arterial blood $D_{O2} = P_{AO_2}$ minus P_{aO_2}

Symbols used in routine pulmonary function testing

VC - vital capacity FRC - functional residual capacity

RV - residual volume TLC - total lung capacity

ME - mixing efficiency

MMFR - maximum mid-expiratory flow rate

FEV - forced expired volume - subscript notes time at which measurement made

$D_{L_{CO}}$ - diffusing capacity of the lung for carbon monoxide

I. INTRODUCTION TO GAS EXCHANGE

The major function of the mammalian lung is to exchange respiratory gases between the external environment, or atmosphere, and the internal environment, or blood, with oxygen (O_2) moving into the blood and carbon dioxide (CO_2) moving out. To effect this exchange efficiently, gas and blood must be brought into close contact over a large surface. The human lung meets these requirements[1]. Pulmonary airways ramify on the order of 22 times and terminate in roughly 300 million alveolar sacs which constitute lung-gas interphase of some 95 m^2. Each alveolus is surrounded by a meshwork of 1800 capillary segments which may contain blood; the potential lung-blood interphase is thus some 90m^2. Between the blood in the capillaries and the gas in the alveoli lie a series of thin membranes (capillary endothelium, alveolar basement membrane and alveolar epithelium) which have an aggregate thickness of $(.36 - 2.5) \times 10^{-4}$cm.

Venous blood is continuously supplied to the capillary network by the right heart, while atmospheric air is cyclically supplied to the alveoli by breathing or ventilation. Gases move from alveolar air to capillary blood or vice versa by passive diffusion; there is no active transport of respiratory gases in the lung. According to the laws of diffusion, the rate of transfer of a substance across a barrier depends on 1) the diffusivity of the substance in the barrier and 2) the relative concentrations or activities of the substance on either side of the barrier[2]. Respiratory gas concentrations in the liquid phase are not always linearly related to their activities;in this case the activity of a gas is accurately represented by the partial pressure of the gas in the liquid. In the case of the lung, the transfer rate of oxygen and CO_2 across the alveolo-capillary membrane depends on the diffusivity of the

gases in the membrane and the partial pressures of these gases (P_{O_2}, P_{CO_2}) in the alveolar gas and capillary blood. As each aliquot of venous blood enters the alveolar capillary, exchange with alveolar gas begins, O_2 and CO_2 being driven across the alveolo-capillary membrane at rates proportional to their partial pressure differences. The proportionality constant in the above relationship is the diffusivity of O_2 and CO_2 in the alveolo-capillary membrane. If these gases are diffusible enough, each aliquot of blood will attain partial pressure equilibrium with alveolar gas as it passes through the pulmonary capillary. Under these circumstances, the alveolo-capillary membrane is not a functional barrier to gas exchange. This question has been investigated extensively, and for the purposes of this discussion it is probably safe to assume that the alveolo-capillary membrane does not constitute a significant barrier to the exchange of O_2 and CO_2; we may consider that end capillary blood is in gaseous equilibrium with the alveolus it subserves(3).

What determines gas tensions in alveoli and capillary blood? This will be considered algebraically. It is assumed 1) that alveolar gas is in equilibrium with end capillary blood and is completely mixed within the alveolus, 2) that ventilation is a continuous, not a cyclic process, 3) that steady state conditions apply and 4) that the volumes inspired and expired by the alveolus are the same. The first assumption has been justified in part above; dimensional analysis justifies the remainder. The next two assumptions will be discussed in detail later; neither is critical to the following argument. The third assumption entails an error of less than 2%. Fig. 1 represents the model considered.

In the steady state, the amount of any gas entering the alveolo-capillary unit equals the amount of gas leaving it:

$$F_I \dot{V}_A + C\bar{v}\,\dot{Q} = F_A \dot{V}_A + \dot{Q} F_A \alpha \qquad \text{I-1}$$

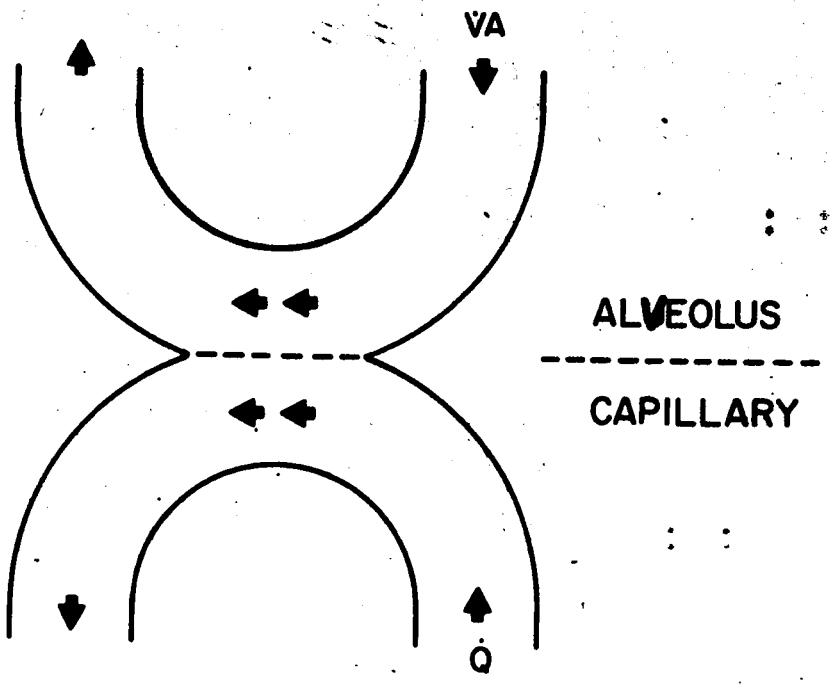


Fig.1. Model of gas exchanging unit. Both alveolar ventilation ($\dot{V}_A$) and capillary perfusion ($\dot{Q}$) are continuous and unidirectional. Blood and gas are separated by a membrane (dotted line) which does not constitute a significant barrier.

The gas can enter the unit either in the gas or blood phase. The amount entering in the gas phase is the product of the inspired concentration (F_I) and the alveolar ventilation ($\dot{V}_A$) and the amount entering in the blood phase is the product is the product of the entering venous concentration ($C\bar{v}$) and the blood flow ($\dot{Q}$). Similarly, gas can leave the unit either in the gas or blood phase. The amount leaving in the gas phase is the product of the alveolar concentration (F_A) and the alveolar ventilation ($\dot{V}_A$) and the amount leaving in the blood phase is equal to the blood flow ($\dot{Q}$) multiplied by the end capillary concentration which is the alveolar concentration (F_A) multiplied by the appropriate solubility coefficient (α). If, as implied by the term steady state, mixed venous and inspired concentrations are constant, alveolar (and capillary) gas concentrations (or partial pressures) are determined by the ratio of alveolar ventilation to capillary perfusion ($\dot{V}_A/\dot{Q}$):

$$\frac{F_I \dot{V}_A/\dot{Q} + C\bar{v}}{\dot{V}_A/\dot{Q} + \alpha} = F_A \qquad \text{I-2}$$

Thus, for any given set of values for inspired and mixed venous gas tensions, the gas tension in any alveolus is fixed by the $\dot{V}_A/\dot{Q}$ of that alveolus. This concept was first delineated by Riley and Cournand[4] and Rahn and Fenn[5] and constituted a major advance in pulmonary physiology. Assuming certain normal values for the gas composition of mixed venous blood and inspired gas, equation 2 was solved for O_2, N_2 and CO_2. Results are shown graphically in Fig. 2. It will be noted that for each value of $\dot{V}_A/\dot{Q}$ there is only one value for each of the gases considered. This, of course, was the implication of eq. I-2. Further, given the composition of mixed venous blood and inspired gas, there is only one combination of gas tensions which can exist at any $\dot{V}_A/\dot{Q}$.

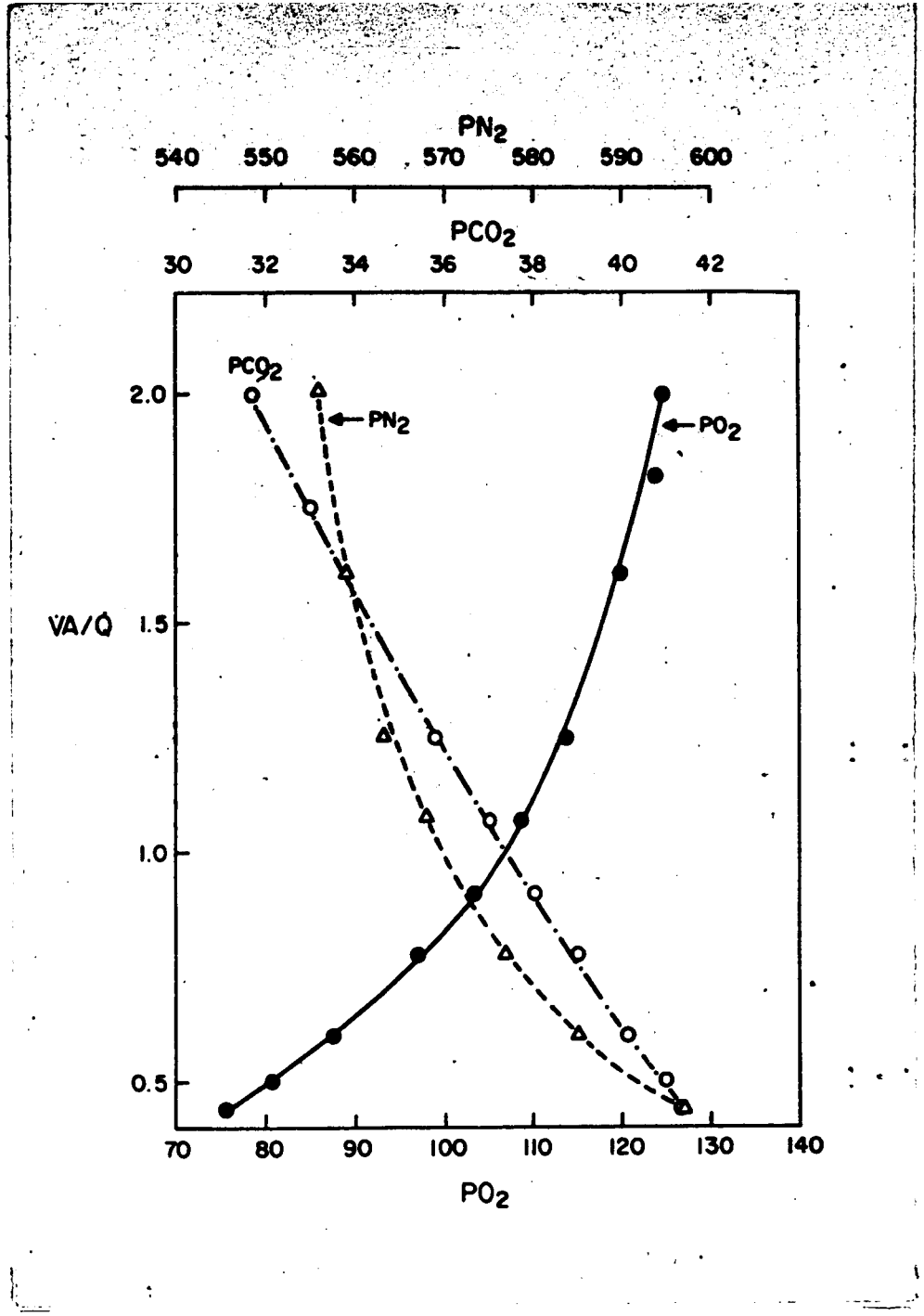


Fig. 2. Alveolo-capillary values for P_{O_2} (solid line), P_{N_2} (dotted line), and P_{CO_2} (dashed line) at various values of $\dot{V}_A/\dot{Q}$. Eq. I-2 was solved, assuming normal values for gas tensions in mixed venous blood and inspired air, and applying blood dissociation curves for O_2 and CO_2. At each $\dot{V}_A/\dot{Q}$ there is a single P_{O_2}, P_{N_2}, and P_{CO_2} which satisfies eq. I-2.

This is shown more strikingly in Fig. 3a and 3b which are simply replots of the data of Fig. 2. The lines of Figs. 3a and 3b originate at points representing the composition of mixed venous blood and terminate at points representing the composition of inspired gas. It is intuitively obvious that alveoli with gas tensions equal to those of mixed venous blood are alveoli with $\dot{V}_A/\dot{Q} = 0$. Similarly, alveoli with gas tensions of inspired gas are alveoli with $\dot{V}_A/\dot{Q} = \infty$. Each point on the lines of Figs. 3a and 3b represents a single $\dot{V}_A/\dot{Q}$, and the curves represent all the possible $\dot{V}_A/\dot{Q}$ and, therefore, all the possible combinations of gas tensions which could exist in alveoli with the given inspired and mixed venous gas tensions. In a given lung it is reasonable to assume (for the present) that all alveoli inspire the same gas and receive the same venous blood, so that points on the lines of Figs. 3a and 3b might represent alveoli in the same lung. If all units in a lung were identical one point on the $\dot{V}_A/\dot{Q}$ line would represent the entire lung. In view of the fact that there are three hundred million alveoli in the normal human lung, such identity cannot be expected. Indeed, it would be reasonable to suppose that a normal lung contains some alveoli with $\dot{V}_A/\dot{Q} = 0$ and a few others with $\dot{V}_A/\dot{Q} = \infty$?

What are the effects of inhomogeneities of $\dot{V}_A/\dot{Q}$? In order to consider this simply we must introduce the concept of the "ideal lung"[4,7]. An ideal lung may be defined as one made up of units which are identical and similar to that shown in Fig. 1. First, there is no effective barrier between alveolar gas and capillary blood so that gas tensions in each alveolus are equal to those of that alveolus' capillaries. Second, there are no effective air or blood shunts, i.e., venous blood does not enter the arterial system without having traversed an alveolus, nor does inspired gas enter the expirate without first entering alveoli and undergoing gas exchange. Finally, alveoli in the ideal lung receive equal shares of the overall alveolar ventilation and equal shares

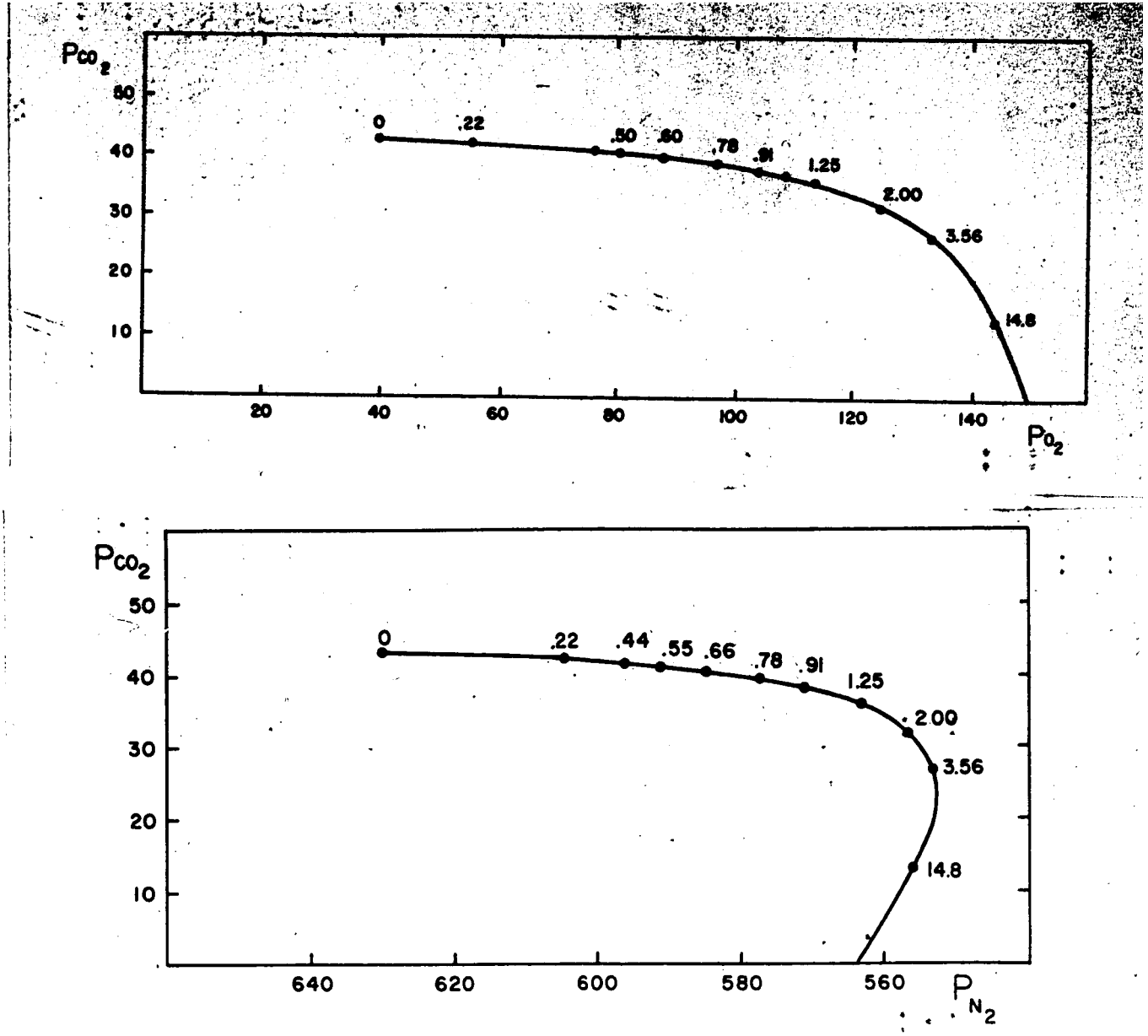
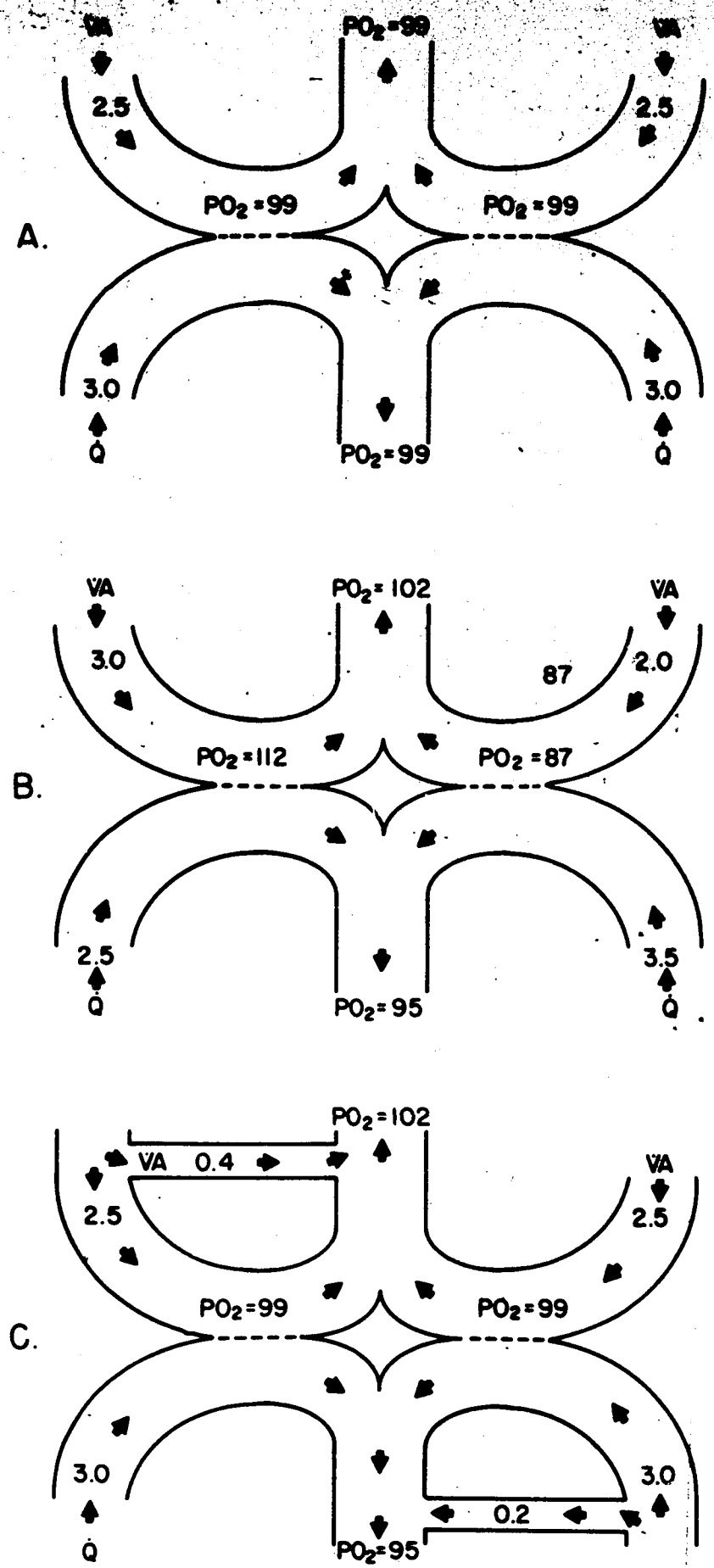


Fig. 3. "$\dot{V}_A/\dot{Q}$ lines." These lines are replots of Fig. 2; at the top P_{CO_2} is plotted against P_{O_2}, and at the bottom P_{CO_2} is plotted against P_{N_2}. Each point represents a given value for $\dot{V}_A/\dot{Q}$, and a sampling of such points and $\dot{V}_A/\dot{Q}$ values are shown.

of the overall capillary perfusion. Thus, the $\dot{V}_A/\dot{Q}$ of all units are the same. In such an ideal lung the mixed alveolar gas has the same composition as the mixed arterial blood. It may not be clear at this point why this situation is desirable, but it will be shown that gas exchange is most efficient when this is the case.

Let us now contrast the ideal lung and the non-ideal lung. First, we shall consider the effects of differences in $\dot{V}_A/\dot{Q}$ among the units of an otherwise ideal lung. This is illustrated in Fig. 4 which shows one lung having two units with the same $\dot{V}_A/\dot{Q}$ (Fig. 4A) and one lung having two units with differing $\dot{V}_A/\dot{Q}$ (Fig. 4B). Both lungs receive the same total blood flow and ventilation and, therefore, have the same overall $\dot{V}_A/\dot{Q}$. Oxygen tensions have been derived from the curves of Fig. 3 and, in the case of arterial blood, from these data plus standard O_2 dissociation curves(6). Since Fig. 4A represents an ideal lung mixed alveolar and arterial O_2 tensions are the same and, further, are equal to those which would be predicted from Fig. 2 on the basis of the overall $\dot{V}_A/\dot{Q}$. The lung shown in Fig. 4B, however, is considerably different, though alveolar and capillary gas tensions in each unit were also derived from the $\dot{V}_A/\dot{Q}$ and the curves of Fig. 3. Mixed alveolar gas has a high P_{O_2} because it contains a relatively large amount of gas from the high $\dot{V}_A/\dot{Q}$ unit. The mixed arterial blood has a low P_{O_2} because it contains a relatively large contribution from the low $\dot{V}_A/\dot{Q}$ unit. Mixed arterial P_{O_2} is below the arithmetic mean of the P_{O_2}'s of the two units due to the alinearity of the O_2 dissociation curve. From the point of view of the organism, which lives by its arterial blood gas tensions, the system shown in Fig. 4B is inefficient. In order for the lung shown in Fig.4B to produce arterial blood of the same composition as the lung of Fig. 4A, it

Fig. 4. Consequences of inhomogeneities of $\dot{V}_A/\dot{Q}$. Three two-alveolus models are shown; their ventilation, perfusion, and P_{O_2} are indicated. In 4A each alveolus has a $\dot{V}_A/\dot{Q}$ of 0.83. Alveolo-capillary and mixed alveolar and arterial P_{O_2} are all 99 mm Hg. In 4B one unit has $\dot{V}_A/\dot{Q} = 1.20$, the other has $\dot{V}_A/\dot{Q} = 0.59$. Alveolo-capillary P_{O_2} differ, and mixed alveolar P_{O_2} exceeds arterial. In 4C the alveolo-capillary units have the same ventilation, perfusion and $\dot{V}_A/\dot{Q}$ as in 4A, but the mixed alveolar and arterial P_{O_2} are the same as those of 4B, because an air shunt of 0.4 L/min has been added as has a blood shunt of 0.2 L/min. Gas and blood shunts are wasted ventilation and perfusion.


A.
VA
2.5
PO_2=99
VA
2.5
PO_2=99
PO_2=99
3.0
Q
PO_2=99
3.0
Q
B.
VA
3.0
PO_2=102
87
VA
2.0
PO_2=112
PO_2=87
2.5
Q
PO_2=95
3.5
Q
C.
PO_2=102
VA 0.4
VA
2.5
2.5
PO_2=99
PO_2=99
3.0
Q
PO_2=95
0.2
3.0

would be necessary to increase the overall ventilation to raise the $\dot{V}_A/\dot{Q}$ and P_{O_2} of the low $\dot{V}_A/\dot{Q}$ unit. The inefficiency of the lung of Fig. 4B may also be demonstrated by the fact that its gas exchanging capacity can be duplicated by a system in which the two lung units have equal $\dot{V}_A/\dot{Q}$ and P_{O_2} (Fig. 4C). Mixed alveolar P_{O_2} has been made equal to that of Fig. 4B by the addition of an "air shunt" or dead space in which inspired air is expired without having undergone gas exchange. This is wasted ventilation. Similarly, the arterial P_{O_2} is the same as that of Fig. 4B because of a blood shunt; this mixed venous blood traverses the lungs to the systemic arteries without undergoing gas exchange. This is wasted perfusion.

We have examined the effect of varying $\dot{V}_A/\dot{Q}$ in an otherwise ideal lung; can these effects be duplicated by other departures from the ideal state? Adding blood or air shunts to an ideal lung violates the assumptions of the ideal lung. The effect of these measures has been illustrated above, and really represents only special cases of $\dot{V}_A/\dot{Q}$ variation; an air shunt being a unit with $\dot{V}_A/\dot{Q} = \infty$ and a blood shunt being a unit with $\dot{V}_A/\dot{Q} = 0$. A diffusion barrier at the alveolo-capillary interphase also represents a departure from the ideal state and is a somewhat different case. If the barrier is thick enough, equilibration of partial pressures across the membrane will not be complete, and a tension difference (gradient) between alveolus and end capillary blood will result. This situation is much more likely in the case of O_2 than CO_2 since the diffusivity of the latter is some seventeen times that of O_2. Thus a barrier sufficient to produce an alveolar-end capillary CO_2 difference would be so thick that very little oxygen transfer could take place across it, and in life diffusion barriers significantly effect only O_2 exchange.

How do these theoretical considerations relate to real lungs, normal and abnormal? Normal lungs are not ideal; the gas tensions of mixed alveolar gas are not the same as those of arterial blood in normal humans[8]. Diseased lungs are, in general, less ideal than normal ones. Let us examine, in the context of the above, factors which could impede gas exchange and briefly indicate their importance in health and a variety of disease states.

The most obvious theoretical cause of failure of pulmonary gas exchange and one which was not mentioned in the analysis of the ideal lung is inadequate ventilation, i.e., there is a subnormal bulk flow of gas in and out of the lungs in response to respiratory efforts. This, by definition, does not occur in normal humans but does in some disease states[9a]. Diseases which compromise the respiratory nerves and muscles may induce hypoventilation and failure of gas exchange. Obstruction, usually acute, of major airways may produce a similar situation. Most lung disease, however, is chronic and these patients, in general, maintain a minute volume of ventilation which is at least normal and therefore adequate for gas exchange if other factors were not involved.

As discussed above, thickening of the alveolo-capillary membrane throughout the lung could produce inefficiency of oxygen exchange. The small alveolar-arterial P_{O_2} difference (D_{O_2}) documented in normal subjects is almost certainly not on this basis[3]. This is because the membrane is thin, the reaction rate of O_2 with hemoglobin is fast, the "contact time" of the average red cell (the time taken for a red cell to traverse an alveolar capillary) is relatively long-about 0.1 sec., and finally the normal inspired and, therefore, alveolar, oxygen tension is rather high ($P_{A_{O_2}}$ = 100 mmHg), giving a high partial pressure gradient ($P_{A_{O_2}} - P_{\bar{v}_{O_2}}$) to drive diffusion. Only under extreme circumstances such as

exercise (decreased contact time, increased O_2 uptake) with low inspired O_2 tension can a barrier effect or diffusion defect be demonstrated in normal subjects[3]. In some pulmonary diseases, particularly those causing interstitial fibrosis, defects in oxygen exchange have been demonstrated which were thought due to thickening of the alveolo-capillary membrane with diffusion block. Though this maybe true to a minor extent, recent work has made it clear that most of the gas exchange difficulty in these patients is not on the basis of hampered diffusion[10]. Finally, for reasons discussed above, abnormality of the alveolo-capillary membrane cannot be evoked to explain the disturbances of pulmonary CO_2 exchange commonly seen in patients with severe chronic lung disease.

Since air and blood shunts are extreme cases of $\dot{V}_A/\dot{Q}$ variation, these will not be considered separately. Variation in $\dot{V}_A/\dot{Q}$ certainly exists in both normal and abnormal lungs. If a normal subject expires through a rapid gas analyzer, a progressive change in gas concentration is seen throughout expiration. This can be true only if gas concentrations are not uniform in the lung and if gas concentrations differ, then $\dot{V}_A/\dot{Q}$ also must differ. This non uniformity is more striking in patients with disease. Indeed, as has been mentioned, the vast majority of patients with chronic lung disease have normal or large minute volumes of ventilation, while at the same time, many demonstrate striking failure of pulmonary gas exchange as judged by the P_{O_2} and P_{CO_2} of their arterial blood. The only possible explanation for this phenomenon is that the patient's large volume of ventilation is not reaching areas which are perfused and, conversely, areas which are very badly ventilated are well perfused so the arterial blood is, in effect, hypoventilated. This, of course, is a description of failure of gas exchange due to extreme imbalance of $\dot{V}_A/\dot{Q}$.

In summary, this section has dealt rather didactically with some of the factors which are important in pulmonary gas exchange. It was pointed out that gas exchange occurs on a basis of passive diffusion so that partial pressures in the blood phase of the lung are fixed functions of those in the gas phase. Under steady state conditions alveolo-capillary gas tensions are dependent on: 1) the gas tensions entering the respiratory unit in the inspired air and mixed venous blood and 2) most importantly, the $\dot{V}_A/\dot{Q}$ of the respiratory unit. The normal lung is enormously complex, the abnormal lung probably more so; variations in unitary function are then to be expected. It was shown that variation of $\dot{V}_A/\dot{Q}$ within a lung could produce inefficiency of overall gas exchange. Finally, it was pointed out that present evidence strongly suggests that such $\dot{V}_A/\dot{Q}$ variation is the most important factor producing differences between the normal and the ideal lung and in producing clinical embarrassment of gas exchange.

The subsequent section will deal with previous attempts at assessing gas exchange in normal and abnormal lungs, and the remainder of this thesis will describe our approach to this problem.

II. PREVIOUS STUDIES OF GAS EXCHANGE

This section does not purport to be a complete review of all physiologic approaches to lung function, nor is it intended to offer a comprehensive review of pulmonary function in respiratory disease. It is hoped that this section will serve to introduce the reader to the lung function tests used in conjunction with the present experimental work and to those tests which led to the present work and aid in its interpretation. Under these restrictions, previous clinical and experimental approaches fall into three general groups: 1) "routine" pulmonary function tests, 2) studies of gas exchange based on analysis of samples obtained from the lung as a whole, such as mixed alveolar gas or arterial blood and 3) previous studies of regional lung function. Technical aspects of methodology will be reviewed only when pertinent to the work on which this thesis is based.

1. ROUTINE PULMONARY FUNCTION TESTS

The routine function tests discussed here are those tests which were carried out on the patients used as subjects for these experiments. These tests were usually carried out as a battery and were often done as part of the patients' clinical evauation. They serve an extremely useful function in that they identify and classify patient material; they are not generally used to study normal lungs but rather for discerning deviations from the normal state.

An enormous bibliography is associated with each routine pulmonary function test. However, we shall cite only a few highly specialized references for these tests. The text of Bates and Christie[9b] gives detailed summaries of the execution and intrepretation of all the tests discussed here, and where no other reference is cited, may be regarded as the source.

Routine pulmonary function tests may easily be considered under four categories: 1) measurement of the subdivisions of lung volume, 2) measurements of expiratory flow rate, 3) measurements of the uneveness of ventilation distribution and gas exchanging competence and, 4) measurements of gaseous composition of arterial blood.

The lung volumes pertinent to this discussion are the total lung capacity (TLC) which is the volume of gas in the lungs when maximally inflated, the vital capacity (VC) which is the maximum volume of gas that the subject is able to inspire or expire, the residual volume (RV) which is the volume of gas in the lungs under conditions of maximum expiratory effort, and the functional residual capacity (FRC) which is the volume of gas in the lungs at the end of a normal expiration. The VC and the difference between FRC and RV are measured by having the subject perform the appropriate manuevers while breathing into a spirometer or other system able to measure gas

volumes. The FRC (and therefore RV and TLC) are measured by having the subject rebreathe from a circuit of fixed volume containing H_e. This gas is so insoluble that it may safely be assumed that all of it remains in the gas phase. If one rebreathes H_e, spirometer and pulmonary H_e concentrations will eventually be equal and if spirometer volume and initial and final H_e concentrations are known, lung volume may be calculated.

Lung volume measurements are made under static (zero air flow) conditions and, therefore, reflect static properties of the lung and chest wall as modified by the respiratory muscles. The static properties of lungs are such that when there is no pressure difference across them, lung volume is essentially zero. Lung tissue, then, opposes expansion at all lung volumes. When no respiratory muscle activity is imposed on the isolated chest wall, its volume is considerably greater than zero; the chest wall resists expansion at high volumes and resists compression at low volumes. Maximal inspiratory volume, or TLC, then reflects a balance between expansive forces exerted by the inspiratory muscles and the passive recoil forces of the lung and chest wall. At FRC there is normally no respiratory muscle activity so at this lung volume the retractive recoil of the lung is equal and opposite the expansile force of the chest wall. These lung volumes, then, are influenced by the recoil properties of the lung. When lung elastic tissue is destroyed as in emphysema, lung recoil diminishes; TLC and FRC increase. In scarred fibrotic lungs, recoil increases; TLC and FRC decrease. The determinants of RV appear to vary with age. In old people expiration appears to be limited by airway collapse; at low lung volumes pressures around the airways do not remain negative enough to keep them open[11]. Younger subjects develop airway collapse in dependent portions of the lungs at RV[12], but other airways remain open and apparently lung volume stabilizes because

these subjects are unable to apply enough force to the chest wall to compress it further. Patients with airway narrowing due to anatomical lesions or spasm develop abnormally large RV; examples are patients with bronchitis or asthma.

Measurements of expiratory flow rate are generally carried out during forced or maximum effort expiratory VC maneuvers. In any given subject, the maximum expiratory flow rate decreases with lung volume because airways narrow as lung volume falls so that progressively less air flow results from a given pressure drop down the airways. Further, as lung volume decreases, so does the maximum pressure available to drive air flow. It would be reasonable to expect expiratory flow rates to depend upon the amount of effort expended on the maneuver, and such is indeed the case at high lung volumes. Over the lower 50-70% of the VC, however, the amount of effort expended has much less to do with the flow rate attained. The effect of "effort" is to induce a pressure difference from lung surface to airway opening. At low lung volumes, increasing pressure at the lung surface also induces compression of airways which increases airway resistance. Increases in driving pressure (effort) are thus cancelled by increases in airway resistance so that once a certain effort or pressure is applied, further increases in effort do not increase air flow. The lower the lung volume, the more prominent this effect of airway compression becomes, so that close to RV the range of flow rates available to the subject is very limited indeed. Maximum flow rate at $<$ 70% VC has been studied extensively from both theoretical and experimental points of view[13,14]. The rate of flow attained appears to be dependent on: 1) the static elastic recoil of the lung which is the major effective force driving air out of the lung, 2) the compressibility of the airways and 3) the resistance of airways upstream from the point of airway compression which is

normally in major airways. Thus, tests of expiratory flow rate, particularly if measured at or below 50% VC, examine both static elastic and flow resistive properties of the lung. Such a test is the maximum mid-expiratory flow rate (MMFR). Diseases involving airways, such as asthma and bronchitis commonly decrease these flow rates. Patients with both bronchitis and emphysema have grossly decreased expiratory flow rates since they have both airway disease and decreased elastic recoil. In fact it is common for these subjects to be so limited that normal breathing must be conducted at maximal flow rates. Tests which measure the volume expired from TLC during one second (FEV_1) or 3/4 of a second ($FEV_{0.75}$) are heavily influenced by the factors discussed above but are also to a certain extent dependent on effort.

As mentioned above, lung volumes are commonly measured by closed circuit H_e dilution. The foreign gas is rebreathed until H_e concentration in the circuit is constant, at which time dilution of spirometer H_e by the volume of gas in the lungs is complete and H_e concentrations constant throughout the system. The speed of this equilibration is related to the volume of the spirometer system, the lung volume of the subject and the rate of volume exchange between them, or the subject's ventilation. However, equilibration is not complete until all units in the subject's lung are equilibrated and if some of these are relatively badly ventilated in relation to their volume, equilibration will be delayed over what would be predicted on the basis of overall ventilation and lung volume. Therefore, the speed of equilibration when compared with theoretical predictions, can be used as a measurement of the uniformity of ventilation per unit volume among units in the lung. As might be expected, normal subjects do not behave as if their lungs were ventilated evenly and this unevenness grows more pronounced with most pulmonary diseases. A similar and

in some ways a simpler approach is that of open circuit N_2 dilution which entails the monitoring of expired N_2 tensions as a subject inspires pure O_2. The N_2 in the lung is replaced by O_2 by ventilation; expired N_2 decreases and the rate of decrease represents the rate of replacement, or ventilation per unit volume. This technique has been combined with other approaches and will be discussed in greater detail later.

The diffusing capacity for CO has been utilized extensively for analyzing the alveolo-capillary membrane. It will be recalled that the diffusion of a gas across a membrane is dependent on the diffusivity of the gas in the membrane and the partial pressure gradient across it. In the case of the lung, measurement of the diffusing properties of the alveolo-capillary membrane can be carried out if the alveolo-capillary pressure gradient for a gas can be determined. It is impossible to literally measure pulmonary capillary gas pressures, but because of its affinity for hemoglobin, appreciable amounts of CO may combine with blood at negligible partial pressures. If low concentrations of CO are used then the alveolo-capillary pressure gradient is essentially equal to the $P_{A_{CO}}$. CO uptake during a single breath or under steady state conditions is commonly measured and, when divided by the appropriate $P_{A_{CO}}$, designated the diffusing capacity ($D_{L_{CO}}$), a term which includes the diffusivity of the gas in the membrane, the area and thickness of the membrane and the pulmonary capillary blood volume. Measurements of $D_{L_{CO}}$ in normal subjects can probably be interpreted in these terms. However, in subjects with pulmonary disease such interpretation is almost certainly incorrect. Studies of patients with chronic obstructive lung disease have produced values for $D_{L_{CO}}$ that are clearly at variance with actual physical diffusing capacity. Units in such lungs commonly exhibit extreme variations in alveolar ventilation, capillary blood flow and probably

capillary diffusing area; such variations do effect measurements of D_{LCO}. In spite of these difficulties, the D_{LCO} is a useful test particularly when done under steady state conditions. This is probably due to the fact that steady state D_{LCO} is very sensitive to variations in function throughout the lung; knowledge of the presence of such variations is valuable. In practice decreases of steady state D_{LCO} are usually noted in patients with pulmonary emphysema, but much less commonly in asthma and chronic bronchitis without co-existent emphysema.

Arterial blood gas analysis is an extremely valuable test clinically but somewhat less so experimentally. Elevation of P_{ACO_2} (>46 mmHg) indicates a decrease in effective ventilation, or ventilation of the arterial blood. This may be due to decreased overall ventilation but is more commonly due to wide and inappropriate variation in $\dot{V}_A/\dot{Q}$. Virtually the same statement can be made relative to decreases in P_{AO_2} or S_{aO_2} ($<94\%$).

2. NON REGIONAL STUDIES OF PULMONARY GAS EXCHANGE

Before serious consideration of these approaches it is necessary to present their major theoretical determinants in fairly complete fashion. Though repetitive, the simplest and most logical method of doing this is to derive the $\dot{V}_A/\dot{Q}$ curves of Fig. 3.

The assumptions involved in this derivation are as follows:

1) gas tensions in alveoli and capillaries reach equilibrium,
2) mixed venous blood is of constant composition and the same for all alveoli,
3) inspired gas composition is constant and everywhere equal to that of atmospheric air ($P_{O_2} = 140$ $P_{CO_2} = 0$),
4) lung metabolism is insignificant in relation to the total exchanges of O_2 and CO_2 which take place across it,
5) standard blood O_2 and CO_2 dissociation curves apply,
6) symbols used are shown in Table 1.

Let us now consider $\dot{V}_{O_2}$, the amount of oxygen removed from inspired gas per minute:

$$\dot{V}_{O_2} = F_{I_{O_2}} \dot{V}_I - F_{E_{O_2}} \dot{V}_E \qquad \text{II-1}$$

Similarly, CO_2 output ($\dot{V}_{CO_2}$) is the amount of CO_2 added to expired gas per minute:

$$\dot{V}_{CO_2} = F_{E_{CO_2}} \dot{V}_E - F_{I_{CO_2}} \dot{V}_I \qquad \text{II-2}$$

Since $F_{I_{CO_2}} = 0$ the last term drops out. The respiratory quotient (R) then may be written:

$$R = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}} = \frac{F_{E_{CO_2}} \dot{V}_E}{F_{I_{O_2}} \dot{V}_I - F_{E_{O_2}} \dot{V}_E} \qquad \text{II-3}$$

This expression is not particularly helpful since it contains terms representing both gas concentration and ventilation. However, the latter may be dispensed with if we assume that there is no N_2 uptake or release across the lung:

$$F_{I_{N_2}} \dot{V}_I = F_{E_{N_2}} \dot{V}_E \qquad \text{II-4}$$

Since there are no gases other than O_2, CO_2 and N_2 present, the sum of these fractional concentrations in any gas sample is unity so $F_{N_2} = 1-F_{O_2}-F_{CO_2}$ and

$$\dot{V}_I = \frac{\dot{V}_E (1-F_{E_{O_2}}-F_{E_{CO_2}})}{1-F_{I_{O_2}}-F_{I_{CO_2}}} \qquad \text{II-5}$$

If this is substituted into equation 3, remembering $F_{I_{CO_2}}$ = zero, the following results:

$$R = \frac{F_{E_{CO_2}} (1-F_{I_{O_2}})}{F_{I_{O_2}} (1-F_{E_{CO_2}}) - F_{E_{O_2}}} \qquad \text{II-6}$$

By multiplying the top and bottom of the right side of this equation by the appropriate barometric pressure, we may convert fractional concentrations to partial pressures:

$$R = \frac{P_{E_{CO_2}} (1-F_{I_{O_2}})}{P_{I_{O_2}} (1-F_{E_{CO_2}}) - P_{E_{O_2}}} \qquad \text{II-7}$$

All gas exchange occurs in alveoli, so alveolar gas must have the same R as that calculated from expired gas concentrations. Mixed expired gas is by definition mixed alveolar gas to which inspired gas has been added;

it follows that further dilution of a mixed expired or alveolar sample by inspired gas does not change the R derived from the sample. Indeed, all of the foregoing relationships could have been derived for alveolar as opposed to expired gas, and alveolar terms may be substituted for expired terms:[16b]

$$R = \frac{P_{A_{CO_2}} (1-F_{I_{O_2}})}{P_{I_{O_2}} (1-F_{A_{CO_2}}) - P_{A_{O_2}}} \qquad \text{II-8}$$

The above may be rearranged to solve for $P_{A_{O_2}}$:

$$P_{A_{O_2}} = P_{A_{CO_2}} \left[\frac{(F_{I_{O_2}} - 1)}{R} - F_{I_{O_2}} \right] + P_{I_{O_2}} \qquad \text{II-9}$$

$P_{A_{O_2}}$ is, then, linearly related to $P_{A_{CO_2}}$, and if the inspired mixture is constant the slope of the linear relationship is determined by R. The origin of the linear plot is defined by $P_{I_{O_2}}$. The above equation is plotted for a variety of R in Fig. 5A which assumes that the inspired mixture is atmospheric air.

Let us now consider the blood entering and leaving the alveoli: By the well known Fick relationship:

$$\dot{V}_{O_2} = \dot{Q} (Ca_{O_2} - C\bar{v}_{O_2}) \qquad \text{II-10}$$

and

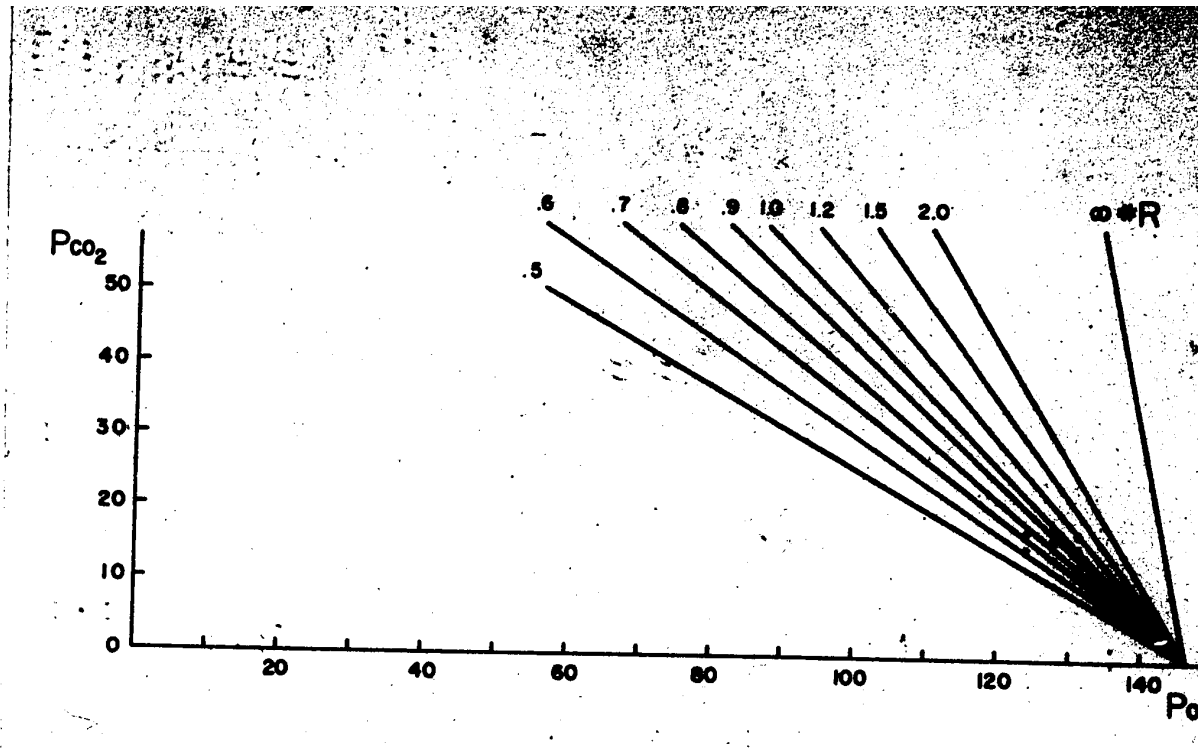
$$\dot{V}_{CO_2} = \dot{Q} (C\bar{v}_{CO_2} - Ca_{CO_2}) \qquad \text{II-11}$$

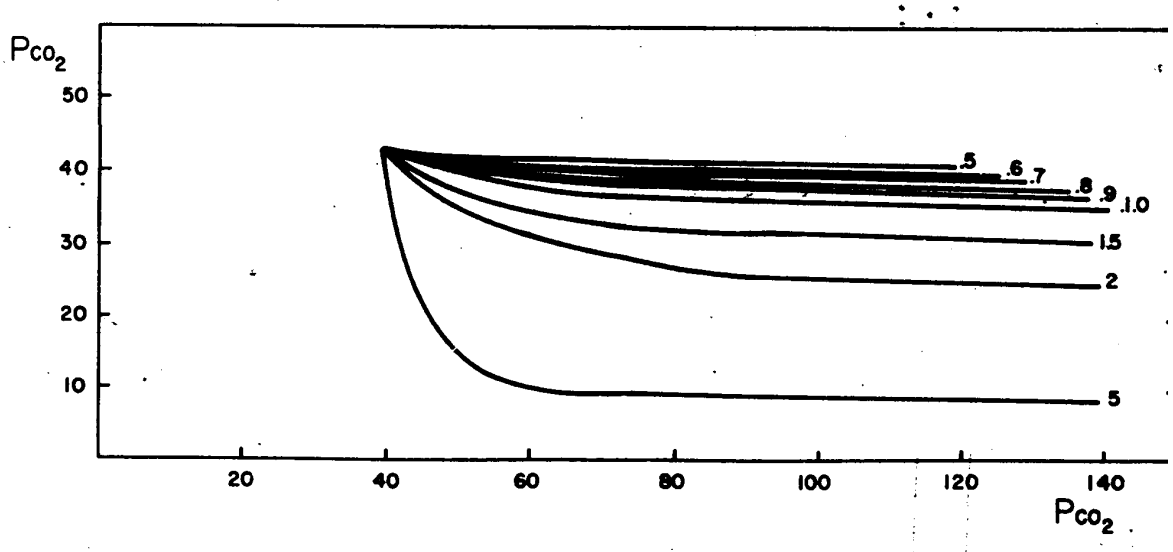
The respiratory quotient of the blood then is:

$$R = \frac{C\bar{v}_{CO_2} - Ca_{CO_2}}{Ca_{O_2} - C\bar{v}_{O_2}} \qquad \text{II-12}$$

If Ca_{O_2} is plotted against Ca_{CO_2} the above equation will also yield a series of straight lines the slope of which are determined by the R chosen. The origin of the lines is in this instance the point with the O_2 and CO_2

Fig. 5. Gas and blood R lines. Ordinates: P_{CO_2}. Abscissae: P_{O_2}. The upper panel shows gas R lines radiating from a point representing inspired gas. Each line is a plot of eq. II-9 using a different value of R. The lower panel shows blood R lines radiating from the mixed venous point. Each line represents a plot of eq. II-12 using a different value for R and converting blood concentrations to partial pressures with the appropriate dissociation curve.


Pco2
50
40
30
20
10
0
20
40
60
80
100
120
140
.6
.7
.8
.9
1.0
1.2
1.5
2.0
∞ R
.5


Pco2
50
40
30
20
10
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40
60
80
100
120
140
Pco2
.5
.6
.7
.8
.9
1.0
1.5
2
5

concentrations of mixed venous blood. However, blood dissociation curves for O_2 and CO_2 are not linear, and so when blood R lines are plotted on P_{O_2} and P_{CO_2} coordinates, curves result as shown in Fig. 5B. A reasonable value for the composition of mixed venous blood has been selected at $P_{O_2} = 44$, $P_{CO_2} = 47$. Fig. 5A may be summarized by stating that if inspired gas undergoes gas exchange at a certain R the composition of the expired gas must be on the appropriate R line. Similarly, Fig. 5B states that if mixed venous blood of the composition shown undergoes gas exchange at a given R, then all possible compositions of blood after such exchange are also represented by the appropriate R line. Now the gas and blood in an alveolus necessarily exchange at the same R. Therefore, the point of intersection of blood and gas R lines having the same value defines the composition of alveolar gas and capillary blood which have exchanged at that R. Several such intersections are shown in Fig. 6A and a complete line including all possible intersections is shown in Fig. 6B. The line of Fig. 6B indicates all the possible gas concentrations which could exist in alveoli with the inspired gas and mixed venous concentrations shown. Each point on the line represents a different R; for each R there must be a unique P_{O_2} and P_{CO_2} in both alveolar air and capillary blood. What determines the R of blood and gas? $\dot{V}_A/\dot{Q}$ is related to R as follows:

$$\dot{V}_{CO_2} = \dot{V}_A F_{ACO_2} \qquad \text{II-2}$$

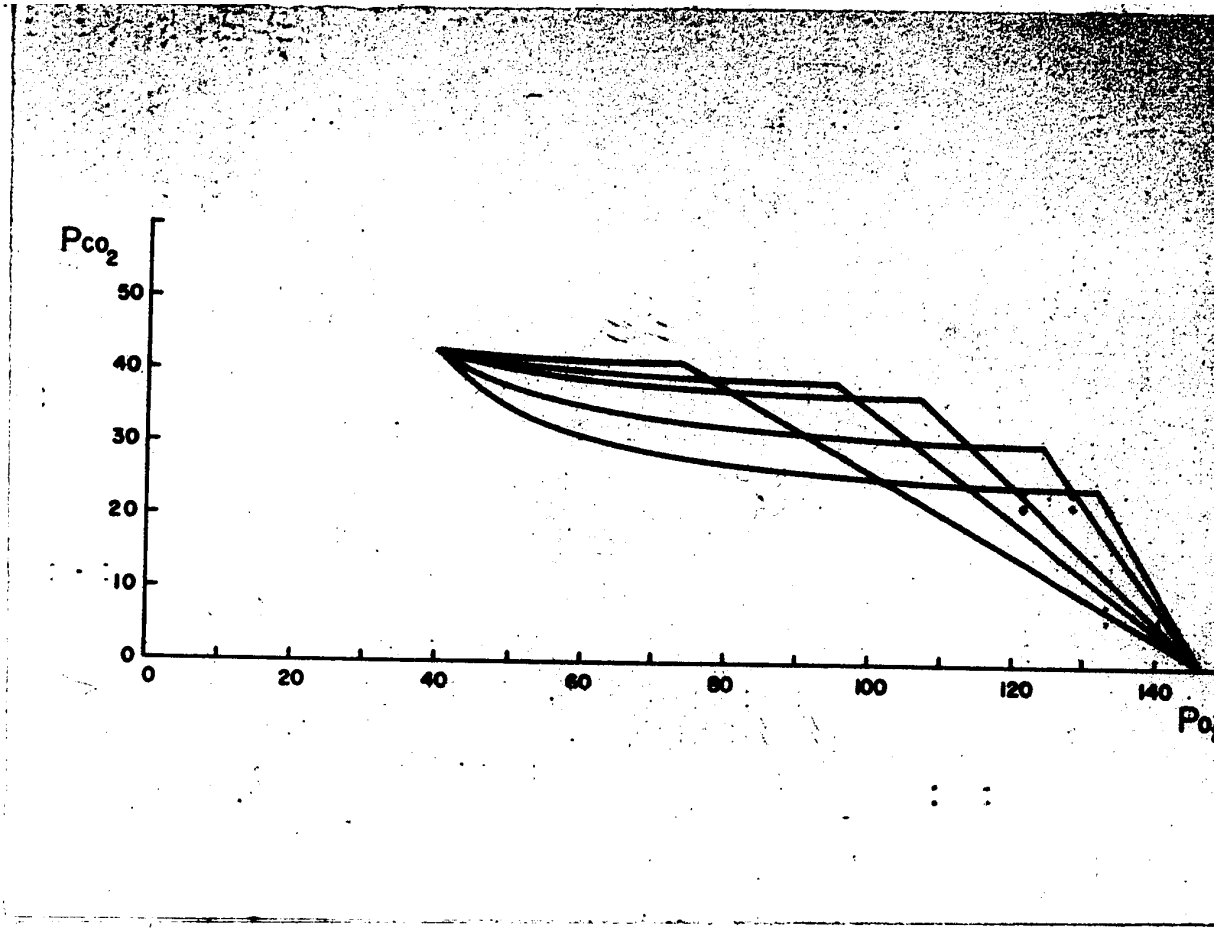
(where $F_{I_{CO_2}} = 0$)

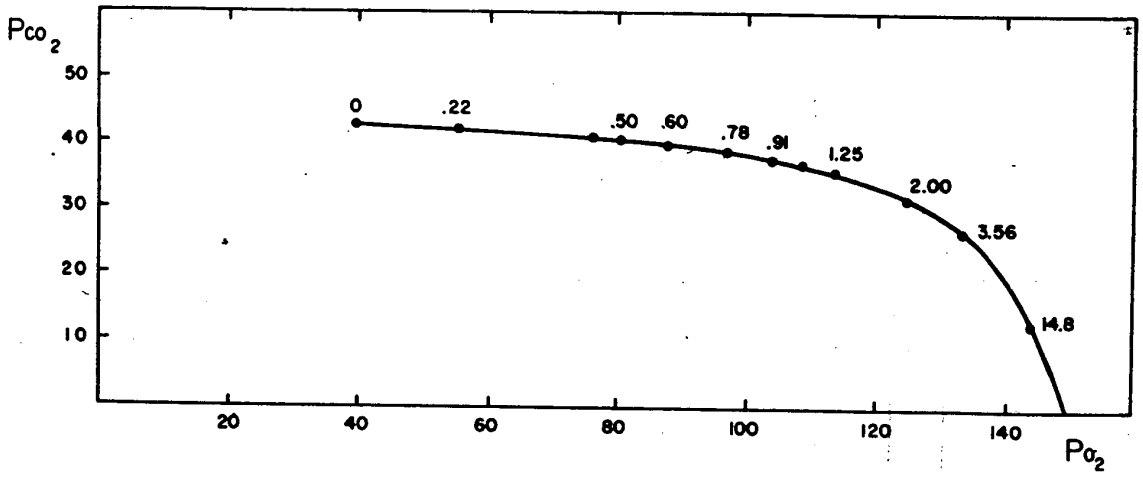
and

$$\dot{V}_{O_2} = \dot{Q} (Ca_{O_2} - C\bar{v}_{O_2}) \qquad \text{II-10}$$

These may be combined:

Fig. 6. Intersecting R lines. In the top panel, the two panels of Fig. 5 have been combined and some points of intersection of gas and blood R lines having the same values are shown. In the lower panel all such points have been connected to form a smooth curve. The numbers on the curve are the $\dot{V}_A/\dot{Q}$ values pertaining to each point (see text).


P_{CO_2}
50
40
30
20
10
0
0
20
40
60
80
100
120
140
P_{O_2}


P_{CO_2}
50
40
30
20
10
0
.22
.50
.60
.78
.91
1.25
2.00
3.56
14.8
20
40
60
80
100
120
140
P_{O_2}

$$\frac{\dot{V}_A}{\dot{Q}} = \frac{R\,(Ca_{O_2} - Cv_{O_2})}{F_{A_{CO_2}}} \qquad \text{II-13}$$

We have just shown that for a given inspired mixture and composition of mixed venous blood, R, Ca_{O_2} and $F_{A_{CO_2}}$ are uniquely related; $\dot{V}_A/\dot{Q}$ then determines the values of all three. Therefore, each R value represents a unique $\dot{V}_A/\dot{Q}$ and this ratio is the physiological determinant of alveolo-capillary R and alveolo-capillary gas tensions.

In a three gas system such as alveolar gas, designation of the concentrations of two gases fixes the concentration of the third. Thus, $\dot{V}_A/\dot{Q}$ by determining R also determines alveolo-capillary P_{N_2} and it is possible to construct a line on a $P_{CO_2} - P_{N_2}$ diagram which represents all possible concentrations of these gases in a lung with given input contents of gas and blood (Fig. 3B). As in the $P_{O_2} - P_{CO_2}$ diagram, each point on the $P_{N_2} - P_{CO_2}$ line represents a unique $\dot{V}_A/\dot{Q}$.

These diagrams obviously give the experimenter a powerful tool for assessing gas exchange. They establish that measurement of gas tensions in gas or blood may be interpreted in terms of specific $\dot{V}_A/\dot{Q}$ and conclusions drawn regarding the determinants of $\dot{V}_A/\dot{Q}$. It follows that inhomogeneities of gas composition within the lungs indicate variation of $\dot{V}_A/\dot{Q}$. Measurements of inhomogeneities of gas concentration in the lungs are not easy to make, however, and most techniques for evaluating variation of $\dot{V}_A/\dot{Q}$ are therefore somewhat indirect.

The respiratory mass spectrometer is capable of instantaneous measurement of a number of respiratory gases in simultaneous fashion. West et al. used this instrument to record O_2 and CO_2 during single expirations[17]. As had

been noted previously the P_{O_2} and P_{CO_2} were not constant throughout indicating differences in pre-expiratory gas concentrations throughout the lung. Concentration differences in the alveolar gas measured in these experiments then represented different $\dot{V}_A/\dot{Q}$ and West et al. interpreted them as such with the aid of the O_2 - CO_2 diagram. Continuous records of expired gas concentrations as measured with the mass spectrometer are shown in Fig. 7. West et al. simply chose two points on these curves and assigned them $\dot{V}_A/\dot{Q}$ according to curves similar to those of Fig. 6B. In addition, they recorded expiratory gas tensions after a single breath which contained argon[18] as well as O_2 and N_2. The argon was distributed according to ventilation per unit volume so that differences in $\dot{V}_A/V$ in pre-expiratory alveolar gas were also available. When differences in $\dot{V}_A/\dot{Q}$ were computed for the same breaths using O_2 and CO_2 tension differences, perfusion per unit volume ($\dot{Q}/V$) could be appreciated. In both normals and abnormals, mostly patients with emphysema, it was found that the alveolar gas expired early contained more O_2 and A, and less CO_2 than did that expired later. This led them to conclude that well ventilated (high $\dot{V}_A/V$) units emptied early, that these had high $\dot{V}_A/\dot{Q}$; and also relatively high $\dot{Q}/V$. The differences were rather small in normal subjects and considerably larger in emphysema. The authors pointed out that these studies could be criticized on a number of counts. The size of the breath taken, the lung volume at which it was taken, and inspiratory and expiratory flow rates were not rigidly controlled; all of these may influence the distribution of ventilation in normals and are likely to be more important in the case of the diseased lung. Secondly, the test measured minimum variations throughout the lung, since it depended not only on pre-expiratory differences

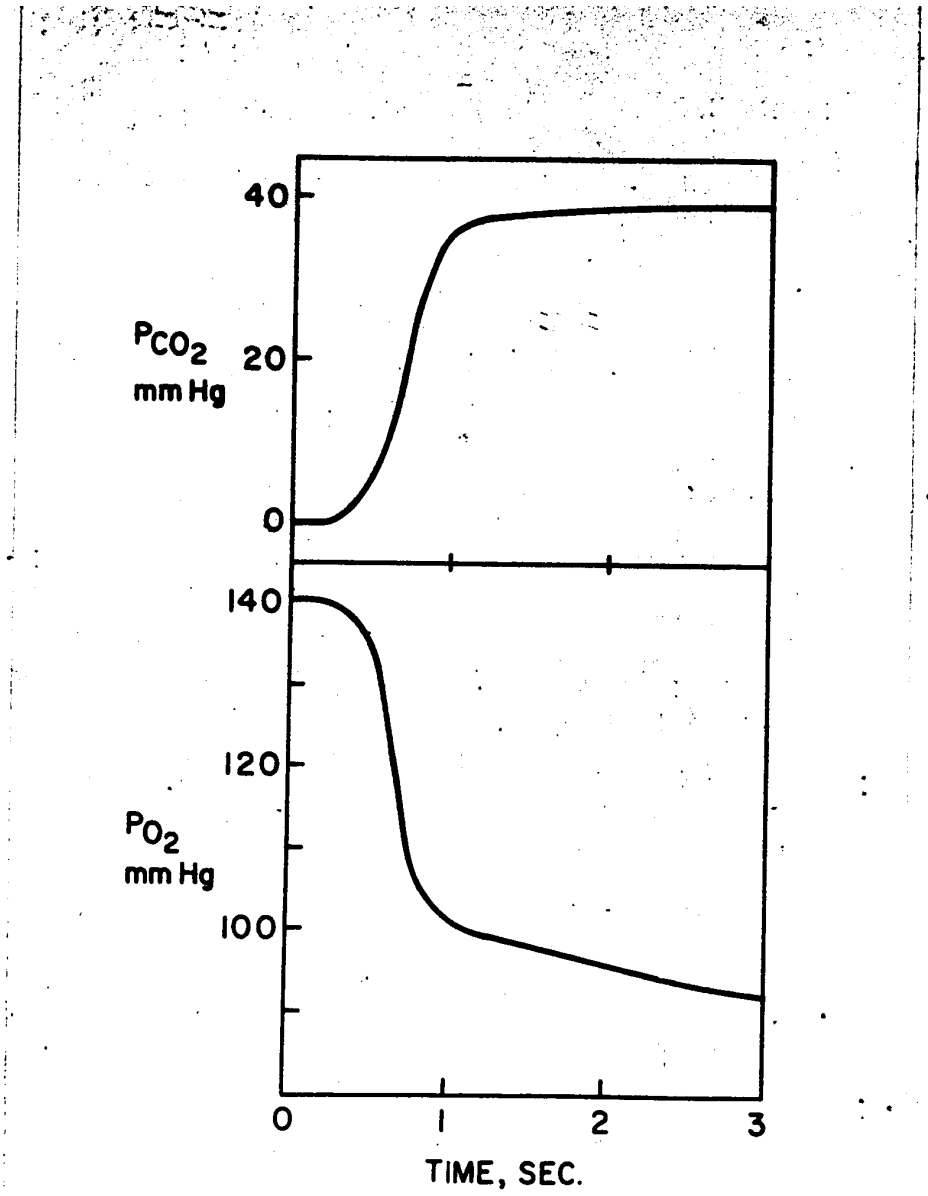


Fig. 7. Simulated mass spectrometer tracings. Ordinates: P_{O_2} and P_{CO_2}. Abscissa: time in seconds. Measurements were made at the mouth during a single expiration. At the onset of expiration (t=0) the conducting airways (dead space) were filled with inspired gas. As this gas is expired and the airways washed out P_{CO_2} rises and P_{O_2} falls rapidly. At 1.0-1.5 sec. alveolar gas is being expired and the rate of change of P_{O_2} and P_{CO_2} decrease. However, both continue to change, indicating inhomogeneity of alveolar gas.

in gas concentrations within the lung, but also on differences in emptying sequence among various units with different concentrations. If emptying sequence were constant, so that each segment of the expirate were made up of fixed fractions from all units, there would be no differences in gas concentration throughout the alveolar portion of expired gas, irrespective of pre-expiratory differences in gas composition (and, therefore, $\dot{V}_A/V$ and $\dot{V}_A/\dot{Q}$) throughout the lung.

Another approach using the respiratory mass spectrometer was devised by Read and Fowler[19,20]. They noted that when a normal subject exhaled slowly through the instrument, pulsatile changes of gas concentration were present as alveolar gas was expired. These pulsatile changes were coincident with the heart beat and were termed cardiogenic oscillations. When the inspirate contained argon, the pulsatile variations seen in the alveolar concentrations of A and CO_2 were in phase and both of these were 180° out of phase with changes in P_{O_2}. On the basis of studies involving posture the authors concluded that the heart beat induced changes in the emptying of upper lung zones in relation to the emptying of lower lung zones; thus, during systole the flow rate from lower zones increased in relation to that from upper zones while the reverse happened during diastole. With the cardiac cycle, then, mixed alveolar gas concentrations alternately approached those of upper and lower zones. The authors concluded that upper zones had relatively high $\dot{V}_A/\dot{Q}$ and low $\dot{V}_A/V$ which was entirely consistent with data derived using radio isotopes. They carried their analysis further by assigning or assuming values for upper and lower zone $\dot{V}_A/V$[20]. This allowed them to calculate the precise effect of the heart on emptying pattern and when this

was applied to the O_2 and CO_2 tracings, to compute upper and lower zone $\dot{V}_A/\dot{Q}$ and $\dot{Q}/V$. Using this approach, the authors examined the effects of exercise and hypoxia[21,22]. Both of these stimuli appeared to increase upper-zone blood flow in most subjects. However, this was not true in all subjects and it was proposed that some otherwise normal individuals do not respond to these stimuli by shifting their blood flow distribution. These experiments, while very ingenious, suffered from the fact that they were most indirect and involved a number of assumptions which were difficult to prove. For instance, direct studies of the effect of the heartbeat on expiratory air flow in major bronchi have shown that this effect was not uniform but tended to vary from individual to individual[23]. Upper and lower zones as studied by this method were undefined as opposed to studies with radioactive gases. Finally, the method was entirely inapplicable to subjects with lung disease.

An obvious method of assessing gas exchange is to measure arterial-alveolar differences for respiratory gases. As discussed in Section I such differences may reflect variations in $\dot{V}_A/\dot{Q}$. The oldest known discrepancy in gas tension between alveolar gas and arterial blood was that for oxygen (D_{O_2}); this difference is also the largest both in health and disease. Unfortunately, D_{O_2} are difficult to interpret for a number of reasons. Normally, the mean $\dot{V}_A/\dot{Q}$ is about 1.0, consonant with mean $P_{A_{O_2}}$ = 90-100 mmHg; normal $P_{I_{O_2}}$ approximates 140 mmHg and $P_{\bar{v}_{O_2}}$ is about 40 mmHg. Therefore, addition of units having either high $\dot{V}_A/\dot{Q}$ ($100 < P_{A_{O_2}} \leq 140$) or low $\dot{V}_A/\dot{Q}$ ($40 \leq P_{A_{O_2}} < 100$) to a lung with $P_{A_{O_2}}$ = 100 could cause an appreciable D_{O_2}; in the first instance by raising $P_{A_{O_2}}$, in the second by lowering $P_{a_{O_2}}$; given a D_{O_2} then it cannot be stated whether this is due to high $\dot{V}_A/\dot{Q}$ units, low

$\dot{V}_A/\dot{Q}$ units or both. Second, it is possible, though improbable, that a D_{O_2} might exist on the basis of alveolo-capillary block. This is particularly likely in units with low $\dot{V}_A/\dot{Q}$ and, hence, low $P_{A_{O_2}}$ so that the P_{O_2} difference driving the diffusion process is reduced. Finally, direct right-to-left shunting has an important influence on D_{O_2}[4] and such shunting may have little to do with lung function, as in cardiac defects. It is important to note that when $P_{A_{O_2}} > 100$ such shunting creates a larger D_{O_2} than might be expected on cursary inspection of the O_2 - CO_2 diagram. This is because of the alinearity of the O_2 dissociation curve[6]. Mixed venous blood ($P_{\bar{v}_{O_2}} = 40$) has an oxygen content of about 14 vol. %. Blood leaving alveoli with $\dot{V}_A/\dot{Q}$ of 1.0 ($P_{A_{O_2}}$=100) has an O_2 content of about 19.5 vol. %. If arterial blood is composed of equal parts of shunted (venous) and non shunted blood, the arterial O_2 content is 16.75 vol. %. This content, using a standard O_2 dissociation curve, is equivalent to about 52 mmHg. Thus, the $P_{a_{O_2}}$ is 52 mmHg and the $P_{A_{O_2}}$ is 100 mmHg, giving a D_{O_2} of 48 mmHg. To put it another way, because of the alinearity of the O_2 dissociation curve, addition of an equal amount of "alveolar" (P_{O_2} = 100) to mixed venous (P_{O_2} = 40) blood has only elevated the P_{O_2} of the latter by 12 mmHg.

In spite of these difficulties, Riley et al. developed a fruitful and important method for the study of normal and abnormal lungs which was based on D_{O_2} measurements[4,7,24]. They introduced the concept of ideal or effective $P_{A_{O_2}}$ which they defined as the $P_{A_{O_2}}$ which would obtain in alveolar gas if all units had the same $\dot{V}_A/\dot{Q}$. They derived effective $P_{A_{O_2}}$ from measuring O_2 and CO_2 in expired gas ($P_{E_{O_2}}$, $P_{E_{CO_2}}$) and used these in eq. II-7 to compute R. Arterial CO_2 tension ($P_{a_{CO_2}}$) was also measured; this was assumed equal to $P_{A_{CO_2}}$. Using R and $P_{a_{CO_2}}$ the ideal alveolar oxygen was computed according to eq. II-8. This was compared with $P_{E_{O_2}}$ and a dead space effect calculated.

This was done by computing the fractional dilution of gas with ideal $P_{A_{O_2}}$ by inspired gas ($P_{I_{O_2}}$) necessary to produce the observed $P_{E_{O_2}}$. Later, as gas analysis technique improved, measured $P_{A_{O_2}}$ was substituted for $P_{E_{O_2}}$. This had the advantage of not including ventilation of major airways in the calculation of dead space effect. $P_{a_{O_2}}$ was also measured; this was uniformly less than ideal $P_{A_{O_2}}$, and if $P_{\bar{v}_{O_2}}$ was known or assumed, the fractional dilution of blood with ideal $P_{A_{O_2}}$ by venous blood which was necessary to produce the observed $P_{a_{O_2}}$ was calculated. This was termed the venous admixture. This approach schematically divides the lung into three compartments, an ideal compartment with uniform $\dot{V}_A/\dot{Q}$ of about 1.0, a dead space or fraction of the ventilation with $\dot{V}_A/\dot{Q} = \infty$ and a venous admixture, or fraction of the cardiac output with $\dot{V}_A/\dot{Q} = 0$. In normal subjects the latter compartments were small, in patients with emphysema they could be quite large. This, of course, was a considerable oversimplification; all compartments were hypothetical in that they could be described in lungs with no true dead space, no true venous admixture, and no alveoli which contained the ideal $P_{A_{O_2}}$. This may be seen by comparing Figs. 4B and 4C. This difficulty with interpretation of alveolar-arterial differences is general -- they can be explained equally well on the basis of a small number of units with extremely biased $\dot{V}_A/\dot{Q}$ or a larger number with less biased values. An additional difficulty with the Riley approach was that the assumption that $P_{A_{CO_2}} = P_{a_{CO_2}}$ is not strictly true in normal subjects and may not be approximately true in subjects with disease.

The measurement of alveolar-arterial differences for CO_2 (D_{CO_2}) and N_2 (D_{N_2}) while technically difficult are more rewarding, at least in theory,

than are measurements of D_{O_2} [25]. The $CO_2 - N_2$ diagram (Fig. 3B) is almost rectangular in form, the usual normal alveolar values ($P_{CO_2} = 39$, $P_{N_2} = 570$) lying near a corner. The difference between $P_{\bar{v}CO_2}$ ($\dot{V}_A/\dot{Q} = 0$) and normal $P_{A_{CO_2}}$ ($R = 0.8$, $\dot{V}_A/\dot{Q} = 0.9$) is small (7 mmHg), while the difference between $P_{I_{CO_2}}$ ($\dot{V}_A/\dot{Q} = \infty$) and normal $P_{A_{CO_2}}$ is large. Because of this, units with high $\dot{V}_A/\dot{Q}$ are more effective in creating a D_{CO_2} in an otherwise normal ($R = 0.8$, $\dot{V}_A/\dot{Q} = 0.9$) lung than are units with low $\dot{V}_A/\dot{Q}$. Because the arterio-venous P_{CO_2} difference is so small (5 - 7 mmHg), direct right-to-left shunting has a small effect on D_{CO_2}. In contrast, the normal $P_{A_{N_2}} = 571$ mmHg, which is not greatly different from that in units with $\dot{V}_A/\dot{Q} = \infty$. On the other hand, units with very low $\dot{V}_A/\dot{Q}$ have $P_{A_{N_2}}$ which are considerably higher than normal. Thus, units with high $\dot{V}_A/\dot{Q}$ are not important in causing D_{N_2} while units with low $\dot{V}_A/\dot{Q}$ are. An additional feature of the D_{N_2} is that it is entirely insensitive to right-to-left shunting. This is because in the steady state there is no N_2 exchange in the periphery so that $P_{a_{N_2}} = P_{\bar{v}_{N_2}}$; therefore, addition of mixed venous blood to arterial blood cannot change $P_{a_{N_2}}$. Neither D_{CO_2} nor D_{N_2} can be attributed to alveolo-capillary block, in one case because of the high diffusivity of CO_2 and in the other because of the very small amount of N_2 actually crossing the membrane [25]. An illustration of the apparent paradox of steady state N_2 exchange is shown in Fig. 8. Though N_2 is exchanged between units of high and low $\dot{V}_A/\dot{Q}$ there is no net pulmonary exchange either with the inspirate or the periphery.

By measuring D_{N_2} and D_{CO_2} simultaneously, it is possible to describe the lung in terms of two compartments each with specific $\dot{V}_A/\dot{Q}$ and specific shares of the overall ventilation and perfusion [26]. A simplified example of this is shown in Fig. 9. Alveolar gas is analyzed and plotted on the

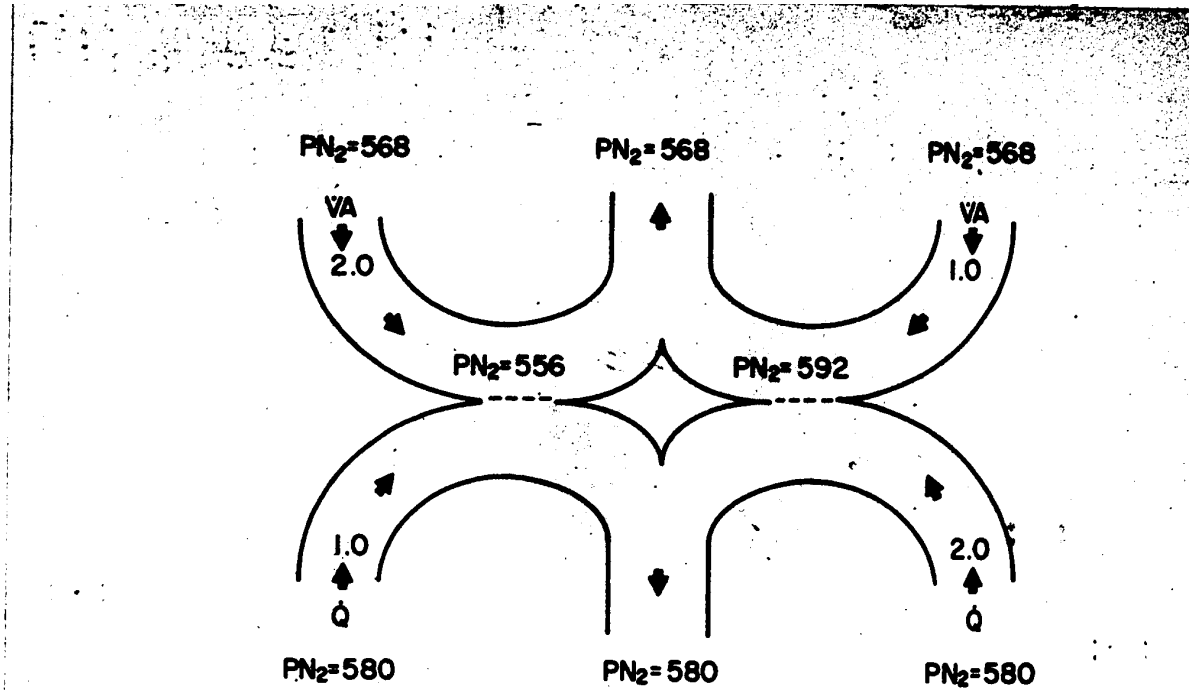


Fig. 8. Steady state N_2 exchange. Two alveoli are shown, one with $\dot{V}_A/\dot{Q}=0.5$, the other with $\dot{V}_A/\dot{Q}=2.0$. Inspired $P_{N_2}=568$ mmHg and mixed venous $P_{N_2}=580$ mm Hg. The capillary blood loses N_2 in the high $\dot{V}_A/\dot{Q}$ unit, the amount being equal to the blood flow times the difference between venous and alveolo-capillary P_{N_2}. This N_2 loss is exactly balanced by blood N_2 uptake in the high $\dot{V}_A/\dot{Q}$ unit so that arterial and venous P_{N_2} are the same, so there is no net uptake or release of N_2 by either blood or gas. Nevertheless, there is an alveolar-arterial P_{N_2} difference.

CO_2 - N_2 diagram, as is a sample of arterial blood. The alveolar sample must fall on the appropriate gas R line, the arterial sample on the blood R line having the same value. The lung is assumed to consist of two compartments each contributing to the alveolar gas and arterial blood; the composition of each compartment must be represented on the "$\dot{V}_A/\dot{Q}$ line" of Fig. 9. If we assume that the blood dissociation curves of CO_2 and N_2 are linear, the composition of the two compartments may be defined simply by drawing a straight line between the arterial and alveolar points; compartmental composition is defined by the intersections of this line with the "$\dot{V}_A/\dot{Q}$ line." Further, the fractional contribution of each compartment is inversely related to the distance between the compositions of the compartments and that of the mixed (alveolar or arterial) sample considered, as shown in Fig. 9. This argument cannot be rigorously derived here, but it can be reasoned in intuitive fashion. If we begin with the two compartments plotted on the CO_2 - N_2 diagram, it is evident that any mixture of gases from them must lie on the line joining them. The precise point on this line is determined by the relative contribution of each; if each compartment contributes equally the resultant mixture will be equidistant from the two original points. If N_2 and CO_2 dissociation curves are linear, precisely the same argument applies in regard to the arterial blood. Plotting both arterial and alveolar compositions, then defines the straight line which in turn defines the two compartments. Using this compartmental data and the O_2 dissociation curve, a D_{O_2} may be calculated which is entirely due to $\dot{V}_A/\dot{Q}$ variance. Comparison of this calculated D_{O_2} with a measured D_{O_2} allows conclusions to be drawn regarding the amount of direct arterio-venous shunting.

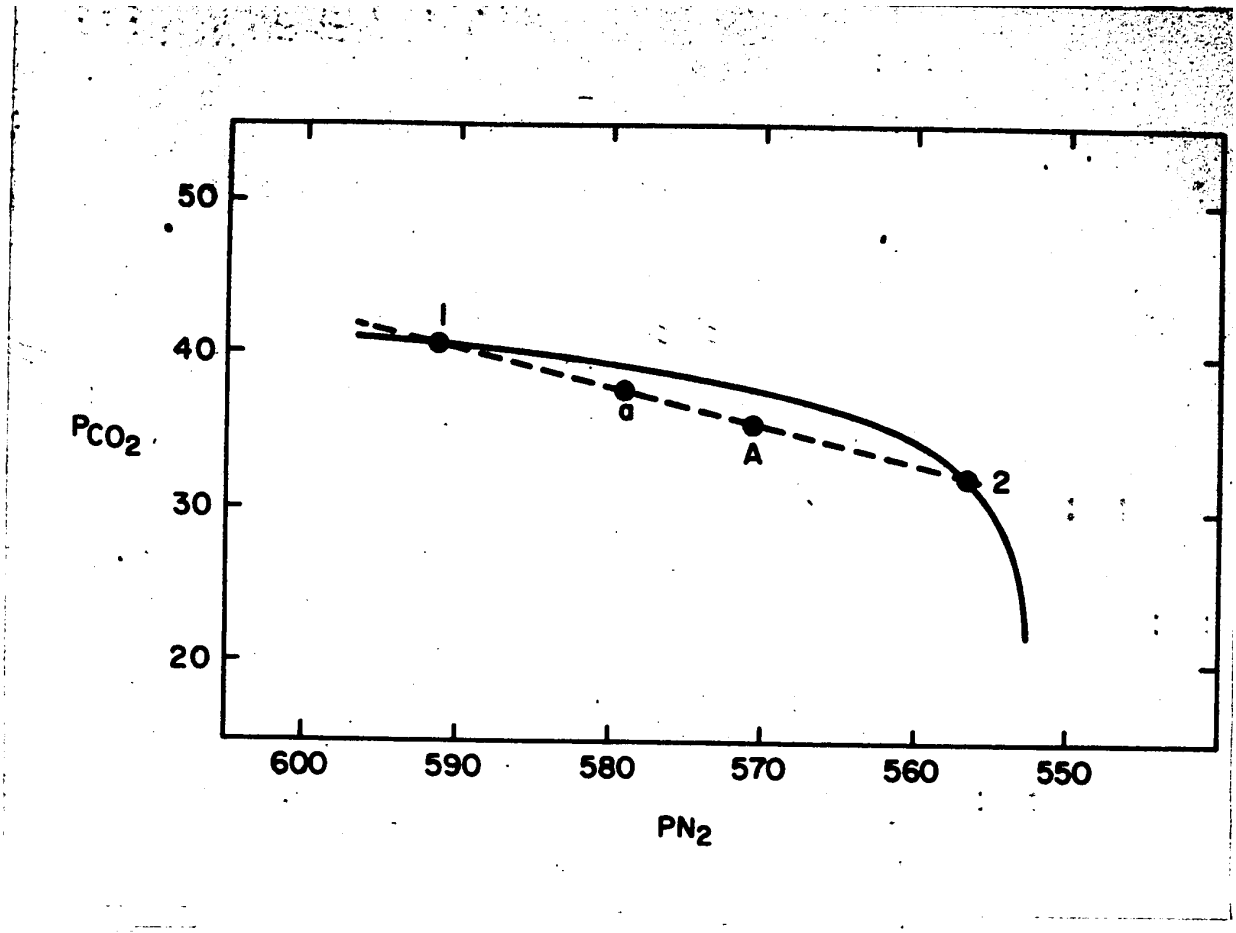


Fig. 9. Two compartment analysis of $\dot{V}_A/\dot{Q}$ inhomogeneity. Shown is a section of the CO_2 * N_2 curve of Fig 3. Samples of mixed alveolar gas (A) and arterial blood (a) are analyzed and plotted on the curve. They must fall on the appropriate whole lung R lines for gas and blood. A straight line is drawn through these points and the two compartments (land 2) defined by the intersection of this line with the "$\dot{V}_A/\dot{Q}$ line." In this example the $\dot{V}_A/\dot{Q}$ of compartment 1 is 0.55 and the $\dot{V}_A/\dot{Q}$ of compartment 2 is 2.00. The fractional contribution of compartment 1 to the arterial blood is defined by the ratio of the distance a-2 to the distance 1-2. The fractional contribution of compartment 2 to mixed alveolar gas is equal to the ratio of distance A-1 to distance 1-2.

The two-compartment model is obviously highly hypothetical: it is perfectly possible to describe a lung in this fashion when the lung in fact contains no alveoli with the gas composition of either compartment. However, measurements of D_{N_2} and D_{CO_2} have been rewarding. D_{CO_2} has been used as a diagnostic and experimental test in pulmonary embolism[27,28] and has been shown to be elevated in patients with emphysema[29]. D_{N_2} has proved to be a relatively sensitive test for $\dot{V}_A/\dot{Q}$ disturbance in the newborn[30] and in patients with emphysema[31].

Lenfant[32] extended this approach in normal subjects by measuring D_{O_2}, D_{CO_2} and D_{N_2} as $P_{I_{O_2}}$ was increased. Increasing $P_{I_{O_2}}$ has the effect of greatly enlarging the range of P_{O_2} and P_{N_2} covered by the $\dot{V}_A/\dot{Q}$ line in both the O_2-CO_2 and the N_2 - CO_2 diagrams. This is because $P_{\bar{v}O_2}$ increases only slightly as $P_{I_{O_2}}$ is raised from 140 to 700. In addition to this, the splay of gas R lines becomes considerably narrower. The net result of these effects is that the difference in composition between units with very low $\dot{V}_A/\dot{Q}$ and those with $\dot{V}_A/\dot{Q} = 1$ is enormously increased, so that if units with such very low $\dot{V}_A/\dot{Q}$ exist their effect in terms of D_{O_2} and D_{N_2} is magnified. It was well known that in normal subjects, D_{O_2} increased with increases in $P_{I_{O_2}}$; this had been attributed to direct right-to-left shunting. Lenfant, however, showed that D_{N_2} also increased as $P_{I_{O_2}}$ was increased; this could not have been due to shunting but must have been due to the presence of alveolar units with $\dot{V}_A/\dot{Q}$ bordering on zero. Other studies of D_{O_2} have since supported this hypothesis[33]

Recently, Farhi[26,34,35] has infused solutions of inert foreign gases and measured their arterial-alveolar differences. The behavior of any such gas under steady state conditions is, as stated in Section I, dependent on

the applicable $\dot{V}_A/\dot{Q}$ and the solubility of the gas. If the gas is infused to steady state:

$$Q\, C_{\bar{v}} = F_A \dot{V}_A + F_A \dot{Q} \alpha \qquad \text{II-14}$$

The left side of the equation represents the input due to infusion; the right represents the lung output. Rearranged:

$$F_A/C_{\bar{v}} = \frac{1}{\dot{V}_A/\dot{Q} + \alpha} \qquad \text{II-15}$$

This equation is plotted in Fig. 10 for two gases of differing solubilities, one, He, being very insoluble and the other, acetylene, being relatively soluble. It can be seen that in the case of He, units with very low $\dot{V}_A/\dot{Q}$ contain very high concentrations relative to other units; if very low $\dot{V}_A/\dot{Q}$ units were present they would be effective in producing an alveolar-arterial difference for He. On the other hand, acetylene concentration changes little over the low $\dot{V}_A/\dot{Q}$ range, so arterial-alveolar differences for this gas could only be produced by relatively high $\dot{V}_A/\dot{Q}$ units. Using this approach with normal subjects, Farhi concluded that normal lungs must contain some units with very high $\dot{V}_A/\dot{Q}$ and others with extremely low $\dot{V}_A/\dot{Q}$. Further, it was suggested that diagrams analagous to the CO_2 - N_2 diagram could be set up and analyzed. Using Fig. 10 an He-acetylene diagram could be composed and if arterial and alveolar samples were obtained, they could be analyzed to produce a two-compartment lung model. This approach is attractive but the analyses are extremely difficult and there must be some provisional question regarding the presence of a steady state in this kind of experiment. In theory, this technique should be applicable to abnormal lungs.

A particularly rewarding technique in diseased lungs has been to use inert gas washout techniques to describe the distribution of ventilation,

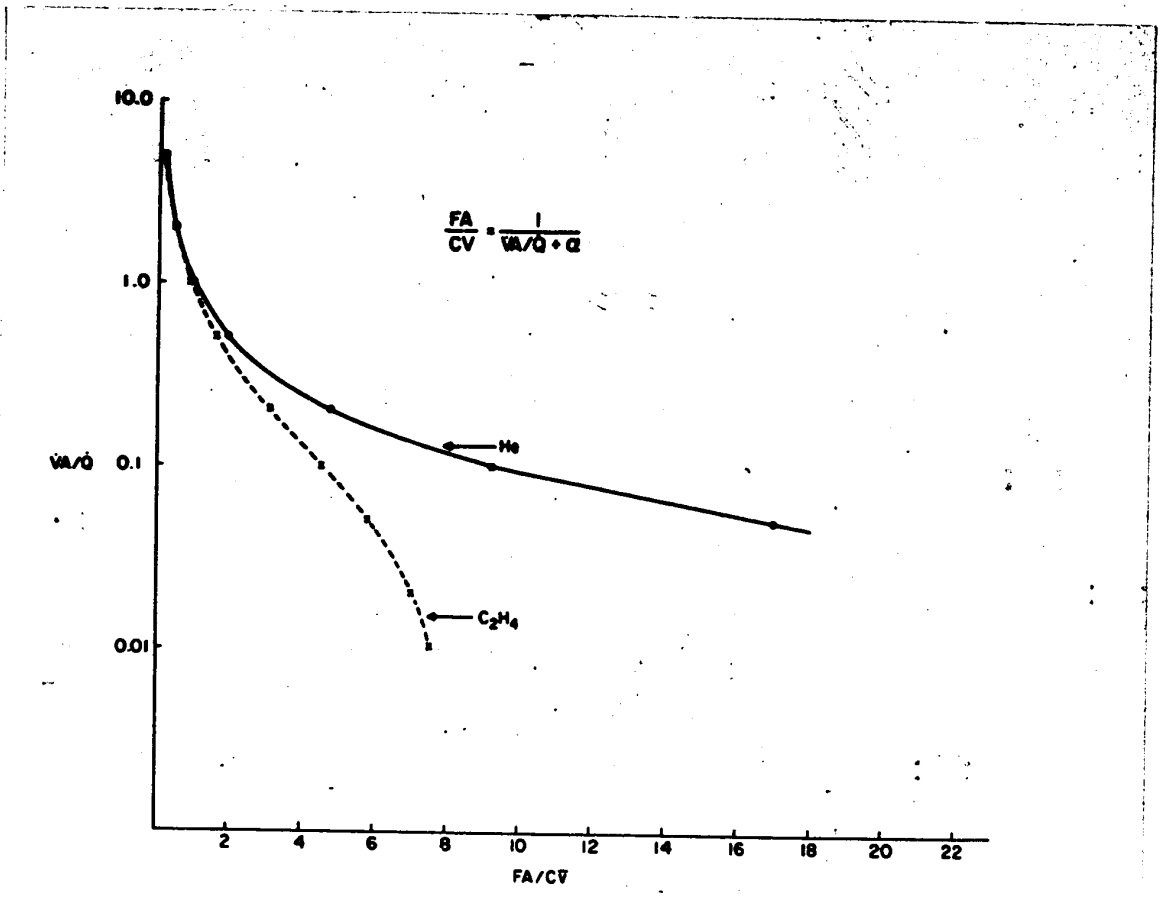


Fig. 10. Effect of $\dot{V}_A/\dot{Q}$ and solubility in determining alveolo-capillary gas concentrations. Solutions of He (solid line $\alpha \simeq 0.0088$) and acetylene (dotted line $\alpha \simeq 0.122$) were infused intravenously to steady state and the resulting alveolar gas concentrations are plotted as fractions of the mixed venous concentration (abscissa). On the logarhythmic ordinate is $\dot{V}_A/\dot{Q}$.

and to compare this data with either blood gases or arterial-alveolar differences.

This approach was introduced by Briscoe[36-38] who used it with particularly good effect in patients with emphysema. They examined open circuit N_2 washout of lungs of patients breathing O_2, analyzing successive breaths for N_2 over a 20 minute period. If the lung were a homogeneous well mixed system during washout $F_{A_{N_2}}$ at any time (t) may be described by:

$$F_{A_{N_2}} = F_{A_0} e^{-\frac{\dot{V}_A}{V} t} \qquad \text{II-16}$$

where F_{A_0} is N_2 concentration at t = 0. If $\ln F_{A_{N_2}}/F_{A_0}$ is plotted against time (t) the result then should be a straight line with slope $-\dot{V}_A/V$. If several homogeneous well mixed compartments were in parallel, the washout function for the whole lung would be:

$$F_{A_{N_2}}(t) = F_{A_0} e^{-(\dot{V}_{A_1}/V_1)t} + F_{A_0} e^{-\left(\frac{\dot{V}_{A_2}}{V_2}\right)t} \qquad \text{II-17}$$

When this equation is plotted as $\ln (F_{A_t}/F_{A_0})$ against t, the result is representative of the algebraic sums of lines with slope of $-\dot{V}_A/V$ (Fig. 11). Since t is related to $\dot{V}_A$ by a constant, the area under each of the lines is proportional to the amount of N_2 in each compartment, and the fraction of the total lung volume occupied by each compartment may be calculated. If overall $\dot{V}_A$ is known, the alveolar ventilation of each compartment may also be calculated. Briscoe made these measurements in patients with emphysema and found washout curves suggesting the presence of a large homogeneous compartment with very low $\dot{V}_A/V$, together with one or more small compartments

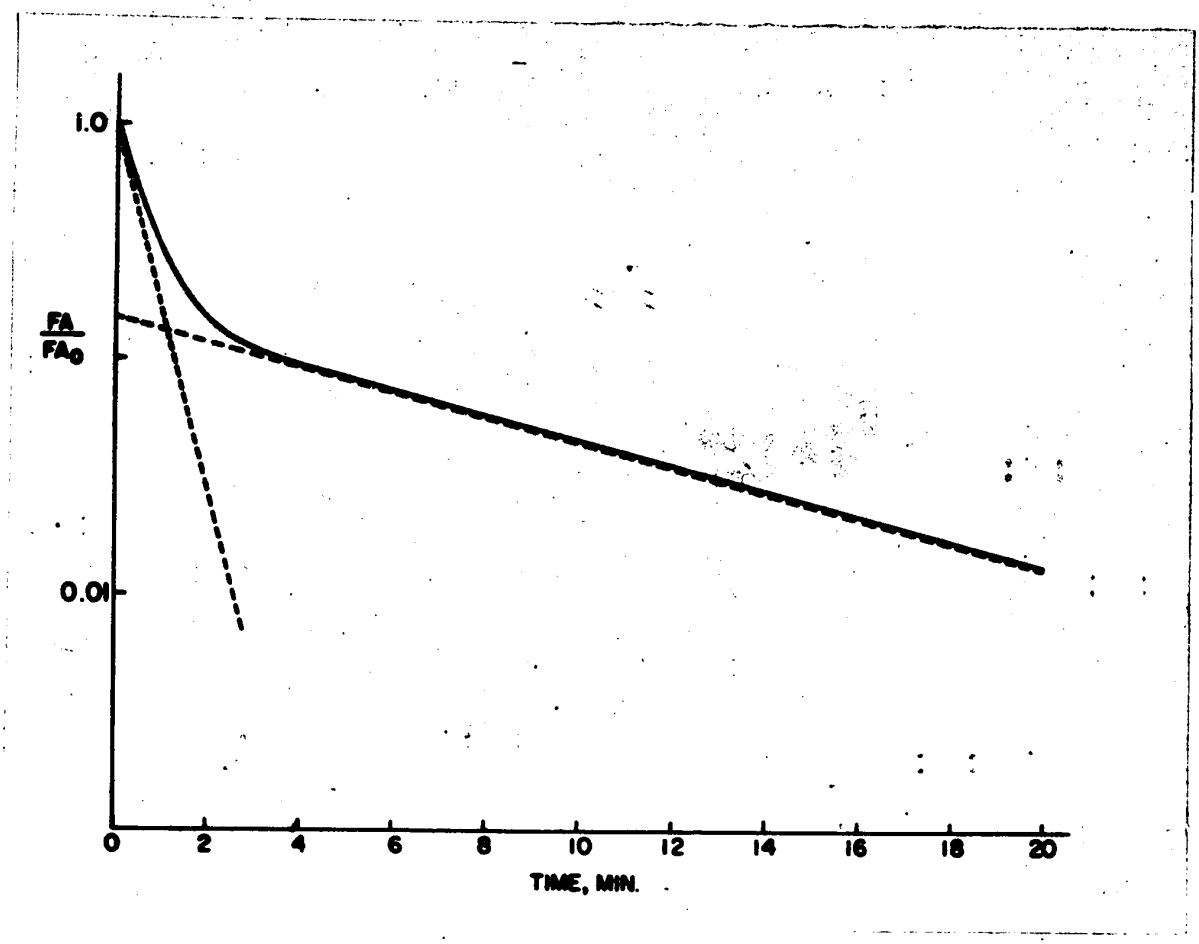


Fig. 11. Simulated nitrogen washout curve from a patient with emphysema. Ordinate: alveolar N_2 concentration expressed as a fraction of that existing at t=0; the scale is logarithmic. Abscissa: time in minutes. The solid represents the experimental curve, and after 5-6 min this curve is essentially linear, defining the washout of the poorly ventilated space (dashed line, $\dot{V}_A/V = 0.116$ L/min/L). Subtraction of this curve from the experimental washout curve yields a second linear plot, which defines the well ventilated space (dotted line, $\dot{V}_A/V = 1.77$ L/min/L).

with high $\dot{V}_A/V$. The patients' arterial oxygen saturation was also measured and an assumption made regarding mixed venous oxygen saturation. It was then assumed that the well ventilated compartments had high $\dot{V}_A/\dot{Q}$ and produced blood which was 98% saturated. This allowed calculation of the upper limit of the fractional blood flow to the well ventilated compartments and, in light of the measured $S_{a_{O_2}}$ allowed unique solutions for the $\dot{V}_A/\dot{Q}$ and fractional perfusion of the poorly ventilated compartment. Briscoe found that patients with emphysema generally gave similar results. The poorly ventilated space amounted to 2/3 of the FRC and was relatively underperfused, receiving about one half the cardiac output. It received only 5 - 10% of the ventilation, and had a $\dot{V}_A/\dot{Q}$ of 0.1 - 0.2. The small space was both over ventilated and overperfused and had a $\dot{V}_A/\dot{Q}$ in the neighborhood of 2.0. Similar studies were carried out in normal subjects[37] but the results were less consistent probably because the N_2 washout curves did not break into linear components as well. These studies by Briscoe were important, particularly those in patients with emphysema. They clearly illustrated the wide disparities in $\dot{V}_A/\dot{Q}$ which could exist in the emphysematous lung. The technique was flexible and could be applied to patients during exercise, hyperventilation and artificial respiration. However, the compartments or spaces described were hypothetical; the assumption of uniformity of $\dot{V}_A/\dot{Q}$ and perfusion within either "compartment" (defined by the washout curve) was unjustified and it has been said that stripping exponential functions from a complex function such as N_2 washout is a dubious procedure. Finally, granting the reality of the two compartments, this approach gives no information beyond their existence and function; their location and anatomy is unknown.

A number of techniques resembling that of Briscoe's have been introduced by other investigators; these will be reviewed briefly. In general, the same criticisms apply to these studies as do to those of Briscoe's.

Finley et al.[10,39] measured $P_{a_{O_2}}$ and $F_{A_{N_2}}$ continuously during N_2 washout. By selecting a two points late in washout they were able to assume that all remaining N_2 was in a badly ventilated compartment and that the blood in this compartment was fully saturated so that the change in $P_{a_{O_2}}$ between the two points selected equalled the change in $P_{a_{N_2}}$ ($P_{a_{CO_2}}$ being constant). Thus, the change in overall $P_{a_{N_2}}$ is known, and the simultaneous change in overall $P_{A_{N_2}}$ was measured. If all the N_2 were in the poorly ventilated compartment, then all the N_2 in mixed alveolar gas and arterial blood originated in this compartment, and the P_{N_2} of compartmental gas and blood must have been the same. Therefore, the change in overall $P_{A_{N_2}}$ represented the change in compartmental $P_{A_{N_2}}$ multiplied by a dilution factor which was the ratio of compartmental to overall alveolar ventilation. Similarly, the change in $P_{a_{O_2}}$ equalled the same change in compartmental P_{N_2} multiplied by a dilution factor, this factor being the ratio of compartmental to overall perfusion. By combining these relationships, the $\dot{V}_A/\dot{Q}$ of the poorly ventilated compartment relative to overall $\dot{V}_A/\dot{Q}$ could be computed. The washout curve could be used for deriving the volume and ventilation of the poorly ventilated compartment. This technique was used to examine patients with pulmonary fibrosis[10] thought to have alveolo-capillary block; it was particularly well adapted to this since the crucial measurements were made when $P_{A_{O_2}}$ was so high that the effect of potential diffusion barriers were minimal. The findings of this study were important in that variations in $\dot{V}_A/\dot{Q}$ in these

patients were considerable, enough to explain observed gas exchange abnormalities without invoking alveolo-capillary block.

Klocke and Farhi[40] monitored inert gas washouts in both alveolar gas and arterial blood and, plotting them semilogarhythmically, analyzed them in the same way as Briscoe[36]. Using the extrapolated intercepts (at t = o) and the slopes of the final portions of the washout curves they calculated the fractional ventilation and perfusion of the poorly ventilated space. By an approach very similar to that of Finley, they also calculated the $\dot{V}_A/\dot{Q}$ of the slowly ventilated space in relation to overall $\dot{V}_A/\dot{Q}$. In normal subjects they found that the poorly ventilated space received small fractions of both the overall ventilation and perfusion and that its $\dot{V}_A/\dot{Q}$ was about 80% of the overall. These differences are not great; by this method it must be concluded that the poorly ventilated space has trivial effects on gas exchange in normals. The same group then studied a group of child asthmatics[41] who unfortunately were not well characterized in terms of overall pulmonary function. However, even in "mild" cases they found the relative ventilation of the slow space to be slightly increased and the relative perfusion of the slow space to be considerably increased. The $\dot{V}_A/\dot{Q}$ of the slow space was 10 - 30% that of the overall $\dot{V}_A/\dot{Q}$. They concluded that the slow space was relatively large even in "mild" asthmatics and that it had rather low $\dot{V}_A/\dot{Q}$.

Lenfant and Pace[42], studying patients with emphysema, combined N_2 washout with measurements of D_{N_2}, D_{CO_2} and D_{O_2}. Analyzing the washout curve he defined three compartments according to $\dot{V}_A/V$ and assumed that these compartments were homogenuously ventilated and perfused. The compartment with the lowest $\dot{V}_A/V$ was assigned responsibility for the D_{N_2}, the best ventilated

compartment was assumed to be responsible for the D_{CO_2}. Knowing the ventilation of the slowest compartment, it was possible to calculate from the D_{N_2} the perfusion and, therefore, the $\dot{V}_A/\dot{Q}$ of this compartment. Similar quantitation of blood flow to the best ventilated compartment was possible based on the measured D_{CO_2}. The remaining compartment was assumed to be responsible for no alveolar-arterial difference. A series of patients with emphysema were graded according to symptoms and studied with the above method. The most severely ill group gave results which were in excellent agreement with those of Briscoe[38] when the badly ventilated compartment was considered. Again the extreme dispersion of $\dot{V}_A/\dot{Q}$ in this disease was demonstrated. As ventilatory function became reduced, the second or normal compartment became smaller and both the over-ventilated and the over-perfused compartments became larger, particularly the latter.

Perhaps the feature common to all these techniques is their ingenuity. All have contributed to our knowledge of gas exchange either in normals or patients. However, all these methods were forced to construct models of the lung; they described the lung as behaving as if the description presented were true. No claim could be made that the description per se was valid. Further, these approaches, particularly in normal subjects, did not in general give insights into the mechanisms responsible for variations in $\dot{V}_A/\dot{Q}$. Finally, in patients with disease the geographic or anatomical distribution of malfunction may be of interest; these techniques did not yield this information.

3. REGIONAL LUNG FUNCTION

The most direct method of studying one area of lung as distinct from others is simply to cannulate the appropriate airway and make measurements via the cannula. Though such measurements had been made[43] physiological use of the technique in humans was not extensive until Carlens developed an endotracheal tube which separated the airways of the right and left lung[44]. Subsequently, Carlens[45] and Young and Martin[46] developed catheters capable of separating the right upper lobe from the right middle and lower lobes, as well as the right from the left lung. With such tubes in place ventilation, inert gas washout and expired and alveolar gases could be measured from the isolated lobe or lobes[45-48]; conclusions could be drawn regarding the relative ventilation, perfusion and $\dot{V}_A/\dot{Q}$ of each lobe. The most consistent and striking finding of these studies was that the distribution of both ventilation and perfusion were gravity dependent. If the subject lay on his left side, the left lung had greater ventilation, greater perfusion and a lower $\dot{V}_A/\dot{Q}$ than did the right. This situation was reversed by turning the subject to his right side. In studies of the right upper lobe, this lobe demonstrated relatively low ventilation and perfusion and high $\dot{V}_A/\dot{Q}$ when the subject was erect. When the subject was supine differences between the right upper lobe and the remainder of the right lung became much less. These studies, then, consistently showed that dependent areas of the lung were relatively over ventilated in relation to their volume and were to a greater extent over-perfused in relation to their volume, resulting in low $\dot{V}_A/\dot{Q}$. Superior areas of the lung, irrespective of body position, were underventilated, considerably more underperfused and had high $\dot{V}_A/\dot{Q}$.

These were most ingenious studies and it may be said that studies with radioactive gases have demonstrated little in regard to normal regional lung function that had not been anticipated on the basis of experiments utilizing bronchospirometry. However, bronchospirometry is a trying technique, difficult for both subject and experimenter. Separation of lobes, though admirable from a surgical point of view, was perhaps not optimal physiologically since lobes are large and are not oriented precisely in relation to gravitational fields.

The advent of radioactive gases was a distinct advance in the study of regional lung function. It had been obvious from studies of other organs that if a radioactive gas could be introduced into the lung and its concentration measured by external radiation detection devices, a great deal of information would become available regarding regional lung function. The particular functions measured would depend on properties of the gas and the ways in which it was administered to the lung. The limitations of the region studied would depend on the power of resolution of the detector employed. Though the earliest experimental work involving radioactive gases in humans was that of Knipping[49], the first extensive series of quantitative experiments originated from the group at Hammersmith Hospital who used ^{15}O [50-53].

Radioactive ^{15}O was produced by cyclotron and since it had a half life of 2 min., it had to be utilized immediately and in close proximity to the cyclotron. Its emission was a positron which in turn immediately produced two gamma rays each with energy levels of .55 MEV (mega electron volts). These two gamma rays traveled in opposite directions, i.e., with an angle of 180° relative to each other. They were detected with scintillation counters placed opposite each other over the front and back of the chest. The counters were set in such a way that only radiations arriving at both counters simultaneously

were recorded. This arrangement, called coincidence counting, guaranteed that all recorded radiation events had occurred in the cylinder of tissue between the two counters, giving excellent spatial resolution.

Though the Hammersmith group originally used ^{15}O (50) and $C^{15}O$ (51) as well, most of their important data was generated using $C^{15}O_2$ (52,53) which was produced by passing ^{15}O over heated charcoal.

The subject was examined seated with counters arranged at equal heights over the front and back of the chest. He took a single 1 L. inspiration from a bag containing the test gas and then held his breath while intrapulmonary count rates were recorded. Fig. 12 presents a schematic representation of a record from parallel (front and back) counters. Count rate rises rapidly to a peak as the subject inspires and then falls as the breath is held, the isotope being taken up by the pulmonary circulation and removed from the counting field. The rate of fall of count rate appeared to be exponential and was related to the blood flow per unit volume in the counter field. When this exponential was back-extrapolated to t = o, the increase in count rate due to the inspired isotope was computed. This increase was related to the amount of ventilation received by the lung in the counter field. This could be compared to data from other lung regions and the ventilation of one lung region relative to another was assessed. Thus, a single breath of isotope, resulting in a trivial amount of radiation dosage, was sufficient to map the regional distributions of ventilation and of perfusion per unit volume. In order to map the distribution of $\dot{V}_A/\dot{Q}$ some further manipulation of the data was required. The rate of fall of regional count rate during breath-hold was related to $\dot{Q}/V$ but the initial increase of regional count rate was related to ventilation per se not ventilation per unit volume. Thus, two lung regions with different

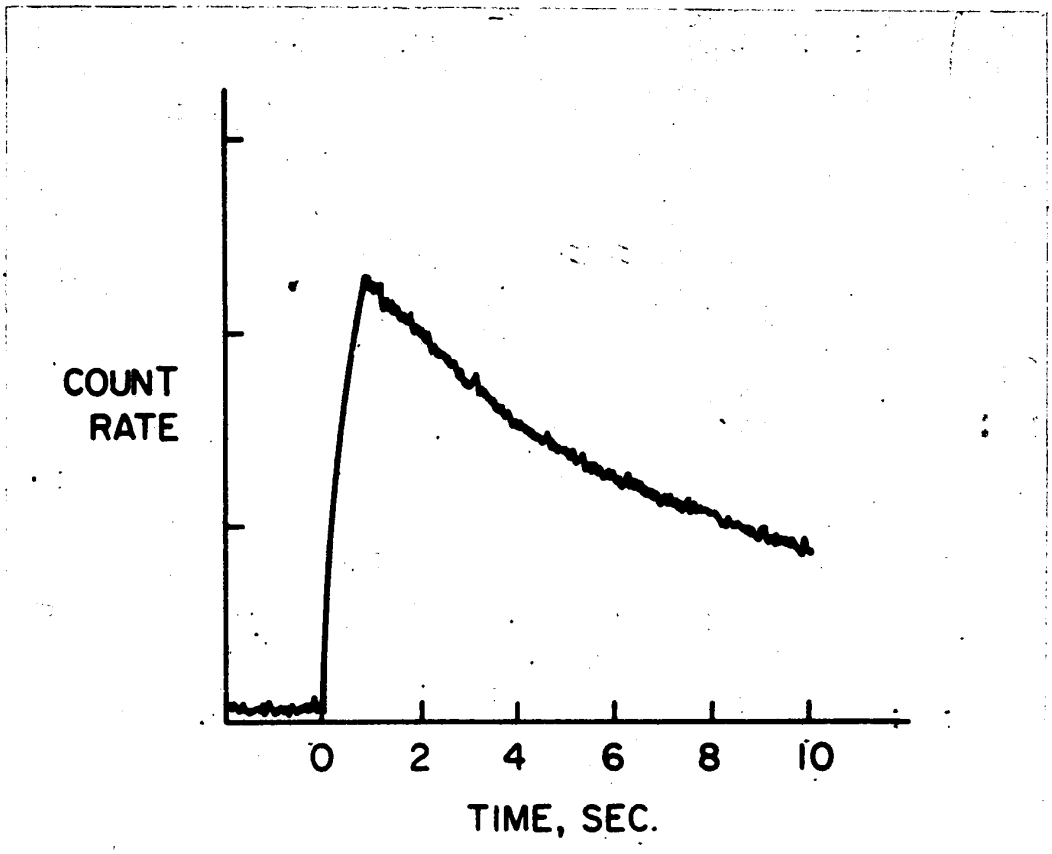


Fig. 12. Simulated record of inhalation of $O^{15}O_2$. Data were gathered from paired scintillation counters positioned at the same horizontal level in the erect subject. At t = 0 the subject inspired isotope, causing a rapid rise in count rate. During the subsequent 10 second breath hold count rate fell due to blood uptake of the isotope.

volumes but the same ventilations would accumulate the same amount of $C^{15}O_2$ with a breath of the gas, and by definition, these two regions would not have the same ventilation per unit volume. In order to compute regional $\dot{V}_A/\dot{Q}$, then, some estimate had to be made of regional volume, that is to say of the lung volume making up the counting field. Because coincidence counting was used, the precise diameter of the cylindrical counting field was constant and known. There remained then only the problem of estimating the length of the cylinder involved. This was done by positioning the counters in standard fashion and by measuring at the appropriate positions the antero-posterior diameter of the internal chest wall of cadavers. With this estimate of regional volume, regional $\dot{V}_A/V$, regional $\dot{Q}/V$ and finally regional $\dot{V}_A/\dot{Q}$ were available.

Fig. 13 presents data gathered in this fashion for normal erect subjects. It will be noted that regional $\dot{Q}/V$ increases dramatically from apex to base in roughly linear fashion; the extreme lung apex appears to be virtually underperfused. Regional $\dot{V}_A/V$ also increases from apex to base but in much more gradual fashion. Regional $\dot{V}_A/\dot{Q}$, as a result, was very high at the apex and decreased steadily as the base was approached; $\dot{V}_A/\dot{Q}$ went through a five-fold variation from top to bottom of the lung. On the basis of these data, a model of the lung was constructed[52,53]. It was assumed that the only differences in ventilation and perfusion existed in the vertical direction; reasonable values for regional lung volumes, cardiac output and overall alveolar ventilation were also assumed. Combining these assumptions with the O_2 - CO_2 diagram, and the data of Fig. 13, gas tensions, respiratory quotients, and blood pH were all calculated for various levels or slices up and down the lung. In addition, by combining the slices, overall alveolar and arterial gas tensions and resulting D_{CO_2}, D_{O_2} and D_{N_2} were computed, and it was found that this model accounted for

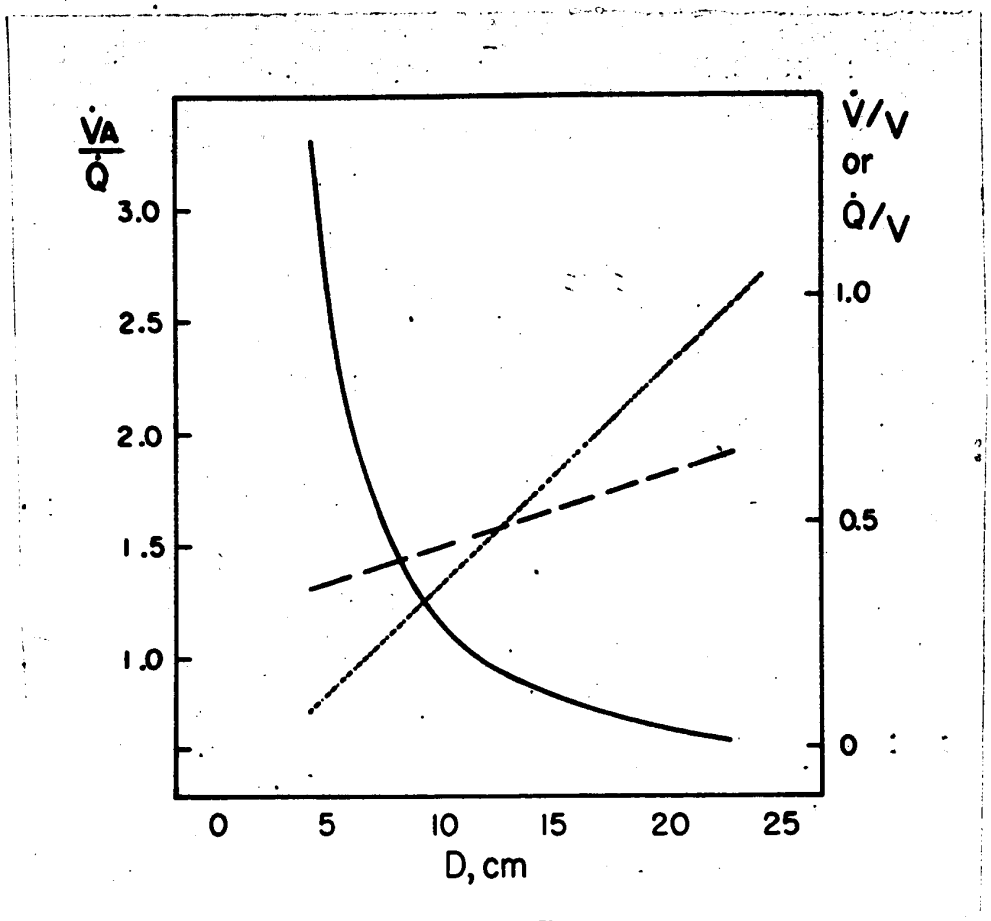


Fig. 13. Regional lung function in erect normals as measured with $O^{15}O_2$. Ordinates: $\dot{V}_A/\dot{Q}$ (solid line), ventilation per unit volume (dashed line), and perfusion per unit volume (dotted line). Abscissa: distance from lung apex (0 cm) to lung base (25 cm).

virtually all the D_{CO_2}, the D_{N_2} and the D_{O_2} (exclusive of that thought to be due to venoarterial shunting) which had been previously measured in erect normal subjects.

It would be difficult to over-estimate the importance of this work; these papers are classics and will remain so. They gave the first clear, indisputable evidence of the distribution and magnitude of real (as opposed to compartmental) variations of gas exchange function in the normal lung. Further, they emphasized gravity as one of the most important determinants of this variation. This cleared the way for later studies of the mechanisms which produced these variations. Nevertheless, this approach had some drawbacks, the most obvious being that because of its short half life use of $C^{15}O_2$ was difficult and expensive. Since the isotope was inhaled, detection of regions with low ventilation and relatively high blood flow was difficult. The volume assumption necessary to the computation of regional $\dot{V}_A/\dot{Q}$ could not always be made with precision. Finally, the method was unsuited for quantitative study of most patients with lung disease, both because of the difficulty in detecting regions with low $\dot{V}_A/\dot{Q}$, and because of the single-breath maneuver involved. Most patients with chronic lung disease exhibit grossly uneven distribution of ventilation throughout the lung. This is probably because the mechanical characteristics of various parts of the lung are grossly different so that they respond differently to the same change in (pleural) pressure around them. It has been shown in mechanical and electrical lung analogs that the distribution of ventilation among terminal units depends on their relative resistance (cm H_2O/L/sec) and compliance (L/cm H_2O) of the units[54]. More specifically, ventilation distribution depends on the product of resistance and compliance, or time constant, of each unit. When time constants vary greatly from unit to unit, ventilation distribution is uneven.

Further, under these circumstances, the distribution of ventilation becomes dependent on the frequency of breathing or the inspiratory flow rate. Therefore, when a patient with chronic lung disease is studied using single breath techniques, the experimenter runs the risk of examining a breath and a ventilation distribution which are in no way typical of the patient's usual performance. Precise control of inspiratory flow rate during single breath maneuvers is most difficult.

Very soon after experiments using $C^{15}O_2$, similar results were reported which were derived using another radiactive gas, ^{133}Xe(55). This isotope was pile produced and has a half life of 5.3 days so that it was relatively cheap and easily transported. It emitted gamma rays of two energies, one of approximately 30 KEV (kilo electron volts) and one of 80 KEV. Though these were relatively low-energy radiations they could easily be monitored by externally placed scintillation counters. Because coincidence counting could not be used, spatial resolution was achieved by collimation -- by limiting the possible angles of incidence of gamma rays on the detector. ^{133}Xe is relatively insoluble so that when inhaled, relatively little was taken up by the blood. In 1956, Knipping(49) had recognized the potential usefulness of ^{133}Xe for tagging ventilation and this group has since used isotope extensively as a diagnostic tool. However, the use of ^{133}Xe as a physiologic tool was introduced by a Montreal group(60) who made two very significant additions to Knipping's approach. First, they developed a technique for determining regional ^{133}Xe concentration and second, they used the isotope to measure regional perfusion distribution.

The crucial step in the use of ^{133}Xe was the conversion of the raw data which were regional count rates, into regional concentrations. A measured

regional count rate (U) is a representation of the amount of isotope in a lung region. The amount of isotope is equal to its concentration (F_A) multiplied by the region's volume. An additional factor (λ) is needed to account for radiation absorption and the geometry of the region. Thus:

$$U = F_A \; V \lambda \qquad \text{II-18}$$

The Montreal group reasoned that since ^{133}Xe was not very water soluble, a subject could rebreathe ^{133}Xe from a closed circuit until equilibrium was reached. In other words if a subject rebreathed ^{133}Xe from a constant volume spirometer ^{133}Xe concentrations in the spirometer would fall and ^{133}Xe concentrations in the lungs would rise, and, if no isotope were taken up by the blood, concentrations in the spirometer and all lung regions would eventually be equal and unchanging. Spirometer concentration (in mc/L) could be measured easily so, after equilibration, equation II-18 was rewritten:

$$U_\varepsilon = F_I \; V_\varepsilon \lambda_\varepsilon \qquad \text{II-19}$$

This is the same expression as eq. II-18 except that the subscript ε denotes that the measurements were made after equilibration.

If then a subject were to take a single breath of gas containing ^{133}Xe, and regional count rates were measured after the breath, eq. 1 applied to these count rates. If the subject were then equilibrated and regional count rates again measured equation 2 applied. If the two sets of count rates were measured at the same overall lung volume, then $V = V_\varepsilon$ and $\lambda = \lambda_\varepsilon$. Then, combining equations II-18 and II-19:

$$\frac{U}{U_\varepsilon} \; F_I = F_A \qquad \text{II-20}$$

The regional concentrations of ^{133}Xe resulting from the initial single breath of the isotope were thus known.

The measurement of perfusion distribution was accomplished by intravenous injection of boli of ^{133}Xe dissolved in saline. It was possible to dissolve several mc of the isotope in 5 - 10 cc of saline with ease, but when the injected material arrived in the pulmonary capillaries, the solubility of ^{133}Xe dictated that 90-95% of the isotope passed into the alveolar gas where its concentration could be measured by regional counters. This concentration was shown to represent regional blood flow per unit regional lung gas volume ($\dot{Q}/V$).

^{133}Xe injections, when combined with data from rebreathing, allowed mapping of the regional distribution of $\dot{Q}/V$. Since regional concentrations of ^{133}Xe after a single breath of the isotope were related to ventilation per unit volume, combining these maneuvers permitted calculation of regional $\dot{V}_A/\dot{Q}$. Early work with ^{133}Xe confirmed that of the Hammersmith group in that perfusion was found to increase sharply from apex to base, with ventilation showing a less striking increase, and $\dot{V}_A/\dot{Q}$ decreasing progressively from apex to base[55]. The only discrepancy between the two sets of results was that ^{133}Xe studies showed slightly lower apical $\dot{V}_A/\dot{Q}$ than did those using $C^{15}O_2$. This was due to higher values for apical $\dot{Q}/V$ as measured with ^{133}Xe. Representative results of ^{133}Xe studies are shown in Fig. 14. Subsequent variations in method[56] resulted in similar data. The Montreal group showed that the distributions of both ventilation and perfusion became somewhat more even with exercise and that apex-to-base differences in regional ventilation and perfusion disappeared when the subject lay supine[57].

Because of the ease with which ^{133}Xe may be obtained and used, the approach outlined above (or a lineal descendant of it) has been used with increasing frequency in the study of normal and diseased lungs. Naturally, objections to these

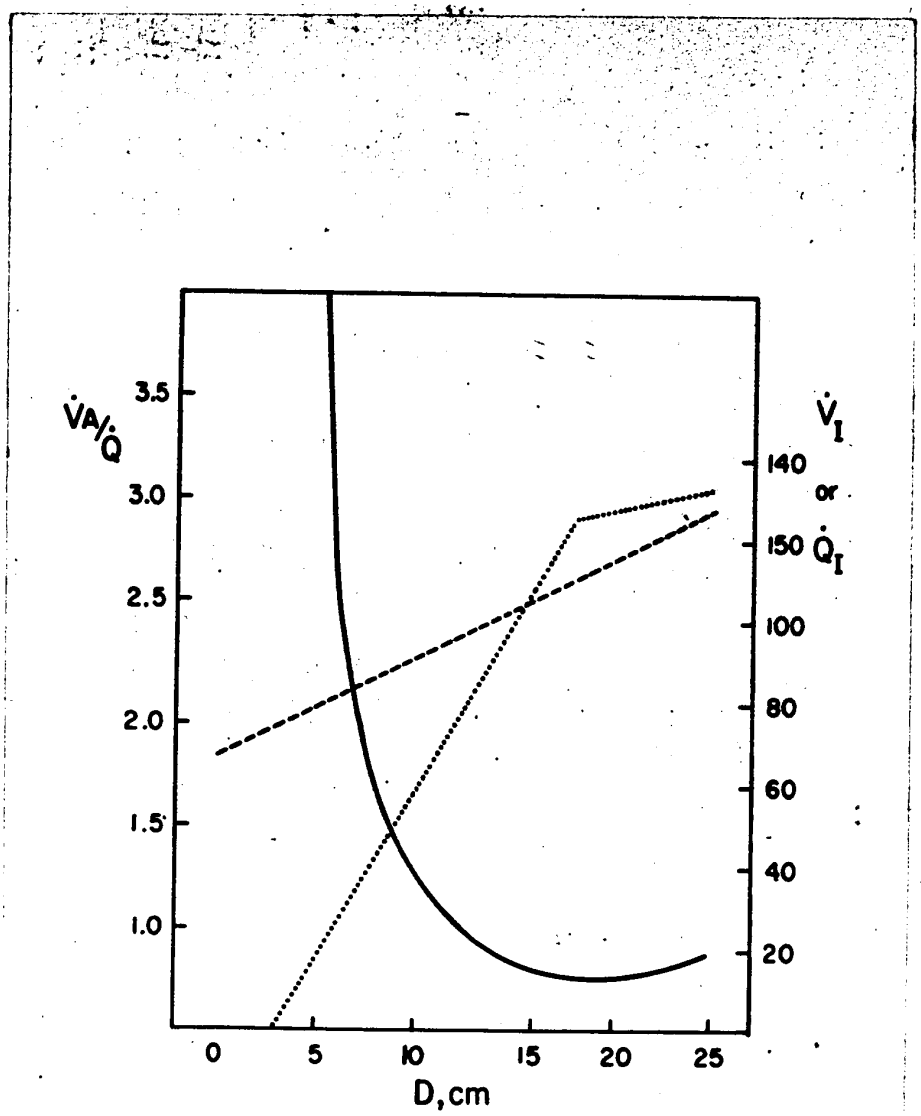


Fig. 14. Regional lung function in erect normals as assessed with ^{133}Xe. Ordinates: $\dot{V}_A/\dot{Q}$ (solid line), ventilation per unit volume ($\dot{V}_I$, dashed line), and perfusion per unit volume ($\dot{Q}_I$, dotted line). Abscissa: distance from lung apex (0 cm) to lung base (25 cm).

experiments may be cited, foremost among them being that ventilation and, therefore, $\dot{V}_A/\dot{Q}$ were measured during a single breath maneuver, and the argument applied to single breath measurements with $C^{15}O_2$ applied with equal force here. Other equally serious limitations of this method could be cited here but will be dealt with as they arise in the presentation of the methods used in the experiments described in this thesis.

To summarize, all methods of study of regional lung function discussed above have been rewarding and all present difficulties. Bronchospirometry, while yielding exact, absolute results of clinical significance as regards possible surgical therapy is by its nature limited to the study of lobes or lungs; further geometric definition is impossible and the method is difficult both for subject and investigator. Radio-isotopic studies of regional lung function were simpler and offered greater geometric resolution. However, results were relative rather than absolute. Regional $\dot{V}_A/\dot{Q}$ were derived from separate measurements of ventilation and perfusion distribution and depended on single breath measurements. While these approaches were probably valid in normal individuals their accuracy could be questioned in diseased lungs. The following section will describe methods for approaching regional lung function which theoretically offer greater quantitative accuracy, particularly in diseased lungs.

III. A NEW APPROACH TO THE STUDY OF REGIONAL GAS EXCHANGE

1. THEORY

In this section, the theoretical background of our measurements of regional lung function are presented. Assumptions inherent in these arguments are noted and their importance assessed. In some instances, corrections for violations of the assumptions are noted. Further consideration of specific sources of error will appear in other, more appropriate sections of this thesis.

a. Measurement of Regional $\dot{V}_A/\dot{Q}$

If a dissolved gas such as ^{133}Xe is infused intravenously at a constant rate, at some point in time exchange of the gas in all lung regions will attain steady state conditions. That is to say, the amount of ^{133}Xe entering the lung region via the mixed venous blood will equal the amount of ^{133}Xe leaving the region via the airway and the arterial (pulmonary venous) blood:

$$\dot{Q}\, C_{\bar{v}} = \dot{V}_A\, F_{A_p} + F_{A_p} \alpha\, \dot{Q} \qquad \text{III-1}$$

where $\dot{Q}$ is regional blood flow, $\dot{V}_A$ is regional ventilation, F_{A_p} is regional ^{133}Xe concentration during ^{133}Xe infusion, $C_{\bar{v}}$ is mixed venous ^{133}Xe concentration and α is the solubility coefficient for ^{133}Xe (58).

Rearranged:

$$F_{A_p} = \frac{C_{\bar{v}}}{\dot{V}_A/\dot{Q} + \alpha} \qquad \text{III-2}$$

Obviously, if F_{A_p} and $C_{\bar{v}}$ (which is the same for all lung regions) could be measured, regional $\dot{V}_A/\dot{Q}$ could be determined under steady state conditions.

Unfortunately, external scintillation counters measure regional count rate, not regional concentration, and the conversion of count rate to concentration requires an additional procedure.

If a subject inhales gas containing a fixed concentration of ^{133}Xe, regional count rates, and, therefore, regional concentrations, will eventually become constant in relation to time. Under these circumstances, regional ^{133}Xe exchange again may be described in steady state terms:

$$F_I \dot{V}_A = F_{A_i} \dot{V}_A + F_{A_i} \alpha \dot{Q} \qquad \text{III-3}$$

where F_I is inspired ^{133}Xe concentration, F_{A_i} is regional ^{133}Xe concentration, $\dot{V}_A$ is regional ventilation, $\dot{Q}$ is regional perfusion and α is the solubility coefficient for ^{133}Xe.

Rearranged:

$$F_{A_i} = \frac{F_I \dot{V}_A/\dot{Q}}{\dot{V}_A/\dot{Q} + \alpha} \qquad \text{III-4}$$

Regional concentration (F_A) is related to regional count rate (U) by a proportionality constant including regional volume (V) and a factor (λ) including geometrical considerations and radiation absorption[55]:

$$U = F_A V \lambda \qquad \text{III-5}$$

Regional count rate may be measured twice, once during ^{133}Xe infusion (U_p) and once during ^{133}Xe inhalation (U_i). If the measurements are made at the same lung volume, V and λ are the same in each instance and:

$$U_p/U_i = F_{A_p}/F_{A_i} \qquad \text{III-6}$$

If equations III-2 and III-4 are substituted into equation III-6 and the whole solved for $\dot{V}_A/\dot{Q}$:

$$\dot{V}_A/\dot{Q} = \frac{C_{\bar{v}} U_i}{F_I U_p} \qquad \text{III-7}$$

Since all quantities on the right of eq. III-7 are measurable, regional $\dot{V}_A/\dot{Q}$ under normal steady state conditions may theoretically be calculated.

Application of the method suggested by the above argument rests on a number of assumptions and approximations which, for the sake of simplicity, are listed below and considered in detail in subsequent paragraphs.

1) Regional inspired ventilation was assumed equal to regional expired ventilation (eq. III-3).

2) Gaseous equilibrium between alveolar gas and capillary blood was assumed.

3) The effect of ^{133}Xe reinspired from the dead space was neglected.

4) It was assumed that none of the ^{133}Xe leaving the lungs in the pulmonary venous blood recirculated to the lung from the periphery.

5) It was assumed that regional steady states could be attained by ^{133}Xe infusion and inhalation within reasonable time and dose limits.

6) In addition, it has been found impractical to conduct experiments involving open circuit (constant F_I) ^{133}Xe inhalation. A ^{133}Xe rebreathing procedure has been substituted.

Inspired ventilation ($\dot{V}_I$) is equal to expired ventilation only when O_2 uptake ($\dot{V}_{O_2}$) equals CO_2 output ($\dot{V}_{CO_2}$): when R = 1. When $R < 1$, $\dot{V}_A < \dot{V}_I$ and as R becomes smaller this difference becomes larger since $\dot{V}_{CO_2}$ becomes smaller in relation to $\dot{V}_{O_2}$. This effect best may be examined in terms of N_2:

$$\dot{V}_I P_{I_{N_2}} = \dot{V}_A P_{A_{N_2}} \qquad \text{III-8}$$

where $P_{I_{N_2}}$ is inspired N_2 tension and $P_{A_{N_2}}$ is expired N_2 tension. It can be seen from the $N_2 - CO_2$ diagram (Fig. 3) that there can be a maximum difference between $P_{I_{N_2}}$ (room air) and $P_{A_{N_2}}$ ($\dot{V}_A/\dot{Q} = 0$) of about 100 mmHg or 15%. This is a gross over estimate of what is in fact likely; in all but the most extreme cases, thus assuming $\dot{V}_I = \dot{V}_A$, does not introduce an error of more than 10%. It should be noted that eq. III-7 can be converted to:

$$\dot{V}_I/\dot{Q} = \frac{C_{\bar{v}} U_i}{F_I U_p} \qquad \text{III-9}$$

in which no assumption is made in regard to equality between $\dot{V}_I$ and $\dot{V}_A$. However, $\dot{V}_I/\dot{Q}$ is an unfamiliar term and since $\dot{V}_A$ is usually very close to $\dot{V}_I$ we have not made this modification.

The assumption of ^{133}Xe equilibrium between alveolar gas and arterial blood is almost certainly valid. Because of its solubility, the pulmonary diffusing capacity for ^{133}Xe is higher than that for CO and O_2[59]. This, coupled with the very small volumes of the gas which are transferred, makes it most unlikely that an alveolo-capillary gradient could exist, even in the presence of disease[2].

During both ^{133}Xe inhalation and infusion, at the end of each expiration respiratory dead space gas contains ^{133}Xe which is subsequently reinspired. This was not considered above, and to deal with this problem quantitatively it is necessary to know the volume, ^{133}Xe concentration and distribution of dead space gas. In normal subjects it is possible to estimate these quantities and this problem will be dealt with in detail when results from normal subjects are introduced. Unfortunately, the same approach is impossible in

most abnormal lungs, and quantitation of the effect of reinspired dead space gas is neglected. As will be shown, such neglect causes underestimation of regional differences in $\dot{V}_A/\dot{Q}$.

Since ^{133}Xe does leave the lungs via the pulmonary venous blood, it is likely that some of this isotope returns to the lungs from the periphery during ^{133}Xe infusion and rebreathing. If the amount of this recirculating isotope is constant or nearly so, eq. III-1 and eq. III-3 may be modified:

$$\dot{Q}\, C_{\bar{v}_p} + \dot{Q}\, C_{\bar{v}} = F_{A_p}\, \dot{V}_A + F_{A_p} \alpha\, \dot{Q} \qquad \text{III-10}$$

and

$$\dot{Q}\, C_{\bar{v}_i} + F_I\, \dot{V}_A = F_{A_i}\, \dot{V}_A + F_{A_i} \alpha\, \dot{Q} \qquad \text{III-11}$$

where $C_{\bar{v}_p}$ is the mixed venous concentration of recirculating isotope during ^{133}Xe infusion and $C_{\bar{v}_i}$ is the mixed venous concentration of recirculating isotope during ^{133}Xe inhalation.

Regional $\dot{V}_A/\dot{Q}$ then becomes:

$$\dot{V}_A/\dot{Q} = \frac{C_{\bar{v}}\, F_{A_i} + C_{\bar{v}_p}\, F_{A_i} - C_{\bar{v}_i}\, F_{A_p}}{F_I\, F_{A_p}} \qquad \text{III-12}$$

In theory recirculating mixed venous ^{133}Xe concentrations ($C_{\bar{v}_p}$, $C_{\bar{v}_i}$) are related to arterial (pulmonary venous) ^{133}Xe concentrations ($F_{A_p}\alpha$, $F_{A_i}\alpha$) by a transfer function (f) representing the peripheral uptake and release of isotope. This transfer function is independent of whether the arterial ^{133}Xe originated from inhalation or infusion. Thus, $C_{\bar{v}_p} = f\, F_{A_p}\alpha$ and $C_{\bar{v}_i} = f\, F_{A_i}\alpha$. If these expressions are substituted into eq. III-12, it will be seen that the recirculation terms cancel each other and it reverts to eq. III-7.

This intoxicating exercise is not representative of the whole truth, however. Since regional $\dot{V}_A/\dot{Q}$ vary, mixed arterial and recirculating mixed venous concentrations will be related to overall mean alveolar ^{133}Xe concentrations, and these will not necessarily be the same as the concentration in any one region (F_{A_p}, F_{A_i}) shown in eq. III-12. Thus, it can be said that while the effects of recirculation during ^{133}Xe infusion and inhalation tend to cancel each other out, this process is not necessarily complete. Specific information in regard to the problem of recirculation is needed.

Peripheral ^{133}Xe uptake was studied in our laboratory (60). Three patients with mitral stenosis who were undergoing left heart catheterization had ^{133}Xe infused into the aortic root. Brachial artery blood and pulmonary artery (mixed venous) blood were sampled continuously. After 5 min. of infusion, mixed venous ^{133}Xe concentration was 30 - 50% of the arterial level and after 10 min., the mixed venous level was 50 - 70% of the arterial. In each instance the mixed venous concentration was increasing less than 10% per minute. There is no reason to believe that normal subjects or patients with lung disease would differ from these patients with mitral stenosis. However, when ^{133}Xe is inhaled or infused intravenously, arterial concentrations do not rise to steady state levels as fast as was the case with aortic infusion. Therefore, after 5 min. of ^{133}Xe inhalation or I.V. infusion, recirculating ^{133}Xe concentrations are probably nearer 30% than 50% of arterial concentrations; similarly after 10 min. of ^{133}Xe inhalation or I.V. infusion recirculating mixed venous concentrations are probably about 50% of the arterial levels.

If it is assumed that recirculating ^{133}Xe concentrations are a constant fraction of arterial ^{133}Xe concentrations, the significance of recirculation

as regards measurement of regional $\dot{V}_A/\dot{Q}$ then depends on arterial Xe concentrations. As implied by equations III-1 and III-3, alveolar and arterial levels depend on $\dot{V}_A/\dot{Q}$. These equations are plotted in Fig. 15, where alveolar concentrations are expressed as a fraction of the appropriate input concentration. It can be seen that F_{A_p}, and therefore, C_{a_p}, is much more sensitive to $\dot{V}_A/\dot{Q}$ than is F_{A_i} or C_{a_i}. Between $\dot{V}_A/\dot{Q}$ of 0.1 and 1.0, C_{a_p} undergoes a five-fold change while C_{a_i} undergoes a two-fold change. Because C_{a_p} increases so profoundly as $\dot{V}_A/\dot{Q}$ decreases, blood leaving low $\dot{V}_A/\dot{Q}$ regions may attain very significant concentrations during infusion. For example, in a region with $\dot{V}_A/\dot{Q} = 0.2$, C_{a_p} is 40% of $C_{\bar{v}}$ (Fig. 15) and after 10 min. recirculating ^{133}Xe concentrations may well be 20% of the concentration attained by the primary infusion.

In subjects with low $\dot{V}_A/\dot{Q}$ regions, then, it is clear that neglect of recirculating isotope may introduce significant error. We have dealt with this by measuring arterial ^{133}Xe concentrations during infusion and rebreathing, and assumed that recirculating ^{133}Xe concentrations were 50% of the arterial values. By appropriate substitution into eq. III-12:

$$\dot{V}_A/\dot{Q} = \frac{C_{\bar{v}} U_i + 0.5 (C_{a_p} U_i - C_{a_i} U_p)}{F_I U_p} \qquad \text{III-13}$$

Failure to introduce this correction for recirculation results in underestimation of regional differences of $\dot{V}_A/\dot{Q}$, in particular by overestimating $\dot{V}_A/\dot{Q}$ in regions where this ratio is very low.

If there were no time limit on ^{133}Xe infusion and inhalation, steady states would necessarily develop in all lung regions. In practice, however, 10 minute periods of infusion and inhalation of ^{133}Xe in concentrations

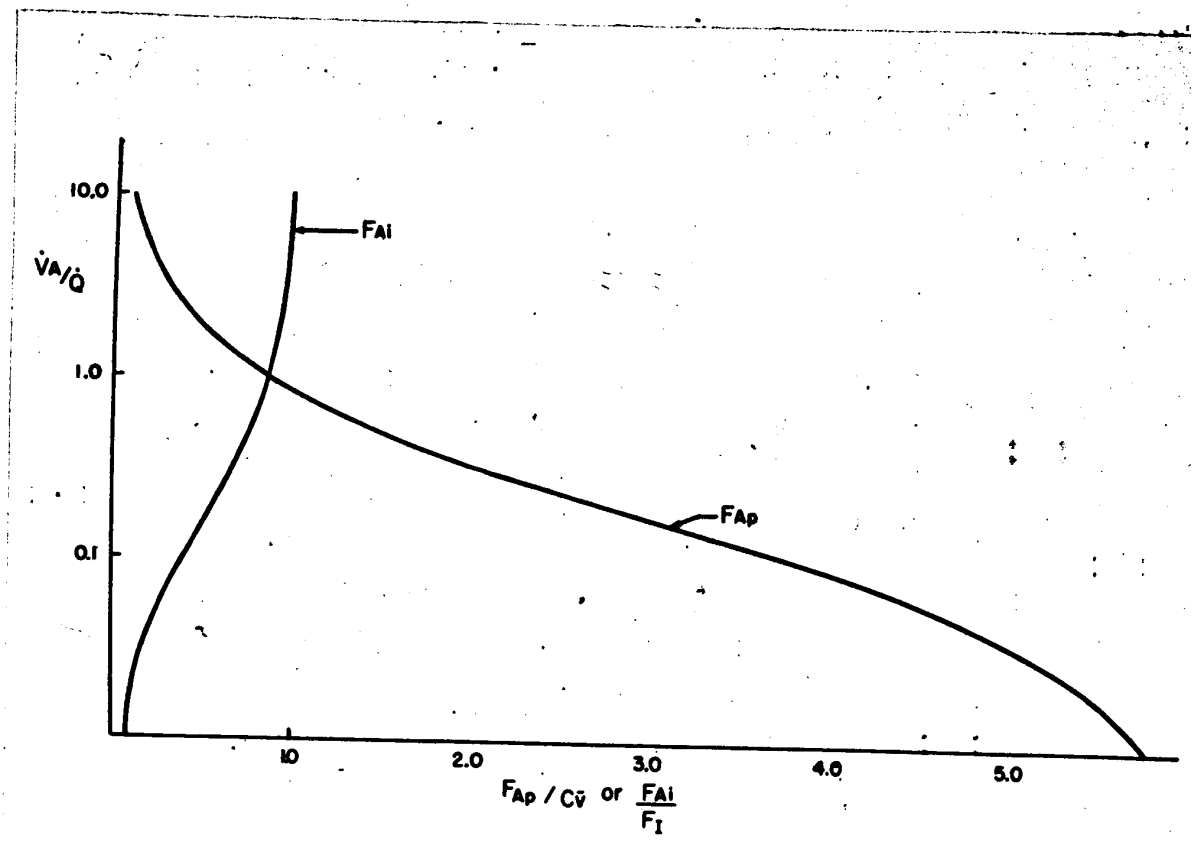


Fig. 15. Regional ^{133}Xe concentrations as a function of $\dot{V}_A/\dot{Q}$. Regional concentrations during infusion (F_{Ap}) and during inhalation (F_{Ai}) are plotted on the abscissa, each being expressed as a fraction of its respective input. Regional $\dot{V}_A/\dot{Q}$ is plotted logarhythmically on the ordinate.

appropriate to external counting results in a combined radiation dose to the lungs of about 300 m rads. While this dose is by no means prohibitive, we would not feel justified in increasing it by prolonging the time of ^{133}Xe exposure. Indeed, 5 minute time periods for infusion and inhalation would be preferable. It is, therefore, important to examine the likelihood of steady state conditions existing after such time periods. This may be done by assuming that each region (or unit) is homogeneous and well mixed. Under these circumstances, non-steady state equations may be written for ^{133}Xe exchange during infusion:

$$F_{A_p}(t)\,V = \dot{Q}\,C_{\bar{v}} - \dot{V}_A \int_0^t F_{A_p} + \dot{Q}\alpha \int_0^t F_{A_p} \qquad \text{III-14}$$

and inhalation:

$$F_{A_i}(t)\,V = F_I \dot{V}_A - \dot{V}_A \int_0^t F_{A_i} + \dot{Q}\alpha \int_0^t F_{A_i} \qquad \text{III-15}$$

where $F_{A_i}(t)$ and $F_{A_p}(t)$ represent regional ^{133}Xe concentrations at time t, during inhalation and infusion, respectively, and where V is regional volume.

These equations may be differentiated and solved:

$$F_{A_p}(t) = F_{A_p}(\infty)\left[1 - e^{-(\dot{V}_A/V + \dot{Q}\alpha/V)t}\right] \qquad \text{III-16}$$

$$F_{A_i}(t) = F_{A_i}(\infty)\left[1 - e^{-(\dot{V}_A/V + \dot{Q}\alpha/V)t}\right] \qquad \text{III-17}$$

where $F_{A_p}(\infty)$ and $F_{A_i}(\infty)$ are regional ^{133}Xe concentrations when t is infinity, or when the steady state is reached.

Attainment of steady state conditions within a given time limit are dependent, then, on the $\dot{V}_A/V$ and the $\dot{Q}\alpha/V$ of the region considered. If these values are low the time necessary to reach steady state will be prolonged. Quantitative use may be made of the above relationships by choosing

appropriate $\dot{V}_A/\dot{Q}$ (and, therefore, steady state concentrations) and finding combinations of $\dot{V}_A/V$ and $\dot{Q}\alpha/V$ which permit attainment of approximately steady state conditions within a fixed time. For a variety of $\dot{V}_A/\dot{Q}$, values of $\dot{V}_A/V$ and $\dot{Q}\alpha/V$ were found which were compatible with $F_A(t)$ being equal to 90% of final steady state concentrations. These values of $\dot{V}_A/V$ and $\dot{Q}\alpha/V$ then were the lowest values compatible with 90% approximation of the steady state within the stated time limit. A series of such values for $\dot{V}_A/V$ and $\dot{Q}\alpha/V$ which apply equally well for inhalation and infusion, are shown in Table 2. Two time periods (5min. and 10 min.) have been used. Values for the shorter time period are compared to those derived by West[53] from study of normal subjects. Because the theoretical minima are less than those measured by West, it may be predicted that steady states regarding regional ^{133}Xe exchange are readily obtainable with 5 min. periods of inhalation and infusion. Figures for minimal $\dot{V}_A/V$ and $\dot{Q}\alpha/V$ when the time periods involved are 10 min. show that such an increase in exposure may represent a useful extension of the method.

The above analysis must, of course, be regarded only as a useful guideline since it did not consider recirculating isotope, or dead space rebreathing and since it assumed that regions were homogeneous and well mixed. While more sophisticated theoretical analysis is possible, it would still be open to serious question. The question of the presence or absence of steady state conditions can best be settled by examining data; if regional count rates are substantially constant in relation to time a steady state may be established; if not, the steady state cannot be present.

Maintaining F_I constant during ^{133}Xe inhalation demands either complicated instrumentation or a large supply of air containing trace amounts of

TABLE 2. THEORETICAL MINIMA FOR ATTAINMENT OF THE STEADY STATE WITH 5 AND 10 MIN INFUSIONS OF ^{133}Xe.

$\dot{V}_A/\dot{Q}$	Minima for steady state		Normal values	
	$\dot{V}_A/V$	$\dot{Q}/V$	$\dot{V}_A/V$	$\dot{Q}/V$
	(t=5 min)			
3.0	0.45	0.15	1.00	0.33
1.0	0.40	0.40	1.67	1.67
0.5	0.35	0.70	2.00	4.00
	(t=10 min)			
3.0	0.23	0.08		
1.0	0.20	0.20		
0.5	0.18	0.35		
0.1	0.09	0.88		

the isotope. We have found neither of these alternatives to be practical and, hence, have used a closed circuit, or rebreathing technique of Xe inhalation. When a subject rebreathes ^{133}Xe from a constant volume spirometer circuit, spirometer ^{133}Xe concentration decreases, at first rapidly, then slowly and finally appears to become constant. The initial decrease in concentration, which takes 1 - 2 minutes in normals and rarely more than 8 - 9 minutes in abnormals, is, of course, due to mixing of the isotope with lung gas. After this process is complete, both regional and spirometer count rates appear constant; two descriptions of this situation have been proposed. The first is that the subject, or at least his lungs, are equilibrated; concentrations throughout the patient's lungs equal the concentration in the circuit. The second hypothesis is that pulmonary Xe uptake continues up in the pulmonary capillaries, but that the amount of this uptake is small in relation to the amount of ^{133}Xe in the spirometer so the spirometer concentration appears constant. We may examine these hypotheses by comparing them graphically. Fig. 16 plots $\dot{V}_A/\dot{Q}$ against regional Xe concentrations (F_{A_i}) expressed as a fraction of inspired concentration (F_I). If equilibration were present $F_{A_i}/F_I = 1.0$ whatever the $\dot{V}_A/\dot{Q}$. If regional steady states were present, however, F_{A_i} must be considerably less than F_I at low $\dot{V}_A/\dot{Q}$. Further, if steady states were present in regions with low $\dot{V}_A/\dot{Q}$, the relatively low F_{A_i} in such regions would limit uptake of isotope from the spirometer, tending to keep spirometer concentrations constant. If it is assumed, then, that constant regional count rates during rebreathing should be interpreted in terms of equilibration, serious errors may be made in regions with low $\dot{V}_A/\dot{Q}$ [61]. In regions with high $\dot{V}_A/\dot{Q}$ it would appear that equilibration

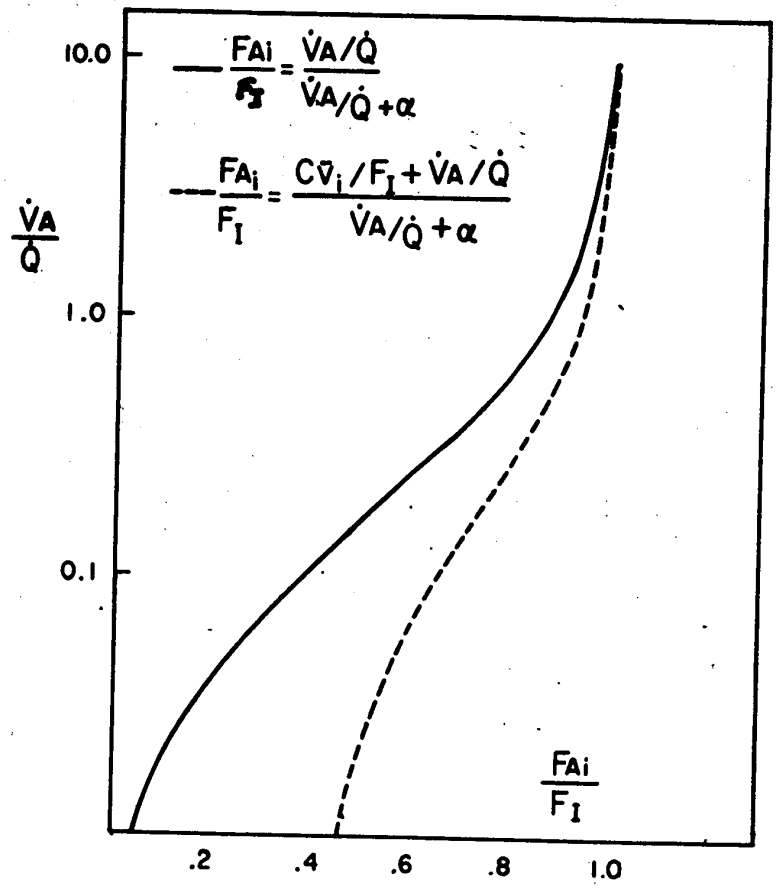


Fig. 16. Regional ^{133}Xe concentrations during steady state ^{133}Xe inhalation. Ordinate: regional $\dot{V}_A/\dot{Q}$ plotted logarhythmically. Abscissa; regional ^{133}Xe concentration, expressed as a fraction of the inspired concentration. The solid line represents the situation when no allowance is made for recirculating ^{133}Xe, while the dotted line indicates the effect of recirculating isotope (see text).

may be assumed with little error. Fig. 16 cannot be interpreted literally, however. It was plotted assuming that inspired equalled expired ventilation and that there was no recirculating isotope. An example of the effect of recirculation has also been plotted in Fig. 16. In the construction of this curve, it was assumed that the mixed arterial ^{133}Xe level reflected a $\dot{V}_A/\dot{Q}$ of 1.0 and that the recirculating concentration was 50% of this arterial level. This represents a generous amount of recirculation. A lower arterial level might have been more realistic, but the basic result remains: at $\dot{V}_A/\dot{Q} = 0.5$ the assumption of equilibration may be in error by about 15%. Correcting the plot for the fact that $\dot{V}_A < \dot{V}_T$, particularly at low $\dot{V}_A/\dot{Q}$, would have an effect similar to, but smaller than, that of recirculation.

It may be concluded, then, that when regional $\dot{V}_A/\dot{Q} < 0.80$, it makes little difference whether ^{133}Xe rebreathing is interpreted as leading to the steady state or to equilibrium. When $\dot{V}_A/\dot{Q}$ are low (< 0.60), however, the assumption of equilibrium conditions may be associated with significant error. In this case, interpretation of constant regional count rates during rebreathing in terms of the steady state is probably more accurate, particularly if corrections for recirculation are made.

To summarize, a method has been proposed for the measurement of regional $\dot{V}_A/\dot{Q}$ in the steady state. The general approach is not new but relies on the well-known fact that in the steady state pulmonary gas concentrations are dependent on $\dot{V}_A/\dot{Q}$. If a steady state regarding pulmonary ^{133}Xe exchange is induced, measurement of regional ^{133}Xe concentrations allows calculation of regional $\dot{V}_A/\dot{Q}$. Such steady states may be produced either by infusing or inhaling ^{133}Xe and when both are done in sequence regional ^{133}Xe concentrations may be estimated. Steady state conditions appear attainable in normal

and diseased humans. The method as presented made a number of assumptions of varying validity. Though designed to measure $\dot{V}_A/\dot{Q}$ it, in fact, assesses $\dot{V}_I/\dot{Q}$; the difference between the two is in most instances negligible. The method as initially presented neglected the effect of ^{133}Xe reinspired from the respiratory dead space; though corrections can and will be made for this in the case of normal subjects this is not possible in most patients with disease. The method as initially presented neglected the effect of ^{133}Xe recirculating from the periphery; this may influence results in an important way when dealing with inhomogeneous systems containing units with low $\dot{V}_A/\dot{Q}$. Finally, closed circuit ^{133}Xe rebreathing was assessed; this procedure probably produces conditions close to those of the steady state and will be treated as such.

b. Independent Measurement of Regional Ventilation and Perfusion Distribution

The measurement of regional perfusion distribution using ^{133}Xe has been mentioned previously; the method introduced by Ball et al.[55] has been modified only slightly. When ^{133}Xe in solution is injected as a bolus, it is distributed to lung regions according to regional blood flow. The solubility of the isotope is such that virtually all of it enters alveolar gas on its first passage through the lung[55,59]. If the subject holds his breath during and after ^{133}Xe injection, regional count rates will rise to a plateau as the isotope evolves into the gas phase and plateau concentrations are representative of regional blood flow per unit regional gas volume ($\dot{Q}/\dot{V}$). Regional count rates are converted to regional concentrations by having the subject rebreathe ^{133}Xe. In the past, it was assumed that rebreathing produced equilibrium conditions throughout the lung and regional concentrations

computed accordingly. Because of the analysis of the rebreathing process presented above, we have also computed regional concentration assuming that regional steady states obtain at the end of rebreathing.

Both regional count rate and regional concentration obviously depend not only on regional $\dot{Q}/V$ but on the amount of isotope injected. To compare different injections, the results must be standardized according to dose. This has been done by expressing perfusion distribution in terms of "perfusion index" which is the regional concentration resulting from the injection (F_{A_B}) expressed as a percent of the regional concentration which would result from the injection if blood flow were even. The latter is, of course, simply the injected dose divided by the lung volume at which the injection is made. Since our subjects rebreathed ^{133}Xe at functional residual capacity, (FRC), injections were made at this lung volume.

In supine normal subjects, regional lung volumes are expanded to the same degree from apex to base[62] so that measurement of regional $\dot{Q}/V$ is the equivalent of measuring regional flow per alveolus or regional flow per unit lung tissue. In erect normals, however, apical alveoli are larger than those at the base at most overall lung volumes[63]. Thus, a given $\dot{Q}/V$ may represent quite different values of blood flow per alveolus, depending on the region involved and the overall lung volume. This difficulty is overcome by making measurements at total lung capacity (TLC) when all alveoli have substantially the same lung volume[63]. Thus, to measure perfusion per alveolus in an erect normal at FRC, the injection is made during breath-hold at FRC. When all the injectate has entered the alveolar gas, the subject inspires room air to TLC and again breath-holds while regional count rates are measured[56]. Resulting perfusion indices are then indices of perfusion per alveolus.

The above techniques have proven quite reliable in assessing regional perfusion distribution. Only two specific major sources of error exist, and both are related to the period of breath-hold required while injections are made and count rate recorded. If the injection is peripheral the breath-hold should be 10 - 15 sec; many patients find this difficult. If the patient breathes during or immediately after injection he exhales isotope, lowering perfusion indices in all regions but most strikingly in those regions which are well ventilated. The second source of error is that it is sometimes very difficult to control precisely the lung volume at which the injection takes place. If this volume is larger than FRC, all perfusion indices will be low; if the volume is smaller than FRC, all perfusion indices will be high. Unless, however, the deviations of lung volume from FRC are large, the relationships among regional perfusion indices in the same patient are not disturbed.

There are, in general, two methods of studying regional ventilation distribution using ^{133}Xe. The first is to measure regional concentrations after a single breath of the isotope. While this approach has been accurate and very rewarding in normal subjects, in many patients ventilation distribution varies with inspiratory flow rate so that it is most difficult to generalize on the basis of single breath measurements. A more attractive approach to such patients is to observe the rate of ^{133}Xe removal from lung regions after administration of the isotope has been stopped. Since ^{133}Xe is not very soluble the speed of washout should be related chiefly to regional ventilation per unit volume.

Washout of inert, highly insoluble gases such as N_2 and H_e has proven a most productive approach to the study of overall ventilation distribution; some of these analyses have been referred to earlier in this thesis. It is

a considerable temptation, then to apply the analytic approach of Briscoe[36] to regional washout curves; in this way subregional compartments with differing ventilation and volume might be identified and quantitated. If ^{133}Xe were analagous to N_2 and the region considered was homogeneous and well mixed, the following relationship would hold:

$$F_A(t)\,V = F_{A_0}\,V - \int_0^t F_A\,\dot{V}_A \qquad \text{III-18}$$

where F_{A_0} is regional concentration at the onset of washout, V is regional volume and $F_A(t)$ is regional concentration at time t. This expression may be differentiated and solved:

$$F_A(t) = F_{A_0}\,e^{-(\dot{V}_A/V)t} \qquad \text{III-19}$$

The same general approach may be applied to regions which consist of more than one compartment.

Unfortunately, ^{133}Xe is a great deal more soluble than N_2; the factors governing ^{133}Xe washout are, therefore, more complex than those relevant to N_2. In addition to regional ventilation, three factors, all dependent on ^{133}Xe solubility, may influence regional ^{133}Xe washout. First, since ^{133}Xe is soluble some isotope must leave the region via the pulmonary venous blood. Second, recirculating ^{133}Xe may enter the region during washout. Third, ^{133}Xe may be present in the chest wall at the onset of washout. When ^{133}Xe administration is stopped, isotope will wash out of the chest wall and separation of the washout curves of chest wall and lung may be difficult.

Removal of ^{133}Xe by pulmonary venous blood could theoretically be a very important factor in ^{133}Xe washout. This may be illustrated by modifying

eq. III-18 and eq. III-19 to include this factor:

$$F_A(t)V = F_{A_0}V - \dot{V}_A\int_0^t F_A - \dot{Q}\alpha\int_0^t F_A \qquad \text{III-20}$$

$$F_A(t) = F_{A_0}e^{-(\dot{V}_A/V + \dot{Q}\alpha/V)t} \qquad \text{III-21}$$

Since α = .162 when regional $\dot{V}_A/\dot{Q}$ = 0.162, one half the regional washout may be ascrived to regional blood flow, not ventilation.

Neglect of recirculating isotope is appropriate when washout measurements are made after a single breath or injection of ^{133}Xe. However, after such maneuvers the overall ventilation tends to vary, rendering interpretation of washout curves more difficult. For this reason, washout curves are best examined after procedures involving tidal breathing, such as ^{133}Xe infusion or rebreathing. After these procedures, however, there may be significant amounts of recirculating isotope entering the lung from the periphery. As washout proceeds the periphery also washes out and the recirculating levels decrease. This relationship may be summarized:

$$F_A(t) = F_{A_0}V - \dot{V}_A\int_0^t F_A - Q\alpha\int_0^t F_A + \dot{Q}\int_0^t C_{\bar{v}} \qquad \text{III-22}$$

where the term $\dot{Q}\int_0^t C_{\bar{v}}$ symbolizes the washout function of the periphery as monitored in the mixed venous blood. This washout function (rate of decrease of $C_{\bar{v}}$) is primarily related to peripheral perfusion per unit peripheral tissue volume, and is slower than and independent of lung washout(61). It can be seen from eq. III-22 that the net effect of circulatory ^{133}Xe exchange on regional washout depends on the relative magnitudes of circulatory ^{133}Xe

removal ($Q\alpha\int_0^t F_A$) and circulatory ^{133}Xe delivery ($\dot{Q}\int_0^t C_{\bar{v}}$). Dominance of the former tends to accelerate washout, dominance of the latter tends to retard washout. In the usual case, circulatory ^{133}Xe exchange probably accelerates early lung washout but delays late lung washout because peripheral ^{133}Xe washes out slowly.

It is impossible to count over the lung in intact humans without also counting over the chest wall. If the chest wall contains isotope, this isotope is measured along with that in the lungs. The general problem of radiation originating from the chest wall will be dealt with later; at the moment let is suffice to say that the amount of ^{133}Xe in the chest wall is usually small. However, if the chest wall released (washed out) its isotope slowly in relation to the washout of the underlying lung, at some time during washout chest wall radiation might amount to a significant fraction of the total radiation observed. Further, it might be impossible to discriminate between the decline in overall count rate due to chest wall washout as opposed to lung washout.

In spite of these difficulties several empirical assessments of regional washouts have shown that they may be of some use in assessing regional ventilation. Bryan,[57] using normal subjects, compared the results of single breath ventilation measurements and those of regional ^{133}Xe washin and washout. He found that agreement between single breath tests and washin measurements was good. Further, both of these tests gave results similar to those afforded by regional washout, if the early part of the washout curve were used. Bryan measured the time necessary for regional count rates to fall to one half their pre-washout value.

Recently, Matthews and Dollery[61] assessed regional ^{133}Xe washout in both normal subjects and patients with emphysema. They compared ^{133}Xe washout to that of $^{15}N_2$, a shortlived and very insoluble isotope. They also considered in detail the effect of ^{133}Xe solubility on regional washout. They measured mixed venous ^{133}Xe concentration during washout, finding that peripheral ^{133}Xe washout was, in fact, independent of pulmonary washout; the decay curve of the mixed venous ^{133}Xe concentration during washout did not vary from subject to subject. With this data, plus their regional $^{15}N_2$ washout curves, they were able to simulate regional ^{133}Xe washout curves on an analogue computer, using reasonable values for regional $\dot{Q}/V$. They concluded that in normal subjects, changing values for chest wall background were troublesome, tending to mimic a small poorly ventilated compartment within the region studied. In abnormal subjects radiation from the chest wall was less of a problem, but in these subjects peripheral washout into the lungs was thought very likely to prolong washout by distorting the later part of the curve. No comment was made regarding acceleration of washout due to removal of ^{133}Xe by the blood.

These studies do not invalidate use of regional washout curves as approximate tests of regional ventilation, particularly if only the early part of the washout curve is used. We have chosen to assess regional ventilation per unit volume in terms of regional half-times ($T\frac{1}{2}$). $T\frac{1}{2}$ is the time, in minutes, necessary for regional count rates to fall to one half their pre-washout values.

In summary, methods for the independent assessment of regional ventilation distribution and regional perfusion distribution have been outlined.

Neither is theoretically capable of measuring absolute ventilation or perfusion, but each may approximate either $\dot{V}_A/V$ or $\dot{Q}/V$. The regional distribution of $\dot{Q}/V$ is estimated from the results of bolus injections of ^{133}Xe; this approach is theoretically sound but susceptible to technical error. Regional washout curves are used to assess regional $\dot{V}_A/V$; this approach has distinct theoretical weaknesses which may, in part, be overcome by analyzing only the early portion of the washout curve. Figures for regional ventilation can only be regarded as semi-quantitative approximations.

2. SOURCES OF ERROR COMMON TO MORE THAN ONE TECHNIQUE OF REGIONAL MEASUREMENT

As implied by the above heading, there are several potential sources of error which may influence regional count rates, irrespective of the procedure involved in their measurement. These include: 1) changes in body position or lung volume, 2) count rates from vascular structures in or near the lung, 3) count rates scattered from region to region and 4) count rates originating from the chest wall. Each of these will now be considered. In addition, the problem of heterogeneity of function within single lung regions will be introduced.

All measurements of regional concentration are derived by taking the ratio of two regional count rates which were measured at different points in time. It is assumed that the same lung region was examined in each instance and that the geometry of the region was also the same. If overall lung volumes differed when regional count rates were measured than regional geometry also differed and subsequent calculation of regional concentration must be erroneous.

Measurements of regional $\dot{V}_A/\dot{Q}$ and $T\frac{1}{2}$ were conducted during normal tidal breathing at FRC after the subject had been acclimated to the equipment, so that changes in lung volume were unlikely. Perfusion distribution was measured at breath-hold, however, without precise control of lung volume. However, experience has shown that if counters are not located near the lung periphery, variations in volume of up to 500 cc. cause only minor changes in the apparent perfusion distribution.

Since the scintillation counters used in these studies were fixed, changes in body position could change the region observed by each counter and invalidate calculations of regional ^{133}Xe concentration. In erect normal subjects this is the most important factor, limiting reproducibility of results with ^{133}Xe. We noted the position of bony landmarks on the thorax of each subject and repeatedly checked their position relative to the counters during the course of the experiment. Abnormal subjects, in whom measurements frequently took more than an hour, were studied in the supine position, every effort being made to insure comfort.

Unfortunately, the thorax contains a number of important vascular structures as well as the lungs. During procedures involving the intravenous administration of ^{133}Xe it is conceivable that counters stationed over the lung would "see" intravascular ^{133}Xe. In the lung periphery important errors of this type are unlikely since peripheral pulmonary vascular volume is very small in relation to gas volume. Counters over the right heart are a more likely source of error, but we have found in normals[64] that posterior counters overlying the heart and pulmonary arteries give results which were similar to peripherally placed counters at the same vertical level of the lung. Nevertheless, except for these experiments, we have avoided such counter placement. Artefacts due intravascular ^{133}Xe definitely do arise if counters are placed at the extreme lung apex on the same side as the arm into which ^{133}Xe injections are made. This is because the subclavian vein crosses from axilla to mediastinum some 2 - 3 cm. below the lung apex. Since intravascular ^{133}Xe concentrations at this site are large and apical lung volumes are small, this represents a major problem. We have tried to circumvent this by subtracting visible (early) injection artefact by making

injections through centrally placed catheters when possible, and, most important, by not placing counters less than 5 cm. below the lung apex.

There are a number of ways by which the paths of gamma rays may be distorted so that a counter records events which occur outside its field of observation [65]. The relative importance of these depends on the energy of the gamma rays involved; because ^{133}Xe yields low energy gammas, Compton scatter accounts for almost all radiation scattered between regions. The importance of such scatter was studied in vitro: A stable ^{133}Xe source was positioned beside an excised lung and count rates measured both over the source and over the lung. These experiments showed that counters positioned over such a lung record about 5% of the radiation present in the source adjacent to the counter field [66]. This is not enough scatter to cause major problems. If, however, the lung was replaced by a container filled with water, scattered radiation often exceeded 10% of radiation recorded over the ^{133}Xe source. This has been confirmed by studies of patients after pneumonectomy (see below). Thus, measurements made near structures such as the mediastinum or diaphragm are likely to be influenced by scatter and such counter positions have been avoided as much as possible.

It has been pointed out previously that counters placed over the thorax of intact humans inevitably examine underlying chest wall as well as lung, and because ^{133}Xe is soluble, radiation may originate in both. Background radiation from the chest wall is not a problem during maneuvers such as single breaths or bolus injections of ^{133}Xe since accumulation in the chest wall is minor and delayed. However, during ^{133}Xe infusion or rebreathing ^{133}Xe accumulates in the chest wall to a greater extent and measurements of regional count rate should take account of this. We studied this problem by measuring count

rates from both thoraces of seven patients 2 weeks after pneumonectomy. At the time of study, there was no mediastinal shift and the operated side was filled with fluid. The patients underwent ^{133}Xe infusion, rebreathing and bolus injections of the isotope. Count rates from the pneumonectomized side at the end of ^{133}Xe rebreathing (W_i) and infusion (W_p) were contrasted to count rates after intrapulmonary washout was complete (W_o) as judged by counters over the contralateral intact lung. Fig. 17 shows the results of such comparison. It is apparent that W_i or W_p averaged 150% of W_o and frequently exceeded this figure. Fig. 17, however, represents an overestimate since it neglected the effect of radiation scattered into the water filled hemithorax from the intact lung. This is illustrated by Fig. 18 which shows records from one counter positioned over lung and another one positioned over the opposite pneumonectomized hemithorax. During rebreathing count rates increase over the operated side and after rebreathing stops count rates decrement. A bolus injection of ^{133}Xe was then given, count rates in both regions were seen to rise and the two records appeared to be in phase with each other. This increase in count rate on the operated side is too rapid in onset and too large to represent anything but scattered radiation. It followed that the response of counters over the operated side to bolus injections could be used to correct for scattered radiation. This was done: the increase in count rate due to bolus injection over the operated hemithorax (W_B) was measured and related to the simultaneous increase in count rate over the lung (U_B). The resulting fraction (W_B/U_B), when multiplied by U_p or U_i gave the scattered radiation present when W_p or W_i were measured at the end of rebreathing of infusion over the chest wall:

$$\frac{W_B}{U_B} \quad X \quad U_p \text{ or } U_i \quad = \quad S \qquad \text{III-23}$$

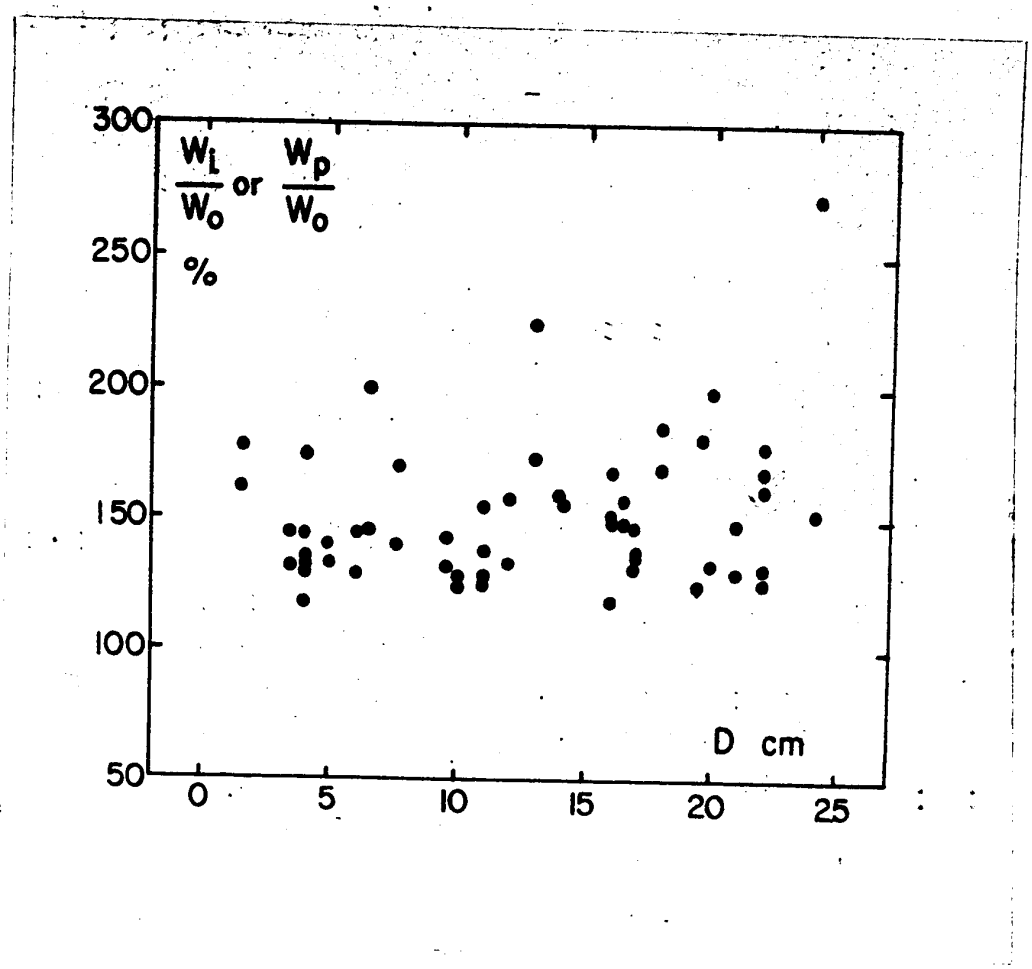


Fig. 17. Count rates recorded from the chest wall at the end of ^{133}Xe infusion and rebreathing. Ordinate: ratio of chest wall count rate at the end of rebreathing (W_i) or infusion (W_p) to the count rate observed after washout of intrapulmonary isotope (W_o). This ratio is expressed as a percentage. Abscissa: distance down the lung (top=0 cm).

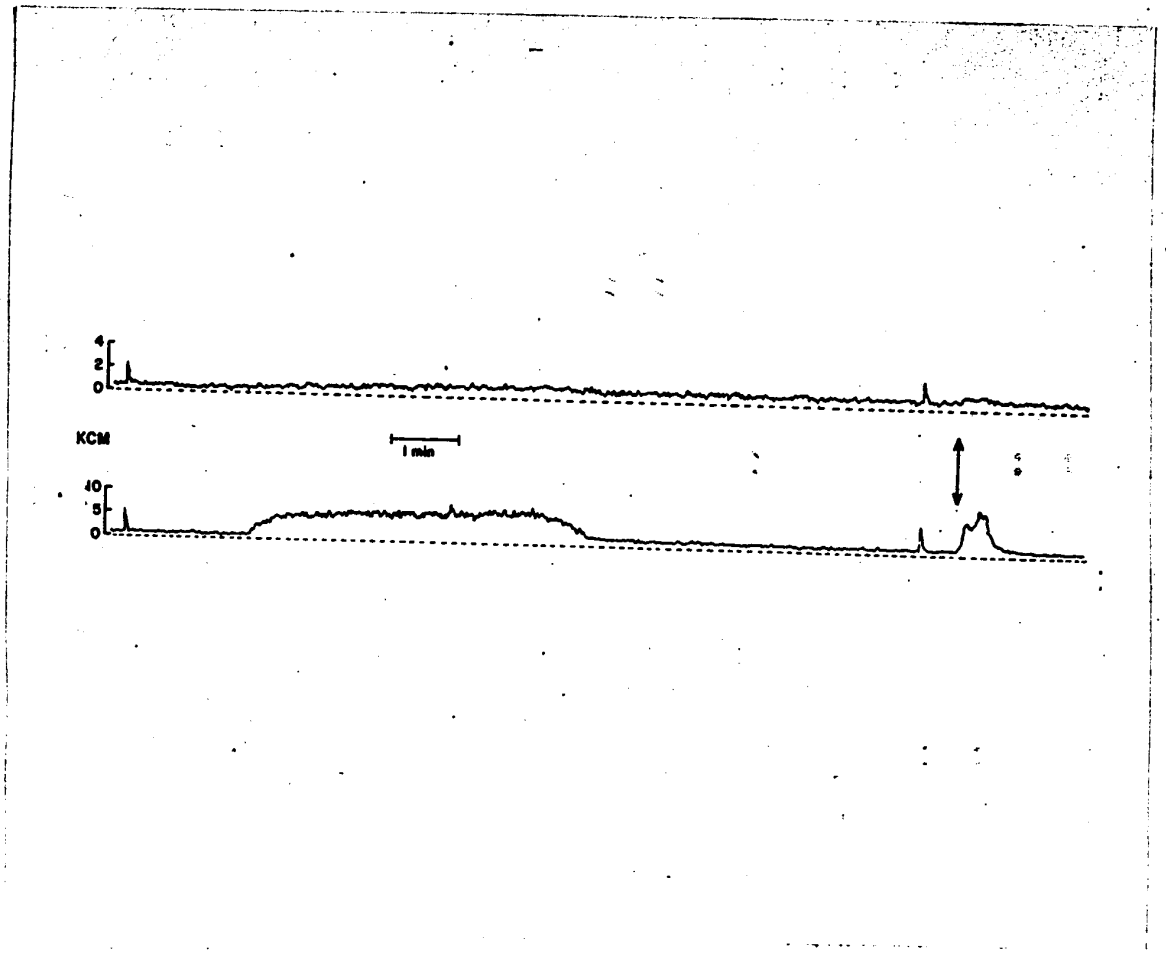


Fig. 18. Regional count rates in a subject with recent pneumonectomy. Shown are recordings of kilocounts per minute (KCM) from a lung region (lower) and the chest wall opposite (upper). The subject rebreathed ^{133}Xe for 5min, then was turned out of the circuit and the isotope was washed out. Finally, at the time indicated by the vertical arrow, the patient received an intravenous bolus of ^{133}Xe.

where S is scattered radiation. This factor (S) was then subtracted from W_p or W_i to derive "true" chest wall radiation. Fig. 19 shows chest wall radiation at the end of infusion and rebreathing after correction for scattered radiation. It will be seen that this corrected chest wall radiation was about 125% of W_o, the chest wall radiation after washout was complete. If it were assumed, then, that chest wall background did not change during washout, an error of about 20% would be made in the estimation of chest wall background. In regions where intrapulmonary count rate is 5 - 10 times that of the chest wall, this error is insignificant. In areas where this is not the case, such as the apex of the erect human lung, this method may lead to erroneous estimates of intrapulmonary count rate. Since chest wall washout is independent of lung washout, it is also theoretically possible to underestimate chest wall radiation significantly in subjects with greatly prolonged intrapulmonary washout. In practical fact, however, in such subjects it is most difficult to separate pulmonary from chest wall washout and the major risk is one of overestimating chest wall background. In accord with the above arguments, we have assumed that chest wall background did not change during washout. We have then obtained regional intrapulmonary count rates at the end of rebreathing and infusion by subtracting from total regional count rates the count rate present after complete intrapulmonary washout. We have also avoided placing counters at the extreme lung periphery, particularly the apex.

The most important limitation of all techniques which assess regional lung function is that they tend to treat lung regions as if they were functionally homogeneous. The ^{133}Xe methods of the preceding pages were derived

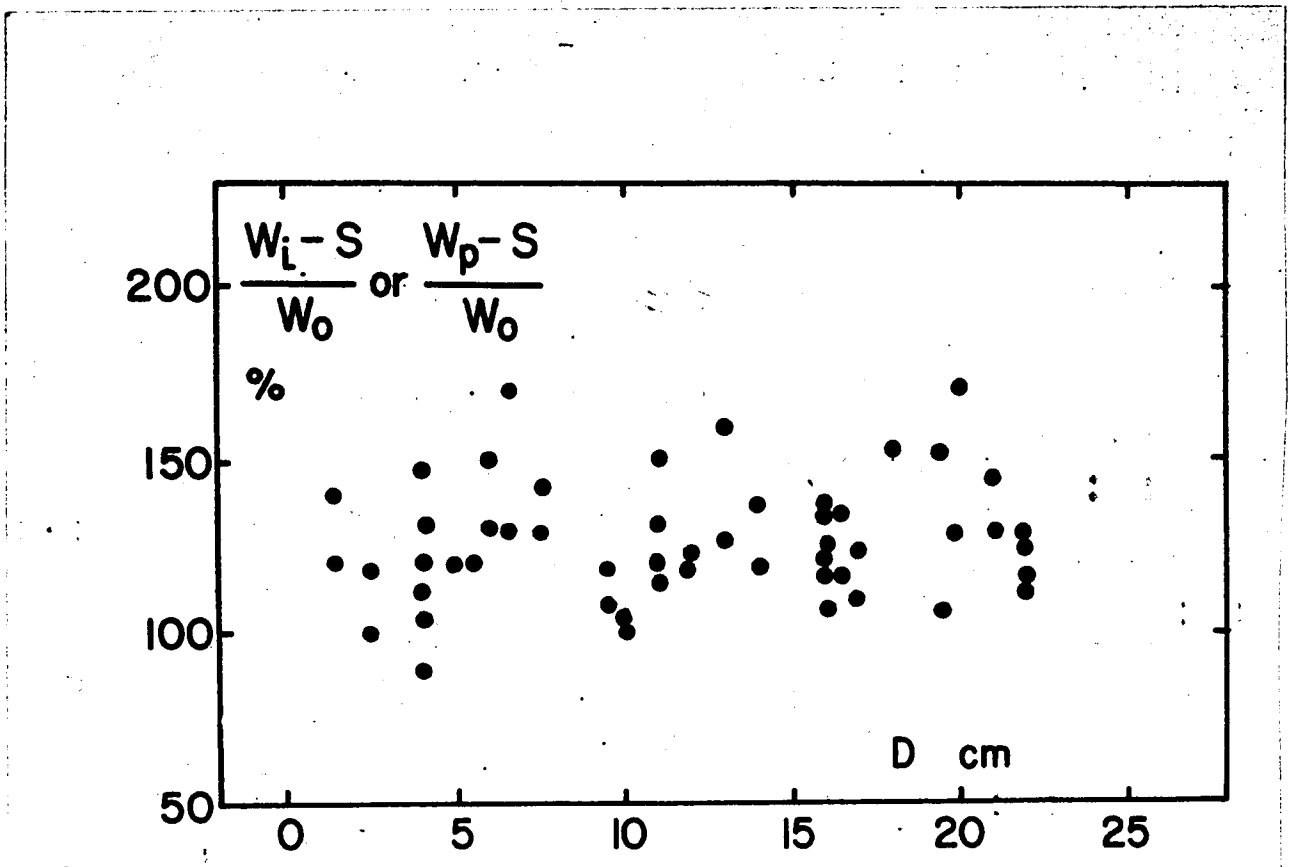


Fig. 19. Corrected count rates recorded from the chest wall at the end of ^{133}Xe adminstration. Ordinate: count rate at the end of rebreathing (W_i) or infusion (W_p) minus a correction factor for scattered radiation (S). This is expressed as a percentage of the chest wall count rate observed after pulmonary washout was complete (W_o). Abscissa: distance down the lung (top = 0 cm).

with the assumption that all units within a lung region functioned in the same way. Since this obviously need not be so, what are the meaning of our methods in the presence of intraregional heterogeneity of function?

In a region consisting of several functional types of units, all these units contribute in some way to measurements derived from the region as a whole. In such a case, a regional measurement represents the average value of the function considered for the region as a whole. In other words, a region with a variety of functional units will develop a variety of ^{133}Xe concentrations when the isotope is administered, and the ^{133}Xe concentration measured in the region as a whole must be between the extremes of concentration present in the various units. The overall regional concentration is not the arithmetical mean of the concentrations which exist in the region. Measurement of regional concentrations are based on measurements of regional count rate, which is related to the amount of isotope in a region. The amount of isotope equals the product of its concentration and the volume containing the concentration. In a heterogeneous region, the measured overall regional concentration is the mean of the various concentrations in the region, each weighted according to its volume. Thus, regional $\dot{V}_A/\dot{Q}$, $\dot{Q}/V$, and $T\frac{1}{2}$ all represent volume weighted mean values when the region examined is not functionally homogeneous. In the case of regional $\dot{V}_A/\dot{Q}$, there is an additional weighting factor. As shown in Fig. 20, ^{133}Xe concentration is much more sensitive to $\dot{V}_A/\dot{Q}$ during infusion than it is during rebreathing. Because of this, low $\dot{V}_A/\dot{Q}$ units develop very high concentrations during infusion and influence the overall regional $\dot{V}_A/\dot{Q}$ measurement in a manner disproportionate to their volume. A simple illustration of this phenomenon is

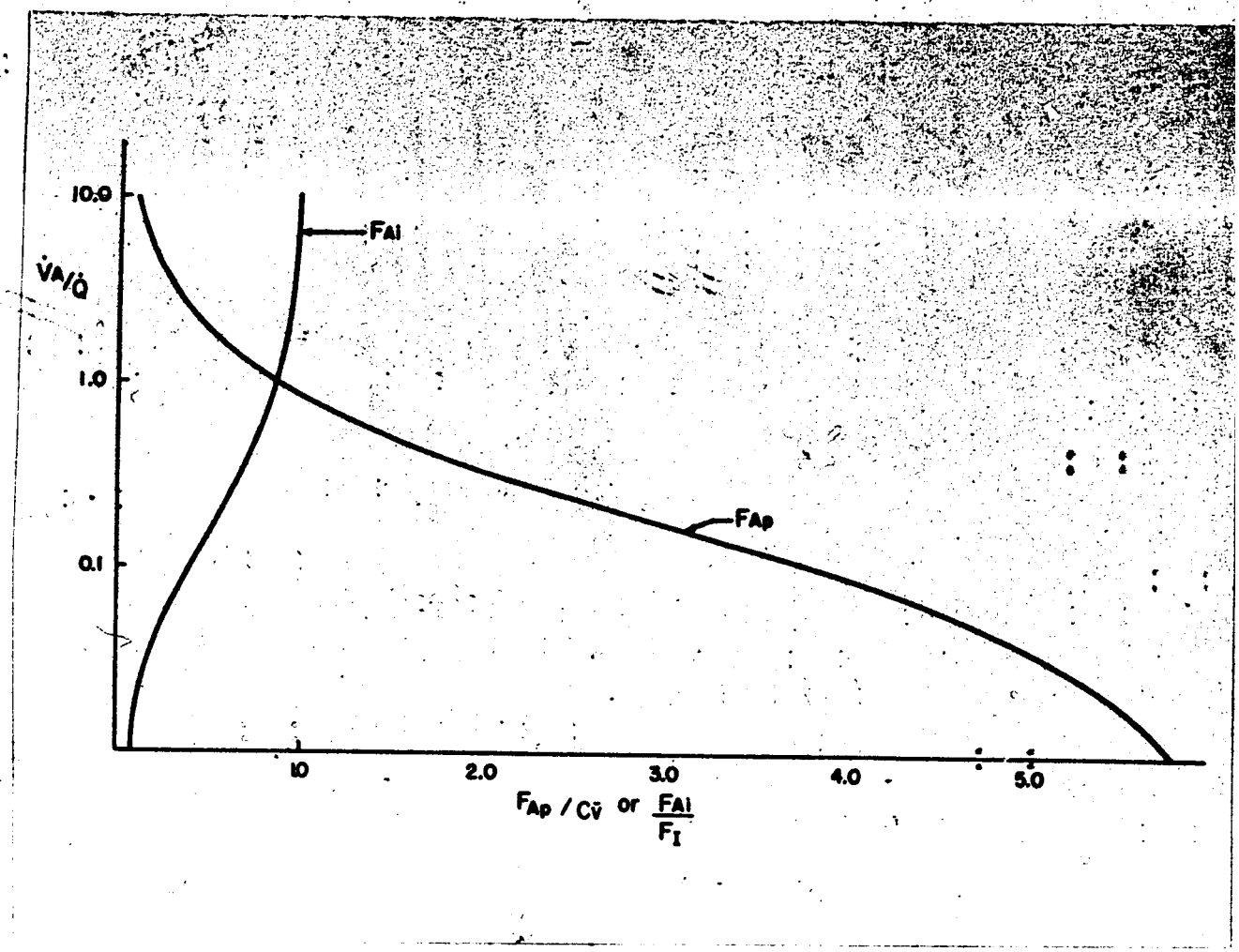


Fig. 20. Regional ^{133}Xe concentrations during infusion and rebreathing. Regional concentrations, expressed as fractions of their respective input concentrations are on the ordinate. On the abscissa is regional $\dot{V}_A/\dot{Q}$.

a region made up of equal volumes of perfused but unventilated units ($\dot{V}_A/\dot{Q}=0$) and ventilated but unperfused units ($\dot{V}_A/\dot{Q}=\infty$). The $\dot{V}_A/\dot{Q}$ of this region is unity when measured by ^{133}Xe infusion and rebreathing; this value is obviously much lower than the arithmetic mean $\dot{V}_A/\dot{Q}$ of the region.

There are two corollaries to the fact that regional values are weighted means when the region considered is not homogeneous. The first is that the measured regional value may not correspond to the function of any unit in the region. A region consisting of two distinct types of units will generate regional $\dot{V}_A/\dot{Q}$, $\dot{Q}/V$ and $T\frac{1}{2}$ intermediate between those of the two populations; the regional values, therefore, are not found in any unit in the region. The second corollary is that in the presence of intraregional inhomogeneity measured differences in function between lung regions are the minimal differences which exist between units throughout the lung. If, for example, the $\dot{V}_A/\dot{Q}$ of one heterogenous region is one half of the $\dot{V}_A/\dot{Q}$ of another, then the lowest $\dot{V}_A/\dot{Q}$ in the first region must be less than one half of the highest $\dot{V}_A/\dot{Q}$ of the second.

Granting that inhomogeneity of function within single regions may be an important limitation of the methods we have outlined, what is the likelihood that significant intraregional functional heterogeneity will be encountered? The answer to this probably depends on the type of subject studied; one might expect more striking variation in function within lung regions of patients with emphysema than in normal subjects. Though this is a reasonable hypothesis, it has never been critically tested, nor has the question of intraregional inhomogeneity of function been studied in patients with other disease. Studies of regional function then should not only document differences between lung regions, but should attempt to assess the possibility

of significant differences in function within single lung regions. Such an assessment would indicate the limitations as well as the fruits of the study of regional function.

3. TEST PROCEDURES AND CALCULATIONS

The preceding section served to introduce the methods employed in these studies, and to give their theoretical background and limitations. This section will be devoted to exactly how the measurements were made: the equipment, procedures and calculations which were used will be outlined.

The most important data gathered during these studies were regional count rates. These were collected using standard (though homemade) scintillation counters with sodium iodide crystals 3/4 inch in diameter and 1/2 inch thick. These counters were fitted with tubular lead collimators which projected 17 cm. beyond the crystal. Fig. 21 shows isocount curves resulting from such collimation. It is important to remember that these isocount curves were derived using a point source of radioactivity. A point source is not analogous to the lung which is perhaps best regarded as a series of plane sources. In the case of a point source, the radiation measured by a detector is inversely proportional to the square of the distance between source and detector, a point illustrated in Fig. 21. This is not true if a detector observes a plane source: as the distance between detector and source increases, the area of the source which is observed by the detector increases as well. In fact, elementary trigonometry demonstrates that the amount of radiation registered by a detector is independent of the distance between detector and plane source. It is perhaps more to the point in this instance then to describe the limits imposed by the collimation used, or the extreme diameters of the planes

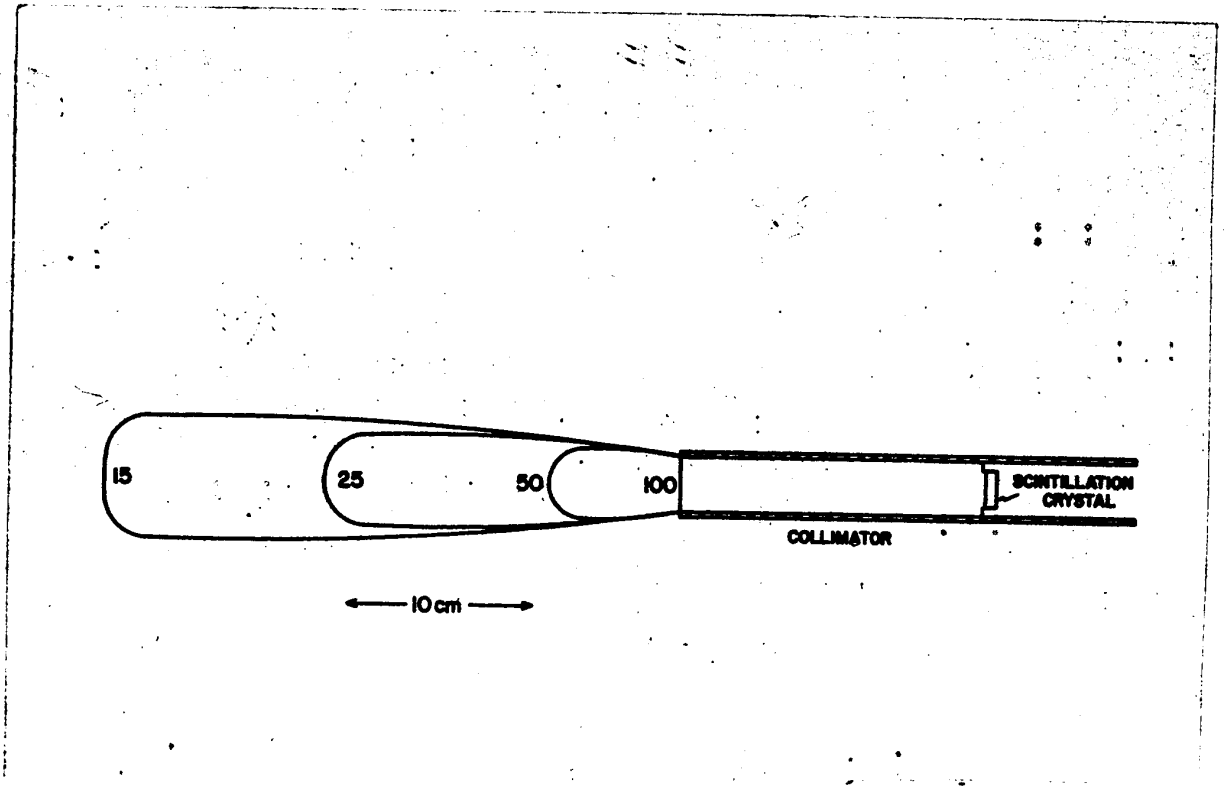


Fig. 21. Isocount curves for the collimation used (17 cm). Numbers on the isocount curves refer to a counting rate of 100% at the end of the collimator.

of lung observed. Using 17 cm. collimators, the diameter of the counting field adjacent to the collimator was 2.5 cm. while the diameter of the counting field was 5.2 cm. at a distance of 20 cm. (roughly the maximum antero-posterior diameter of the lung). It must be recalled that if concentration were equal throughout the counting field, each of these two planes would produce the same count rate. Therefore, small lesions producing variations in count rate are much more easily detected when adjacent to the collimator then when distant to it. Abnormalities which are smaller than a counter field behave like point sources.

Regional counters were positioned over the dorsal aspect of each lung as follows. The counters were fixed to a rack in such a way that the projecting end of the collimator was in contact with one side of a transparent plastic grid. The other side of the plastic grid was in contact with the dorsal (posterior) surface of the subject's thorax. The rack to which the counters were fixed allowed adjustment of the position of each counter relative to the x and y axes of the grid. Such adjustments were made, thereby selecting the lung regions to be studied, by means of placing a chest radiograph over the grid. The radiograph was positioned so that bony landmarks (the midline, the dorsal process of the seventh cervical vertebra) coincided with fixed positions on the grid. As noted above, the counters were dorsal to the chest and "looked" ventrally. Generally, 4 - 6 counters were used over each lung ranging from apex to base; positions over the lung periphery, especially the extreme apices, were avoided.

The amplification, electronic processing and recording of data from regional counters has been well reviewed in the past [55,59] and since we

made no changes in these techniques, they will not be outlined in detail here. In brief, all data from regional counters was recorded on a 32-channel magnetic tape recorder. Each "count" or gamma ray was recorded as an event, and gamma rays were distinguished from background electronic "noise" by setting a voltage threshold which had to be exceeded for an event to be recorded. In these experiments the threshold was analogous to 25 KEV, so that both the low (30 KEV) and the high (80 KEV) energy gamma rays emitted by ^{133}Xe were recorded. The tape recordings of regional count rates functioned as data storage facilities. Subsequent to the experiment, the tape was replayed and the counts on the tape were measured by analogue counting rate meters (time-constant=0.1 sec) and recorded on an oscillograph. The result were records of regional counts per unit time (count rate) plotted against time. During experiments, a regional counter was played from the tape through a rate meter to the oscillograph so that lung regions could be monitored.

In addition to measurement of regional count rate, radiation detectors were utilized to measure ^{133}Xe in mixed inspired gas (F_I), in mixed expired gas (F_E), and sometimes in end tidal gas and arterial blood (C_a). F_I and F_E were measured in shielded cuvettes (see below) using counters and recording techniques similar to those employed in the measurement of regional concentrations. End tidal and arterial concentrations were measured using scintillation counters with larger (2 in. diameter) thinner ($\frac{1}{4}$ in.) NaI crystals, which were therefore "more efficient", that is more counts (disintegrations) were measured per millicurie of isotope. The output of these counters was measured by a two channel digital rate-meter which

literally noted the number of counts registered by the detector during repeated preselected time intervals. If the time interval selected were short, very rapid changes in ^{133}Xe concentration could be measured. The counts measured by the digital rate meters were recorded directly on the oscillograph.

Calibration of the various cuvettes was accomplished using a fixed, shielded counter (scalar counter) which was not collimated. The output of this counter could be read off the face of a digital rate meter, and the time interval over which counts were accumulated could be varied. A known amount (in mc.) of ^{190}Th; an isotope with a very long half life was exposed to the counter under fixed specific geometrical conditions. This resulted in a factor which converted count rate to millicuries, if counting was conducted under the same conditions. Using this counter then, any discrete sample of ^{133}Xe could be quantitated in terms of mc. In addition to its use in calibrating cuvettes, the scalar counter was used to measure the amount of ^{133}Xe present in infusion and injection syringes.

Two breathing circuits were used in each of these experiments, an open circuit and a closed circuit. The patient's mouthpiece could, by means of a two-way tap, be connected to either circuit. The closed, or rebreathing circuit, consisted of a spirometer which recorded on a kymograph, a mixing motor, CO_2 absorber and a tubular cuvette and scintillation counter for measuring F_I. In the open circuit, inspired gas was separated from expired gas by a small valve (dead space = 30 cc). In the inspired line was a dry gas meter with potentiometer which recorded inspired ventilation. In the expired line was a 1.5 L baffle box situated just proximal

to a tubular cuvette which contained a scintillation counter for measuring F_E. The expiratory line also contained a port for taking samples of mixed expired gas. Both circuits were shielded with lead 1/8 in. thick.

End-tidal ^{133}Xe was measured with a high efficiency counter positioned over the breathing valve in the open circuit. This system allowed recording of rapid changes in concentration -- the 90% response time was 0.2 sec. Arterial ^{133}Xe concentrations were measured by drawing arterial blood through a flattened spiral coil of glass, over which a high efficiency counter was positioned[67]. Counters and cuvettes were also shielded with 1/8 in. - 1/4 in. thick lead.

During most experiments, several measurements of the cardiac output ($\dot{Q}_T$) were made. Dye dilution technique was used, a bolus of dye being injected intravenously. Both Coomassie Blue dye and indocyanine green dye were used[68,69]. When green dye was used, arterial blood was drawn through a cuvette which measured dye concentrations photometrically and a curve of dye concentration vs. time recorded. When blue dye was used, dye concentrations were measured photometrically in the intact ear using a specially designed cuvette[68]. Once again a curve of dye concentration vs. time was recorded. Cardiac outputs were calculated from dye dilution curves using the method of Hamilton[70].

From the subject's point of view, the experiments went as follows. On arrival in the laboratory, bony landmarks on the posterior thorax were marked and according to these the subject was positioned in front of the preset regional counters. An intravenous catheter was then threaded into an anticubital vein, and pushed centrally so that its end lay in the axillary vein, subclavian vein or superior vena cava. In some subjects

a Cournand needle was then introduced into the opposite brachial artery. The subject was then fitted with mouthpiece and nose clips and allowed to rest for some minutes and become used to the experimental situation. Then, in no particular order, he underwent three procedures:

1) He received a 5-10 minute constant volume infusion of a known amount of ^{133}Xe in saline. During and after this period the subject breathed normally in the open circuit. At the end of the infusion, the infusion line was rapidly flushed with saline to facilitate observation of subsequent regional washouts.
2) He rebreathed ^{133}Xe in trace amounts from the closed circuit. Circuit volume was kept constant by adding oxygen to the spirometer in amounts equal to the subject's oxygen uptake. At the end of this period the subject was turned out of the closed circuit and breathed on the open circuit as intrapulmonary ^{133}Xe was washed out. Throughout these procedures the subject also breathed normally.
3) The subject held his breath at FRC, and received 2-4 intravenous bolus injections of ^{133}Xe.

During these procedures cardiac output was measured 2-4 times. In some instances arterial ^{133}Xe concentrations were measured during the last 4-5 min. of ^{133}Xe infusion and rebreathing. End tidal ^{133}Xe concentrations were measured during infusion in a few instances.

Regional $\dot{V}_A/\dot{Q}$ were generally calculated according to eq. III-7:

$$\dot{V}_A/\dot{Q} = \frac{C_{\bar{v}}\ Ui}{F_I\ Up} \qquad \text{(III-7)}$$

where Ui is regional count rate during rebreathing, Up is regional count rate during infusion, F_I is inspired concentration at the end of rebreathing. Mixed venous ^{133}Xe concentration during infusion was computed by dividing the infusion rate (mc/min) by the cardiac output.

In some patients arterial ^{133}Xe concentrations were measured during infusion (Ca_p) and rebreathing (Ca_i). In these subjects eq. (III-7) was corrected to take account of recirculating ^{133}Xe. It was assumed that recirculation produced mixed venous ^{133}Xe concentrations to 50% of the arterial levels and $\dot{V}_A/\dot{Q}$ calculated according to eq. (III-13):

$$\dot{V}_A/\dot{Q} = \frac{C_{\bar{v}}\, Ui + 0.5\,(Ca_p\, Ui - Ca_i\, Up)}{F_I\, Up} \qquad \text{(III-13)}$$

Regional perfusion was estimated on the basis of the distribution of bolus injections of ^{133}Xe. Regional ^{133}Xe concentrations were calculated:

$$F_{A_B} = \frac{U_B}{Ui}\, F_I \qquad \text{(III-23)}$$

where F_{AB} is regional ^{133}Xe concentrations after injections, and U_B is regional count rate after injection.

In patients with low regional $\dot{V}_A/\dot{Q}$, F_{Ai}, regional concentration during rebreathing was substituted for F_I. F_{A_i} was calculated with knowledge of regional $\dot{V}_A/\dot{Q}$:

$$F_I\, \dot{V}_A/\dot{Q} = F_{A_i}\,(\dot{V}_A/\dot{Q} + \alpha) \qquad \text{(III-3)}$$

In subjects in whom FRC was known, perfusion distribution was expressed in terms of perfusion indices:

$$\dot{Q}_I = F_{A_B} / \frac{mc \text{ injected}}{FRC} \qquad \text{(III-24)}$$

$\dot{Q}_I$ is perfusion index when F_{A_B} was calculated using F_I; when F_{A_i} was used, steady state perfusion indices ($\dot{Q}_i$) resulted.

Regional ventilation was assessed by measuring regional washout half times ($T\frac{1}{2}$). $T\frac{1}{2}$ are related to the reciprocal of ventilation per unit volume ($\dot{V}/V$) so that when $T\frac{1}{2}$ were short very small differences of $T\frac{1}{2}$ resulted in large differences in $\dot{V}/V$ which were of dubious significance. For this reason, when $T\frac{1}{2}$ were short only regional $T\frac{1}{2}$ were calculated. In subjects with long $T\frac{1}{2}$, the reciprocal of regional $T\frac{1}{2}$ were calculated and presented as regional $\dot{V}/V$. In some instances, regional $T\frac{1}{2}$ were standardized to take account of overall ventilation and FRC:

$$1/T\tfrac{1}{2} \; FRC/\dot{V}_I \times 100 = \tilde{\dot{V}} \qquad \text{III-25}$$

where FRC is functional residual capacity and $\dot{V}_I$ is overall minute ventilation (inspired). $\tilde{\dot{V}}$ then is a dimensionless index of regional ventilation per unit volume.

In addition to the above several non-regional measurements were made routinely. These included cardiac output and minute ventilation. In some subjects, end tidal ^{133}Xe concentration (F_A) and arterial ^{133}Xe concentrations were also measured. During infusion mixed expired ^{133}Xe concentrations (F_E) were measured in all subjects. Multiplying F_E by the appropriate minute ventilation gave respiratory ^{133}Xe output ($\dot{V}_{Xe}$) which was compared with the infusion rate to evaluate the presence of a steady state. In most subjects mixed expired O_2 and CO_2 concentrations were measured by the Scholander method[71]. Using these values, the minute

ventilation and the alveolar air equation respiratory exchange ratio (R) oxygen uptake ($\dot{V}_{O_2}$) and carbon dioxide output ($\dot{V}_{CO_2}$) were calculated. These measurements also served to assess the presence of steady state conditions.

In addition to the above, routine pulmonary function tests as outlined above were carried out in most patients. These tests were carried out in clinical laboratories in several hospitals; no special precautions were taken in studying the subjects of the ^{133}Xe experiments. Results of these routine pulmonary function tests were compared to predicted normal values[9c].

Normal regional function

In the erect position, ventilation blood flow and $\dot{V}_A/\dot{Q}$ differ from apex to base of the normal lung; we shall present results documenting the extent of this variation. The fact that regional function depends on gravity is of less interest in patients with lung disease, however. Indeed, to avoid the influence of gravity we studied patients in the supine position using posteriorly (dorsally) placed counters. Under these circumstances ventilation and perfusion are the same in all lung regions[59,62]. We have measured steady state regional $\dot{V}_A/\dot{Q}$ in a few supine normals and found no difference from apex to base. Thus, by eliminating the influence of gravity on regional lung function we were able to assess the normality of any lung region in each patient by comparing it to other lung regions instead of comparing it to arbitrary normal standards. Assigning criteria for normality have been done in some cases to help present the data, but changing these criteria would not seriously influence either the results or their interpretation.

The $\dot{V}_A/\dot{Q}$ of any region obviously depends on the overall ventilation and blood flow which obtain at the time the measurements are made. It has been pointed out that in erect subjects these values are normally such that overall $\dot{V}_A/\dot{Q}$ varies from 0.8 to 1.0. In patients studied in the supine position with

posteriorly placed counters, $\dot{V}_A/\dot{Q}$ in all regions should be in the neighborhood of 0.80 - 1.00. However, with tilt from the erect to the supine, cardiac output increases and alveolar ventilation decreases, so $\dot{V}_A/\dot{Q}$ must decrease. These relationships have been summarized as[72]:

$$\dot{V}_A/\dot{Q} = \frac{0.863\ R\ (Ca_{O_2} - C\bar{v}_{O_2})}{P_{A_{CO_2}}}$$

In normal supine subjects values of R = .8, $(Ca_{O_2} - C\bar{v}_{O_2})$ = 40 ml/L and $P_{A_{CO_2}}$ = 42 mmHg are all acceptible[73,74]; these values dictate a $\dot{V}_A/\dot{Q}$=0.67. We have seen regional $\dot{V}_A/\dot{Q}$ as low as 0.60 in normal subjects. In any event, in no subject in this series was the normality of a lung region defined by its $\dot{V}_A/\dot{Q}$.

Regional perfusion was not measured in absolute terms; perfusion indices connote the regional perfusion per unit volume relative to the value which would obtain if perfusion were distributed evenly. The most that can be said about a region, then, is that it is over perfused or under perfused relative to other lung regions in the same subject. The accuracy of the method is such that differences among regions of less than 20% may not be significant. Thus, normal values for perfusion index are 100 ± 20. As mentioned previously, in some subjects all lung regions exhibit perfusion indices outside these limits. This was the result of technical error; in most instances valid conclusions could still be drawn regarding the perfusion of one region relative to that of another.

Regional $T\frac{1}{2}$ are inversely related to regional ventilation per unit volume, but as we have seen this relationship is by no means rigorous. Because of this we have hesitated to define regions as normal or abnormal on the basis

of their $T\frac{1}{2}$; we have simply compared regional $T\frac{1}{2}$ (or its reciprocal) in the same patient. In some subjects, however, it was necessary to separate normal and abnormal regions according to their ventilation. In order to do this overall ventilation and FRC had to be taken into account. As previously noted, this was done by computing $\tilde{V}$:

$$1/T\tfrac{1}{2} \times \dot{V}_I/FRC \times 100 = \tilde{V} \qquad \text{III-25}$$

$\tilde{V}$, a dimensionless index of ventilation per unit volume, was measured both after rebreathing ($\tilde{V}_i$) and after infusion ($\tilde{V}_p$). Theoretically, normal values for $\tilde{V}$ should approximate 100. If ^{133}Xe were insoluble, the reciprocal of $T\frac{1}{2}$ would be equal to regional ventilation per unit volume multiplied by ln 2 (0.693). Normally overall alveolar ventilation is about 70% of overall minute ventilation, so the numerical constants cancel out:

$$\tilde{V} = \frac{.693\ \dot{V}_A/V}{.7\ \dot{V}_I/FRC} \times 100 \qquad \text{III-26}$$

However, normal regions often produce $\tilde{V} < 100$. We have defined $\tilde{V} < 50$ as abnormal and values $50 < \tilde{V} < 60$ as borderline. These definitions are probably conservative.

Before presenting the results of these studies, note should be taken of the radiation dose to which our subjects were exposed. Normal subjects received 5 min. of infusion and 5 min. of rebreathing while in most abnormal subjects these procedures were continued for 10 min. In the case of normal subjects, the total dose to the lung was always less than 200 m rads and to the remainder of the body the dose was about 25 m rads. Subjects with lung disease received 300-400 m rads to the lung and 50 rads to the rest of the body. Methods of dose calculation with examples are included in the appendix of this thesis.

IV. RESULTS

1. NORMAL SUBJECTS

Four normal young men were studied while seated; regional measurements were made by 4-6 counters set posterior to each lung ranging from apex to base. Regional $\dot{V}_A/\dot{Q}$ and $T\frac{1}{2}$ were measured, but no attempt was made to assess the regional distribution of perfusion. End tidal ^{133}Xe concentration during infusion was measured by positioning a counter over the breathing valve in the open circuit. Cardiac output was not measured in any instance; values which were normal for each subject were assumed to be present.

In all subjects steady states were achieved in 5 min. of ^{133}Xe infusion. Fig. 22 shows end-tidal ^{133}Xe concentration as well as count rates from two lung regions during infusion (Subj. AP). All three records attain virtually constant values within three to four min. Table 3 compares respiratory ^{133}Xe output ($\dot{V}_{Xe}$) with infusion rate; the two are nearly equal, and values of $\dot{V}_{Xe}$ did not change from the fourth to the fifth minute in those cases in whom separate measurements were made.

Fig. 23 shows regional $\dot{V}_A/\dot{Q}$ in our four normal erect subjects, as calculated using eq. III-7. Apical $\dot{V}_A/\dot{Q}$ was high, ranging from 1.50 to 1.80. Below the apex $\dot{V}_A/\dot{Q}$ fell progressively until at the base values ranged from 0.50 to 0.80. Measurements of regional washout showed that $T\frac{1}{2}$ were longest at the apex and grew progressively shorter as the base was approached. Ventilation per unit volume, then, increased progressively from apex to base (Fig. 24). When these data were combined with the measurements of regional $\dot{V}_A/\dot{Q}$, it was concluded that regional perfusion per unit volume must also increase from apex to base. Further, the rate of increase of perfusion must

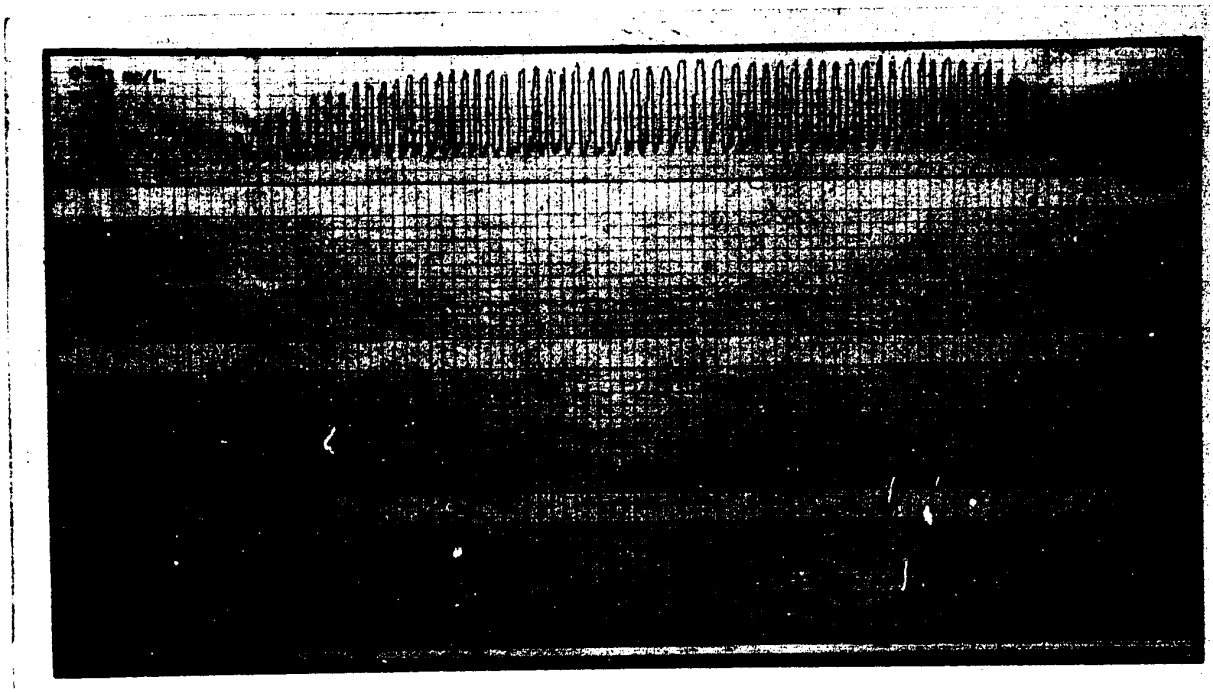


Fig. 22. Experimental record during ^{133}Xe infusion in subject AP. The signal on the bottom channel indicates when the infusion pump was turned on and off. The middle two records are from counters over the right lung (D- distance from the lung top) and are calibrated in counts per minute (cpm). The top tracing is from a counter over the breathing valve and is calibrated in mc/L. This tracing has been slightly retouched for purposes of reproduction.

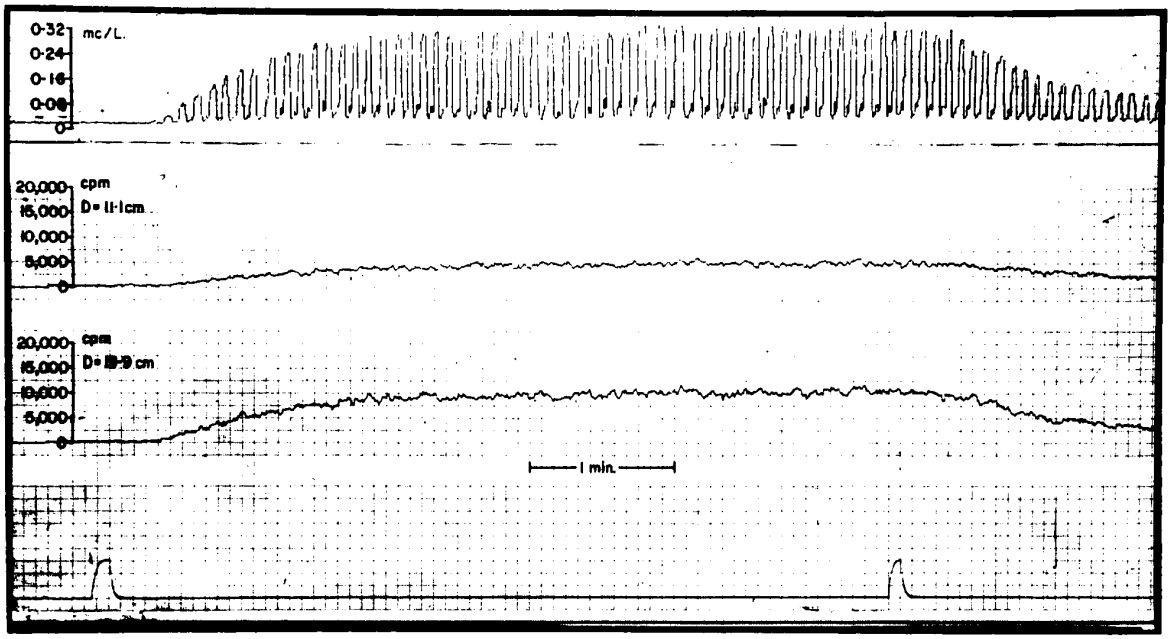


Fig. 22. Experimental record during ^{133}Xe infusion in subject AP. The signal on the bottom channel indicates when the infusion pump was turned on and off. The middle two records are from counters over the right lung (D- distance from the lung top) and are calibrated in counts per minute (cpm). The top tracing is from a counter over the breathing valve and is calibrated in mc/L. This tracing has been slightly retouched for purposes of reproduction.

TABLE 3. COMPARISON OF INJECTION RATE AND RESPIRATORY ^{133}Xe OUTPUT ($\dot{V}_{Xe}$) IN NORMAL SUBJECTS DURING ^{133}Xe INFUSION

Subject	Injection rate (mc/min)	$\dot{V}_{Xe}$. mc/min			% injection rate
		4th min	5th min	mean of 4th and 5th min	
MJ	2.05	1.78	1.83	1.81	88
TA	1.83	1.61	1.50	1.56	86
MR	2.22			2.09	93
AP	2.08			1.94	93

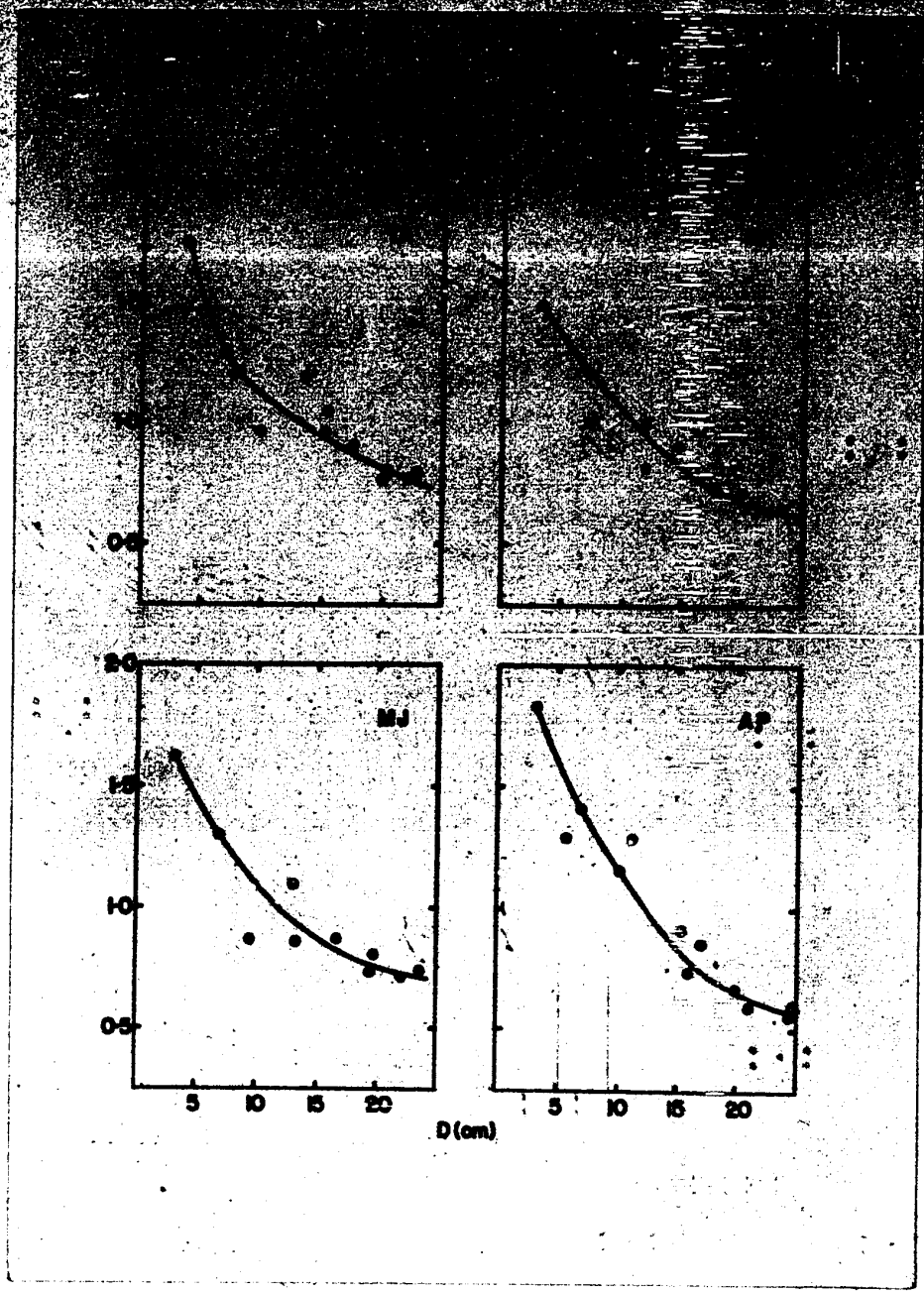


Fig. 23. Regional $\dot{V}_A/\dot{Q}$ in four normal erect subjects. Ordinate: $\dot{V}_A/\dot{Q}$ calculated from equation III-7. Abscissa: distance down the lung (0 cm = lung top).

Fig. 24. Regional ventilation distribution in erect normal subjects. Ordinate: ventilation per unit volume (reciprocal of $T_{\frac{1}{2}}$). Abscissa: distance from lung apex (0 cm) to base (30 cm). These data represent analyses of the washouts after rebreathing of the four subjects of Fig. 23. Apical ventilation is approximately one half of that observed at the base.

have been greater than the apex-to-base increase in ventilation.

This, of course, is precisely what was described by West et al. in their experiments involving $C^{15}O_2$ [52,53]. However, the apex to base variation in $\dot{V}_A/\dot{Q}$ of Fig. 23 is less striking than that found by the Hammersmith group (see Fig. 13). One obvious reason for this difference lies in differences in technique. The $C^{15}O_2$ measurements were made during single breaths of isotope. All isotope which entered lung regions therefore had originated external to the subject; there was no $C^{15}O_2$ in the respiratory dead space. This was not the case in steady state measurements made with ^{133}Xe. During infusion and rebreathing, at the end of expiration, the airways contained isotope which was subsequently reinspired by the lung. Eq. III-7, which was the basis of Fig. 23, neglected this effect, assuming that all gas inspired by a region had the same ^{133}Xe concentration as that measured at the mouth during inspiration. Because of the dead space this was not so. The ^{133}Xe concentrations of regional inspirates were more than zero during infusion and less than F_I during rebreathing. Regional gas concentrations depend on regional $\dot{V}_A/\dot{Q}$ and the compositions of mixed venous blood and inspired gas. The last of these is affected by the dead space so that regional $\dot{V}_A/\dot{Q}$ derived from regional gas concentrations without assessing the effect of the dead space must be erroneous. $\dot{V}_A/\dot{Q}$ derived using single breaths of $C^{15}O_2$ were obviously not affected by the dead space and are, therefore, theoretically more accurate.

However, the reinspiration of dead space gas is a fact of life; regional O_2 and CO_2 concentrations during normal breathing depend in part on the effect of the dead space on inspired gas composition. It, therefore, would be

advantageous to measure regional $\dot{V}_A/\dot{Q}$ in such a way that the dead space effect was recognized and assessed.

One generalization is possible: the effect of the dead space is to lessen differences in gas concentration among regions, and therefore to decrease apparent differences in $\dot{V}_A/\dot{Q}$ resulting from gas concentration measurements which neglect the dead space. This is because much of the respiratory dead space is common to all lung regions in that it contains contributions from each. Dead space ^{133}Xe concentration, therefore, must represent some kind of average of the concentrations of the contributing regions. Inspiration of such gas must lower ^{133}Xe concentrations in regions where it is highest and raise ^{133}Xe concentrations where it is lowest.

The dead space problem may be approached quantitatively if the volume, composition and distribution of dead space gas is known. Since all three may be reasonably approximated in normal subjects, the following paragraphs will assess the effect of reinspired dead space gas.

The approach used is similar to that of Ross and Farhi [75] who examined the effect of the dead space on the O_2-CO_2 diagram; this was initially derived assuming the alveolar inspirate had the same composition as room air. These authors worked in terms of the total ventilation of an alveolus ($\dot{V}e$) which consisted of the conventional alveolar ventilation ($\dot{V}_A$) plus the ventilation of the dead space ($\dot{V}_D$). Making assumptions regarding the composition, volume, and distribution of dead space gas, they then derived $\dot{V}_e/\dot{Q}$ from which it was possible to deduce alveolar gas tensions which were not in error due to the effect of the dead space.

Precise definition of the dead space is difficult. In normal men the dead space is thought to consist almost entirely of conducting airways. It

is usually measured by the Bohr equation[76] which assumes that a steady state prevails and that no gas exchange takes place in the dead space. Thus, for CO_2:

$$F_{E_{CO_2}} \dot{V}_E = F_{A_{CO_2}} \dot{V}_A + F_{I_{CO_2}} \dot{V}_D \qquad \text{(IV-1)}$$

which states that expired gas is alveolar gas diluted by dead space gas which has the same composition as inspired gas.

This expression assumes two homogeneous species of gas in the lungs at end inspiration: alveolar gas and inspired gas. While this may be questioned, the simplification is even more dubious when one considers dead space gas at end expiration. The mainstem bronchi, trachea, and upper airway are common in that they contain gas which originated in all lung regions; their contributions are related to the ventilations of each region. This we define as the common dead space (V_D'). Distal to the mainstem bronchi, the conducting airways do not contain contributions from all lung regions, but only from the regions they subserve. Finally, in the distal reaches of the dead space, there may be gas from only one region; this we define as the regional dead space (V_D''). It is clear that the composition of the common dead space (V_D') may be measured in terms of end tidal ^{133}Xe concentration (F_{A_T}). Similarly, external counters can measure ^{133}Xe concentrations in regional dead spaces (V_D'') by measuring regional concentrations (F_A). ^{133}Xe concentrations in the dead space between these extremes cannot be measured, so in order to carry this analysis further, we must assume this portion of the dead space does not exist. In other words, because of our limited capacity for measurement, we are forced to deal with the dead space as though it contained two compartments: a common dead space (V_D') with composition defined by end tidal

sampling and a regional dead space (V_D") with composition defined by measurement of regional concentrations.

The relative sizes of these two compartments are, unfortunately, not clear. It has been estimated that some 50% of the total dead space is common[77], but this is not a certainty. Because of this problem, we have chosen to examine extreme conditions: we have alternately assumed that the entire dead space was regional or that the entire dead space was common.

It is very difficult to measure the regional distribution of inspired dead space gas. However, measurements of the regional distribution of inspired gas have indicated that, in young normal subjects at lung volumes around FRC, ventilation is not sequential[63]. That is to say, under these conditions, the distribution of any fraction of the tidal volume is the same as any other fraction. If there is no sequential ventilation involving dead space gas, the volume of the reinspired dead space amounts to a fixed fraction of the tidal volume throughout all lung regions; this fraction must equal the ratio of overall dead space to overall tidal volume. The above discussion may be summarized as follows:

1) The dead space (V_D) is divided into two parts, the common dead space (V_D') which has the same composition as end tidal air, and the regional dead space (V_D") each portion of which has the same composition as the region it subserves.
2) The total alveolar ventilation of a region ($\dot{V}_e$) is equal to the regional alveolar ventilation ($\dot{V}_A$) plus the regional share of the dead space ventilation ($\dot{V}_D$). Similarly, the total overall alveolar ventilation ($\dot{V}_{e_T}$) is the overall alveolar ventilation ($\dot{V}_{A_T}$) plus the overall dead space ventilation ($\dot{V}_{D_T}$).

3) The distribution of gas inspired from the dead space is the same as that the remainder of the inspirate, i.e.:

$$\frac{\dot{V}_D}{\dot{V}_e} = \frac{\dot{V}_{D_T}}{\dot{V}_{e_T}} \quad \text{and} \quad \dot{V}_D = \frac{\dot{V}_{D_T}}{\dot{V}_{e_T}} \dot{V}_e \qquad \text{IV-2}$$

By applying these principles, expressions for regional $\dot{V}_e/\dot{Q}$ may be derived as well as expressions for regional $\dot{V}_A/\dot{Q}$, where "$\dot{V}_A$" represents the ventilation exclusive of dead space ventilation. On the next page, the derivation of regional $\dot{V}_e/\dot{Q}$ is shown in detail and contrasted with the previous expressions which neglected reinspired dead space gas. Also shown is an expression for "true" $\dot{V}_A/\dot{Q}$, i.e., $\dot{V}_A/\dot{Q}$ in which the effect of dead space has been removed. Dead space Xe concentrations are symbolized as F_D. The dead space may be broken into compartments with specific concentrations. Alternatively, extreme conditions may be considered, i.e., the whole dead space is regional and $F_D = F_A$, or the whole dead space is common and end tidal Xe concentrations (F_{A_T}) substituted for F_D. We have chosen to examine the extremes.

End tidal ^{133}Xe concentrations were measured during infusion ($F_{A_{PT}}$). These together with mixed expired ^{133}Xe concentrations and minute ventilation, allowed calculation of $\dot{V}_{D_T}$ and $\dot{V}_{D_T}/\dot{V}_{e_T}$. End tidal ^{133}Xe concentrations during rebreathing ($F_{A_{i_T}}$) were not measured but calculated on the basis of overall $\dot{V}_A/\dot{Q}$ and $F_{A_{PT}}$. Two curves for regional $\dot{V}_e/\dot{Q}$ are shown for each of two subjects in Fig. 25. In each case, the upper curve was based on the assumption that the total dead space was common ($V_D = V_D'$, $F_D = F_{A_T}$) and the lower curve was based on the assumption that the total dead space was regional ($V_D = V_D''$, $F_D = F_A$).

$\dot{V}_A/\dot{Q}$ Neglecting Dead Space:

Infusion:

$$\dot{Q}\, C_v = F_{Ap}\, \dot{V}_A + F_{Ap}\, \dot{Q}$$

Rebreathing:

$$F_I\, \dot{V}_A = F_{Ai}\, \dot{V}_A + F_{Ai}\, \dot{Q}$$

$\dot{V}_e/\dot{Q}$:

Infusion:

$$\dot{Q}\, C_v + F_{Dp}\, \dot{V}_D = \dot{V}_e\, F_{Ap} + F_{Ap}\, \dot{Q}$$

Rebreathing:

$$F_I\, (\, \dot{V}_e - \dot{V}_D\,) + F_{Di}\, \dot{V}_D = \dot{V}_e\, F_{Ai} + F_{Ai}\, \dot{Q}$$

Substitute for V_D:

$$\dot{V}_D = \dot{V}_e\, \dot{V}_{D_T} / \dot{V}_{e_T}$$

Combine both equations:

$$F_{Ap} / F_{Ai} = U_p / U_i$$

$$\dot{V}_A / \dot{Q} = C_v\, U_i / F_I\, U_p$$

$$\frac{\dot{V}_e}{\dot{Q}} = \frac{C_v\, U_i}{F_I\, U_p\, (\, 1 - \dot{V}_{D_T}/\dot{V}_{e_T}\,) + \dot{V}_{D_T}/\dot{V}_{e_T}\, (\, F_{Di}\, U_p - F_{Dp}\, U_i)}$$

"True" $\dot{V}_A/\dot{Q}$:

$$\frac{\dot{V}_A}{\dot{Q}} = \frac{C_v\, U_i}{F_I\, U_p - \dot{V}_{D_T}/\dot{V}_{A_T}\, (\, F_{Di}\, U_p - F_{Dp}\, U_i\,)}$$

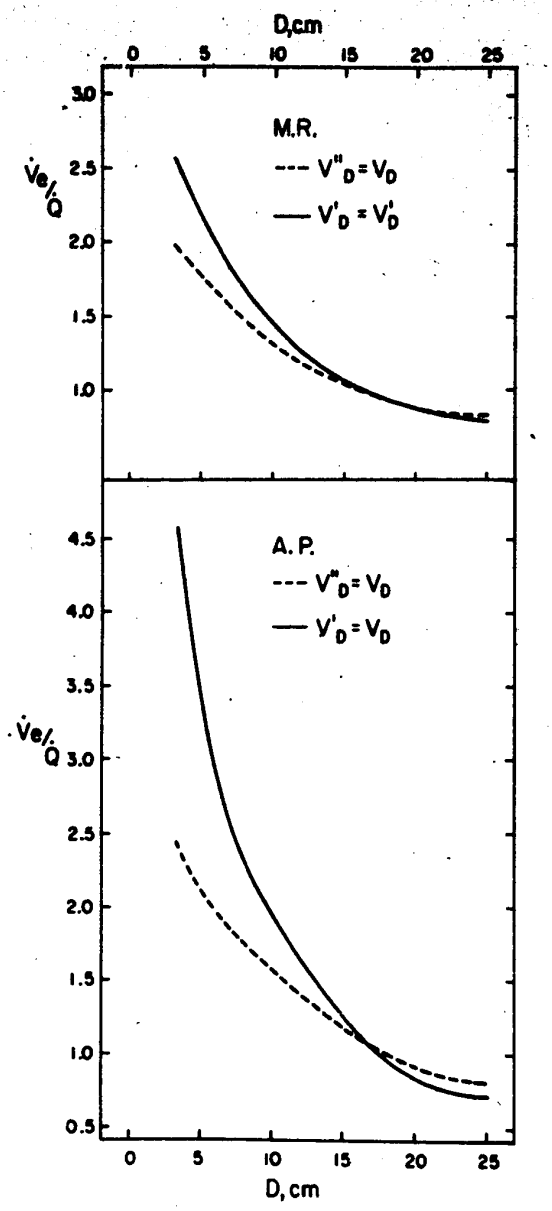


Fig. 25. Regional $\dot{V}_e/\dot{Q}$ in subjects M.R. and A.P. Ordinates: regional $\dot{V}_e/\dot{Q}$. Abscissa: distance from apex (0 cm) to base (25 cm). The solid lines represent the $\dot{V}_e/\dot{Q}$ which would obtain if the total respiratory dead space were common to all lung regions ($V_D' = V_D$). The dotted lines represent results obtained by assuming that the entire dead space was regional ($V_D'' = V_D$). True values for $\dot{V}_e/\dot{Q}$ must lie between the two lines.

True regional $\dot{V}_e/\dot{Q}$ must lie between the two curves. Differences between the two curves are large, particularly at the apex where the amount of reinspired dead space was large in relation to blood flow. The curves intersect at the point at which regional concentrations equaled end tidal concentrations ($F_A=F_{A_T}$) and the common dead space was, in effect, regional.

Fig. 26 shows, for one subject, $\dot{V}_A/\dot{Q}$ derived with consideration of reinspired dead space gas. Again two extreme assumptions have been made in regard to the composition of dead space gas. The broken curve ($V_D=V_D''$, $F_D=F_A$) is the same as that shown for this subject in Fig. 23. The solid curve ($V_D=V_D'$, $F_D=F_{A_T}$) is rather similar to that derived by West et al.[52,53] on the basis of data gathered with $C^{15}O_2$ (see Fig. 13).

Using the O_2-CO_2 diagram and the curves of Fig.26, it is possible to calculate regional gas tensions down the lung. One of the curves of Fig. 26 would yield results quite similar to those presented by West. However, it must be remembered such gas tensions are derived assuming that capillary blood exchanges only with "$\dot{V}_A$", or ventilation exclusive of gas reinspired from the dead space. Capillary blood must exchange gases with the reinspired dead space if the composition of the dead space gas is not the same as that in the alveolus. For this reason, it is more realistic to compute regional gas tensions on the basis of regional $\dot{V}_e/\dot{Q}$. This can be done if the O_2-CO_2 diagram is modified according to the principles of Ross and Farhi[75]; the modification chiefly amounts to use of the dead space in calculating the composition of inspired gas. Fig. 27 shows regional gas tensions calculated by this method; it can be seen that the large differences in $\dot{V}_e/\dot{Q}$ generated by different assumptions regarding the dead space make surprisingly little

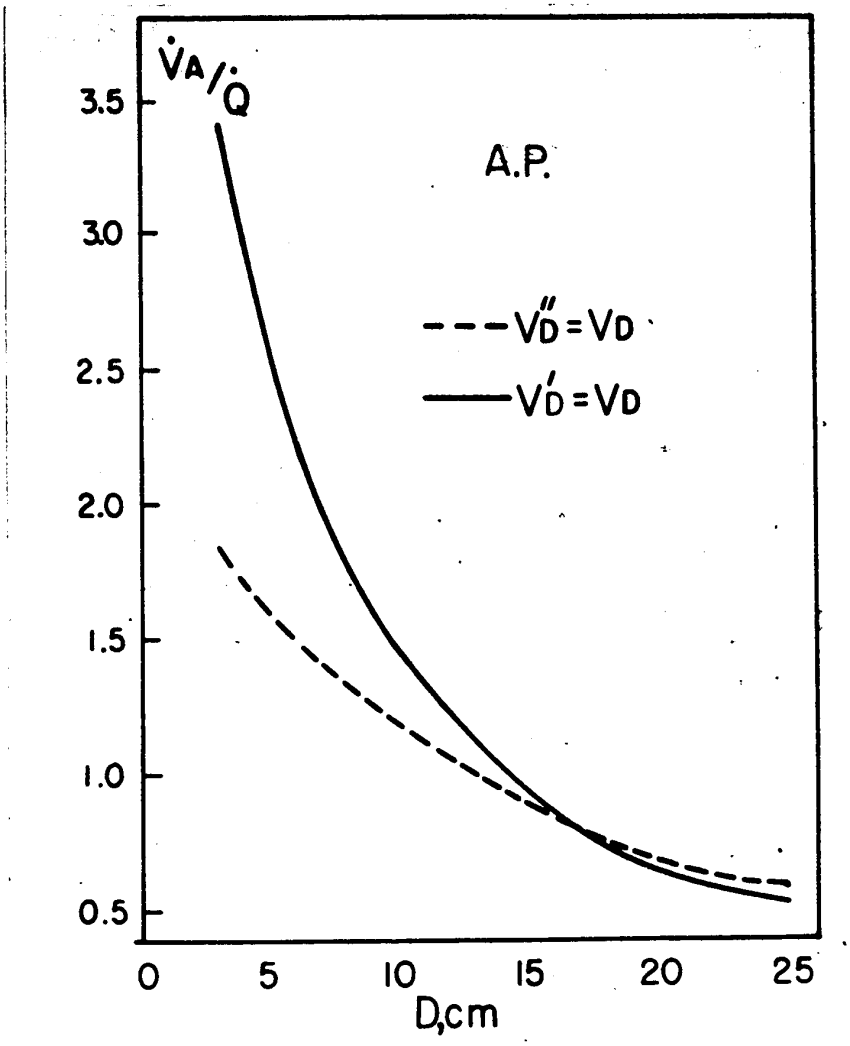


Fig. 26. True regional $\dot{V}_A/\dot{Q}$ in subject A.P. Ordinate: regional $\dot{V}_A/\dot{Q}$, derived taking account of reinspired dead space gas. Abscissa: distance from apex (0 cm) to base (25 cm). The solid line represents data derived assuming the entire measured dead space was common ($V_D' \simeq V_D$). The dashed line represents results when it was assumed that the whole dead space was regional ($V_D'' \simeq V_D$).

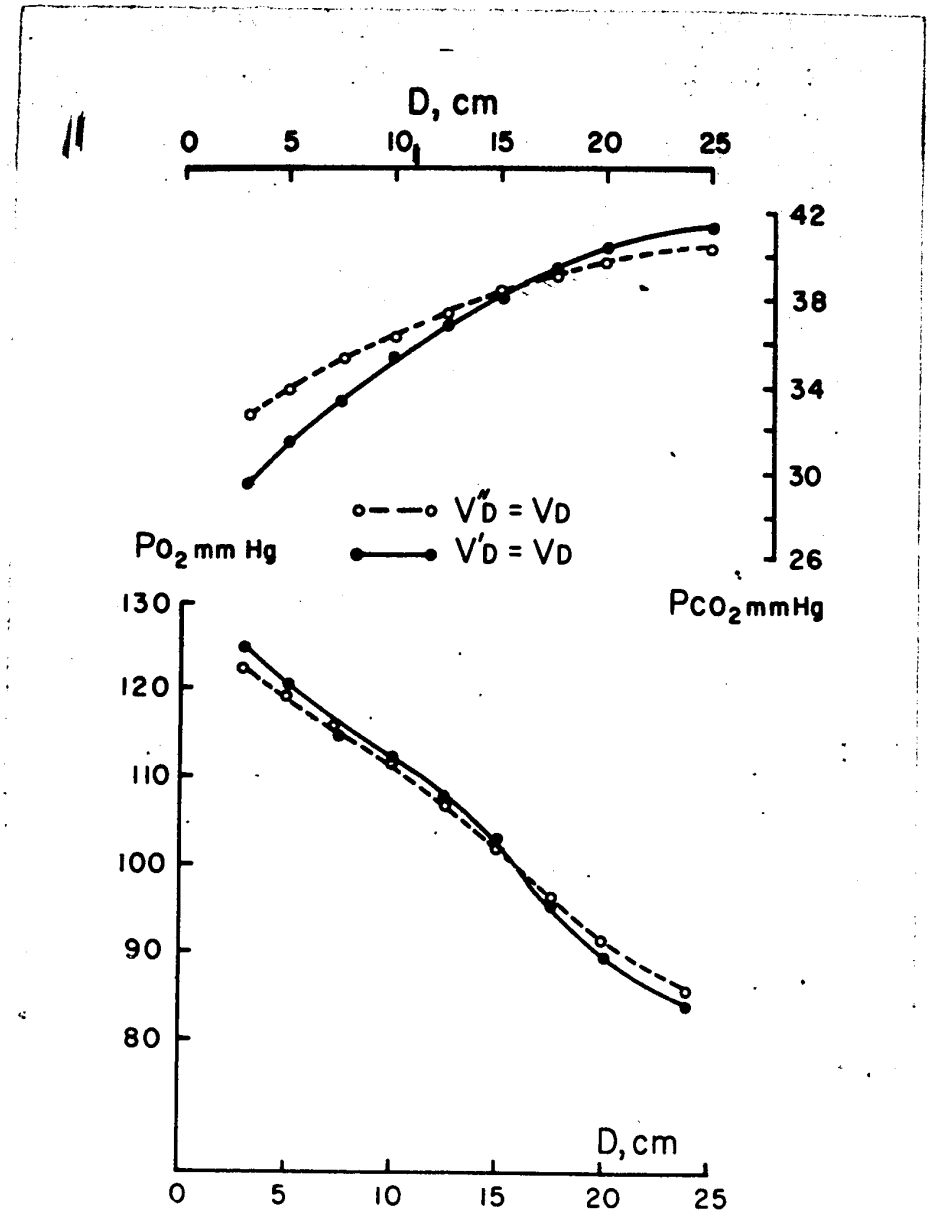


Fig. 27. Regional gas tensions in subject A.P., calculated from regional $\dot{V}_e/\dot{Q}$. Ordinates: regional P_{O_2} and P_{CO_2}. Abscissa: distance from apex (0 cm) to base (25 cm). The solid line represents the gas tensions which result when the whole dead space was assumed to be common ($V_D' = V_D$); the dotted line resulted from assuming that the whole dead space was regional ($V_D'' = V_D$).

difference in regional gas tensions. The apex to base gradient for O_2 and CO_2 is about 3 mmHg larger when $V_D=V_D'$ than when $V_D=V_D''$. In other subjects, these differences were less well marked. The gas concentrations derived when $V_D=V_D''$ are the same as those found when the curve of Fig. 23 was used with the unmodified O_2-CO_2 diagram. It may be said, then, that the original method of measuring regional $\dot{V}_A/\dot{Q}$, which neglected the effect of reinspired gas, yielded regional gas tensions which were useful approximations when it is combined with the O_2-CO_2 diagram of Rahn and Fenn[6]. This is because the classic O_2-CO_2 diagram also neglected the effect of reinspired dead space gas.

The apex to base variations in gas tension shown in Fig. 27 are not as striking as those derived by West. Though this might be due to technical errors in the course of the ^{133}Xe measurements, part of the difference must be due to the fact that the curves of Fig. 27 took account of the reinspiration of dead space gas while gas tensions derived from $C^{15}O_2$ measurements did not. As discussed earlier, reinspired dead space gas necessarily lessens gas tension differences among lung regions.

West was able to compute overall arterial and alveolar gas tensions from his data and found the resulting P_{O_2}, P_{CO_2} and P_{N_2} agreed well with differences measured in erect normals[53]. He concluded that regional variations in $\dot{V}_A/\dot{Q}$ might account for all the gas exchange inefficiency due to $\dot{V}_A/\dot{Q}$ imbalance in the normal lung. Computation of overall alveolar and arterial gas tensions on the basis of the present data involves highly questionable estimates (guesses) of regional volume. For this reason, such calculations

are not presented. However,if the range of regional gas tensions was less than that found by West, resulting overall alveolar-arterial gas tension differences must also be smaller. If such regional measurement cannot account for observed inefficiencies of gas exchange due to $\dot{V}_A/\dot{Q}$ variation, it follows that in normal subjects there are non-regional variations in $\dot{V}_A/\dot{Q}$ which are significant. This is supported by the work of Lenfant[32] and Farhi[26] who have demonstrated the presence of units with $\dot{V}_A/\dot{Q}$ far below those measured on a regional basis. Farhi has also demonstrated units with $\dot{V}_A/\dot{Q}$ higher than those found on regional study, but these units could constitute regions at the extreme lung apex which is inaccessible to present measurement. Extrapolation of the curves of Fig.23 and Fig.25 to the extreme apex would indicate these units had very high $\dot{V}_A/\dot{Q}$ and $\dot{V}_e/\dot{Q}$.

In summary, steady state regional $\dot{V}_A/\dot{Q}$ were measured in 4 seated normal subjects: $\dot{V}_A/\dot{Q}$ at the apex was high (1.5 - 1.8) and decreased progressively down the lung to the base (0.50 - 0.80). Regional ventilation per unit volume increased from apex to base, indicating that regional perfusion must have increased even more sharply from apex to base. These results are in qualitative agreement with those of other studies. However, the present experiments showed less apex to base variation in $\dot{V}_A/\dot{Q}$ than that derived from single breath tests using $C^{15}O_2$. This was, in large part, due to reinspiration of dead space gas during the steady state experiments, a factor not present in the work with $C^{15}O_2$. An attempt was made to quantitate the effect of reinspired dead space gas and regional $\dot{V}_e/\dot{Q}$ calculated. "$\dot{V}_e$" represents total alveolar ventilation; $\dot{V}_e/\dot{Q}$ are better indices of gas exchange than $\dot{V}_A/\dot{Q}$, where "$\dot{V}_A$" represents ventilation exclusive of reinspired dead space gas. Regional gas

tensions were calculated from regional $\dot{V}_e/\dot{Q}$; regional variations in gas tension were not large enough to explain all the $\dot{V}_A/\dot{Q}$ dependent inefficiency of gas exchange in normal subjects. It is concluded, then, that normal subjects must have significant non-regional inhomogeneities of $\dot{V}_A/\dot{Q}$ and $\dot{V}_e/\dot{Q}$.

2. PNEUMONECTOMY

After one lung is removed, the remaining lung receives the entire cardiac output, which is unchanged[78]. When the remaining lung is normal, post pneumonectomy patients afford an excellent opportunity to study the effects of an increase in blood flow through the lung in the absence of complicating cardiac lesions, drugs and neurohumors.

We have studied four subjects having one normal lung; all were examined 10 - 14 days after pneumonectomy, before the remaining lung expanded and crossed the midline (Fig. 28). The patients had all undergone pneumonectomy as treatment for lung cancer. Clinical characteristics and pulmonary function tests are noted in Table 4. With the exception of patient AR, all these tests were normal. It was thought that the high residual volume present in this patient was due to his tumor, which also involved his chest wall. He was included in this series because his regional function was similar to that of the other patients. At the time they were studied, all patients appeared to be in fairly good shape, but it became apparent after the studies that JC had been anemic (hemoglobin = 9.5 gm%) and that AR had had a wound infection. The other two subjects, GD and PB, recovered from surgery uneventfully.

The patients were studied while seated erect, with six counters ranging from apex to base of the remaining lung. Regional $\dot{V}_A/\dot{Q}$ were measured using eq. III-7; no attempt was made to take account of the effect of reinspired dead space. Regional $T_{\frac{1}{2}}$ were measured after both rebreathing and infusion. Regional perfusion distribution was assessed by measuring, as perfusion indices, regional perfusion per alveolus ($\dot{Q}_{Tal}$).

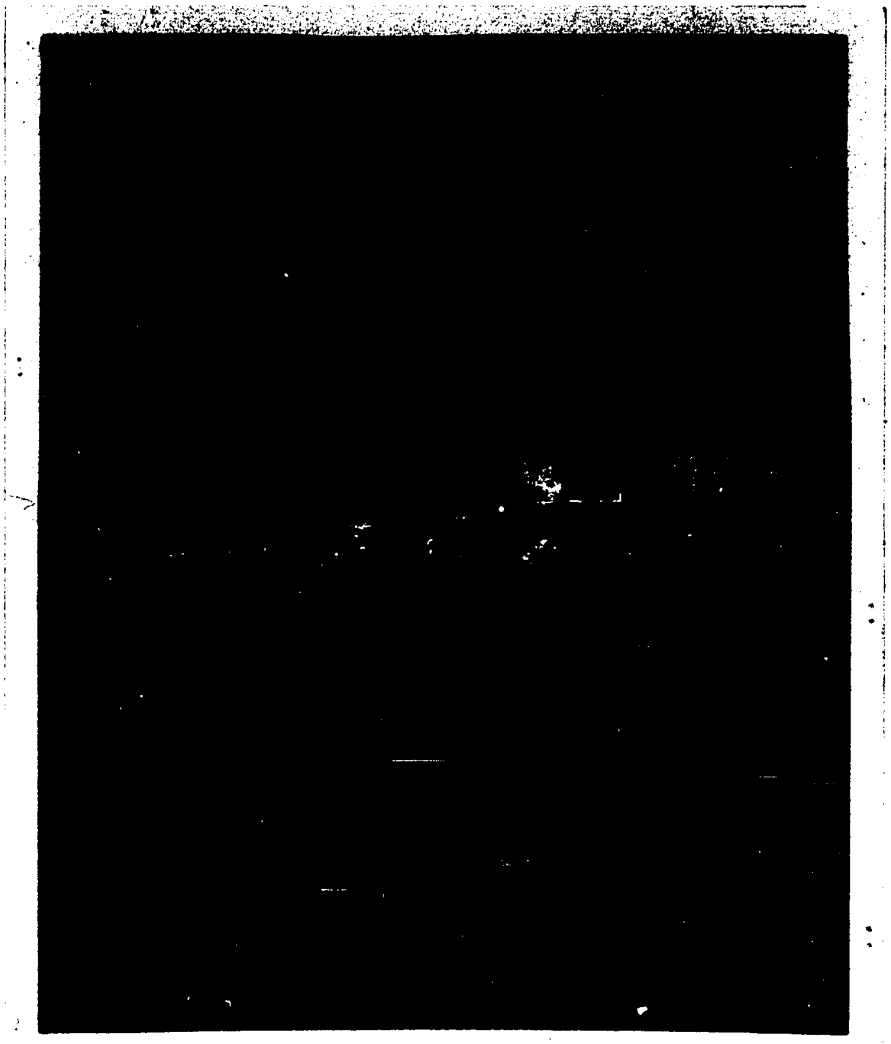


Fig. 28. Chest x-ray of patient P.B., done the same day as the ^{133}Xe study. The left hemithorax is filled with fluid, and the mediastinum is shifted slightly to the right, toward the remaining lung.

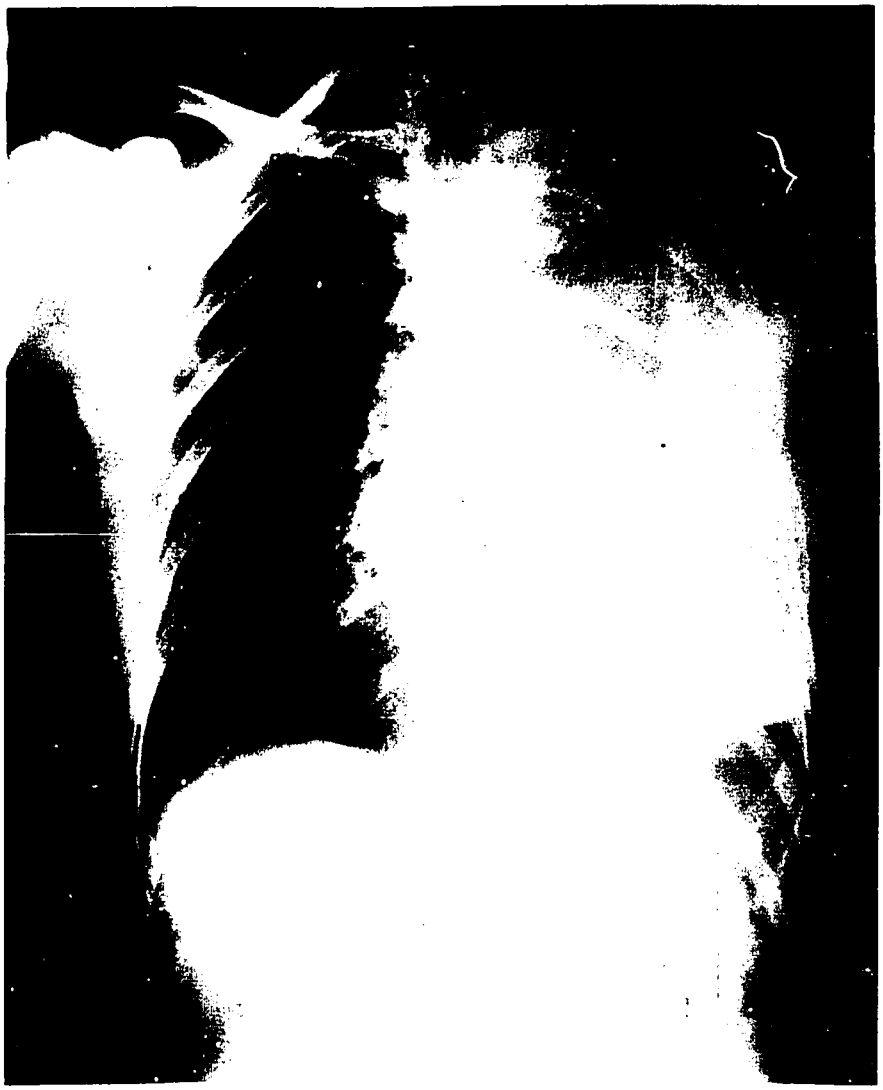


TABLE 4 - ROUTINE PULMONARY FUNCTION TESTS IN SUBJECTS WITH ONE NORMAL LUNG

(Predicted normal values for subjects with two lungs in parentheses)

Patient	VC (L)	RV (L)	MMFR L/Sec	$FEV_{0.75}$ (L)	ME (%)	$D_{L_{CO}}$ ml/min/mmHg
GD	3.24	1.22	3.38	2.50		24.3
	(3.14)	(1.78)	(2.50)	(1.78)		(12.1)
PB	1.25	0.86	1.06	.85	58	7.6
	(2.64)	(1.36)	(2.61)	(1.85)	(57)	(19.8)
JC	3.50	2.09	3.50	2.69	56	19.2
	(4.05)	(2.01)	(3.39)	(2.62)	(53)	(16.5)
AR	2.96	3.72	4.20	2.10	42	21.9
	(4.06)	(2.32)	(3.07)	(2.35)	(50)	(14.1)

[a] These studies were carried out after pneumonectomy. In the other subjects, tests were done before surgery.

Before considering perfusion distribution in patients after pneumonectomy, we must review the regional distribution of perfusion in erect subjects with two normal lungs. As previously noted, early studies with radioactive gases showed that the lung apices were much less perfused than were the bases[52,55]. The mechanical bases for this phenomenon have been beautifully elucidated by Permutt[79] and West[80]. They pointed out that since pulmonary vascular pressures are low and the lungs large, hydrostatic factors play an important role in defining local or regional pressures. Further, the small pulmonary vessels are exposed to intrapulmonary or alveolar pressure which is not subject to hydrostatic considerations, i.e., it is the same throughout the lung. When these principles were combined with the very reasonable assumption that small pulmonary vessels (capillaries) are unstable with flaccid walls, the lung model shown in Fig. 29 resulted. This figure depicts an isolated dog lung which is perfused from the artery to the vein. Pulmonary artery (P_a) and pulmonary venous (P_V) pressures are indicated by their respective manometers. Because of the laws of hydrostatics, these pressures increase about 1 cm H_2O per cm descent down the lung. Alveolar pressure (P_A) is atmospheric and the same throughout the lung. Under the conditions shown P_a is not high enough to perfuse the lung top. Accordingly above the level where $P_a=0$, $P_A > P_a$ and no flow occurs (Zone I). Below this is a zone in which $P_a > P_A > P_V$ (Zone II). Under these circumstances, the capillary functions as a Starling resistor, i.e., flow is proportional to the difference between arterial and alveolar pressure ($P_a - P_A$). Venous pressure does not influence flow[79]. Since P_a increases with descent down the lung and P_A does not, flow increases rapidly. Finally at the base $P_a > P_V > P_A$ (Zone III). The capillary is widely

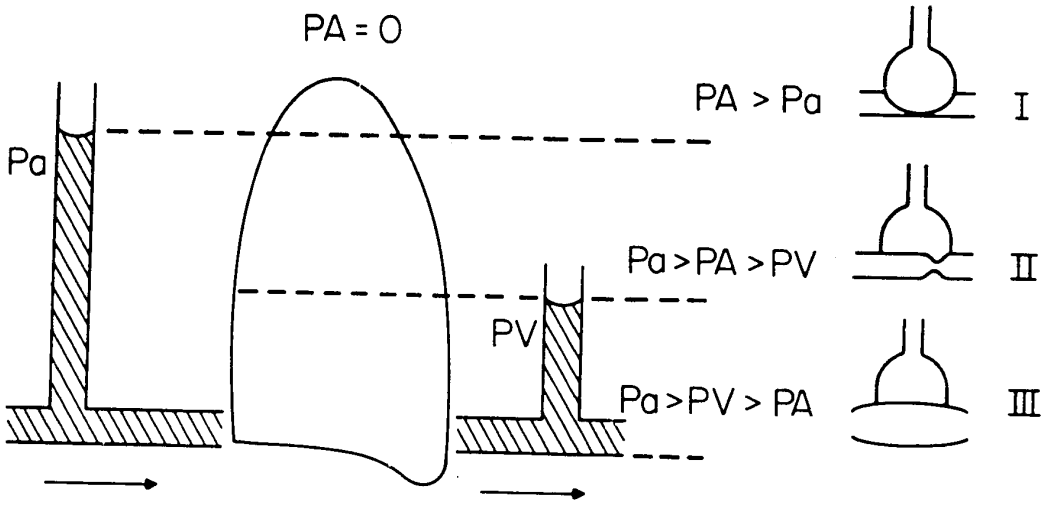


Fig. 29. Model of pulmonary blood flow distribution (after West). The lung on the left is perfused from artery to vein at the pressures (Pa and Pv) indicated by the manometers. Alveolar pressure (PA) is atmospheric throughout the lung. The configuration of collapsible blood vessels is shown schematically on the right. The top of the lung is higher than Pa so in this area PA>Pa, capillaries are squeezed flat and there is no flow; this is Zone I. Below this, in Zone II, Pa> PA> Pv and the capillaries develop constricted segments at their downstream ends and function as Starling resistors, flow being proportional to the arterial-alveolar pressure difference (Pa - PA). At the bottom of the lung, in Zone III, Pa> Pv> PA; the capillaries are distended and flow is proportional to the arteriovenous pressure difference (Pa - Pv).

opened and the arteriovenous pressure difference (P_a-P_V) governs flow. Since this is independent of height, any further increase in flow at the base must be due to distention of vessels.

Fig. 30 shows perfusion distribution at FRC in three normal subjects[56]. These plots show a striking resemblance to predictions based on Fig. 29 with three well-marked zones. Further, estimates of P_a (Zone I - Zone II junction) and P_V (Zone II-Zone III junction) agreed reasonably well with directly measured pulmonary artery and pulmonary wedge pressures. It may be concluded then that the model of Permutt and West applies rather well to the intact human.

Fig. 31 shows regional perfusion distribution in three subjects after pneumonectomy. Two kinds of curves were evident: patients PB and GD showed distinct Zones II and III but do not show a Zone I. Patients JC (not shown in Fig. 31) and AR showed rather even distribution of blood flow from apex to base, without obviously separate zones. The regional flow patterns seen in GD and PB were interpreted as resulting from an increase in pulmonary artery pressure - the junction of Zones I and II was above the lung apex as opposed to below it as was the case in the subjects shown in Fig. 30. Subjects AR and JC, on the other hand, did not show flow patterns which could be separated into zones; it appeared that either the whole lung was in Zone III or that the slope of Zone II was such that the junctions of Zones II and III were not discernable. These two patients were studied at a time when their cardiac outputs may well have been increased due to anemia and wound infection and their relatively even distribution of blood flow may have been due to this factor.

Whatever the differences among these four subjects, the lung apices of all of them were perfused while similar studies in subjects with two normal

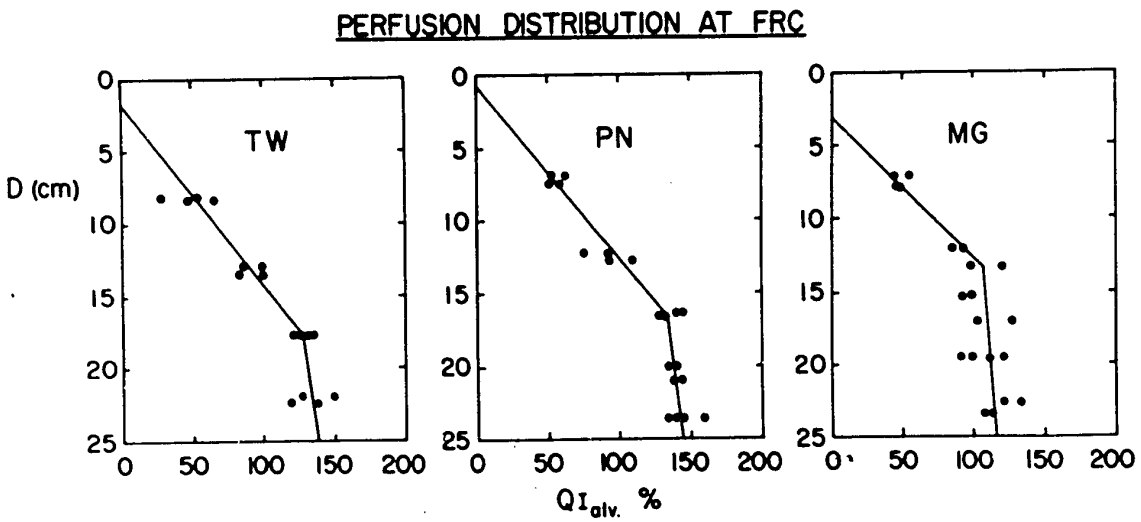


Fig. 30. Perfusion distribution in erect normals with two lungs. Ordinates: distance from lung apex (0 cm) to base (25 cm). Abscissae: Perfusion per alveolus. If perfusion were evenly distributed $\dot{Q}_{Ialv}$ would be 100 in all lung regions.

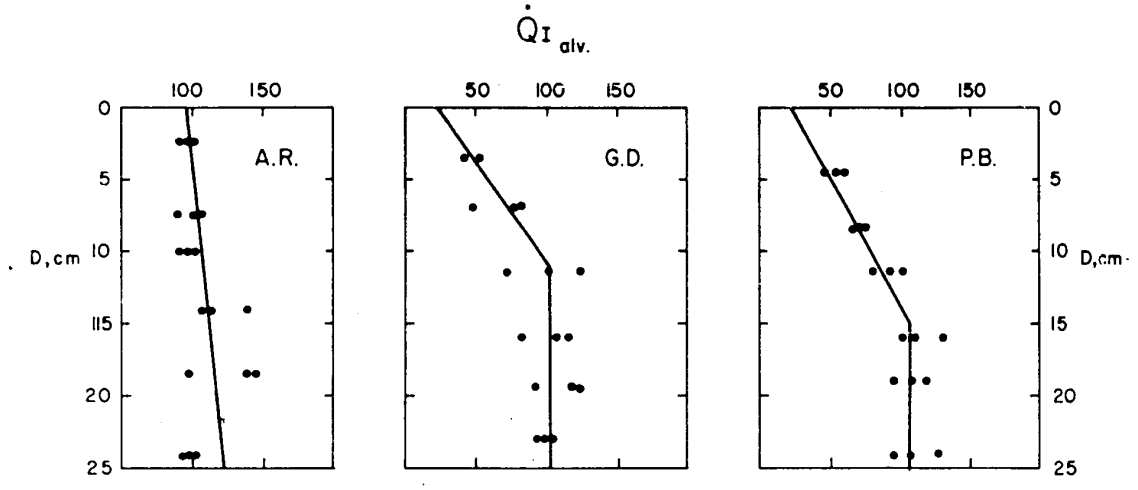


Fig. 31. Perfusion distribution in erect subjects with one normal lung. Ordinates: distance from apex (0 cm) to base (25 cm). Abscissae: perfusion per alveolus. These results are compared with those shown in Fig. 30 (see text).

lungs showed an absence of apical perfusion. A consistant result, then, of pneumonectomy is an increase in perfusion of the apex of the remaining lung. Presumably, this was due to the fact that flow through this lung was doubled by pneumonectomy, with a resulting rise in pulmonary artery pressure.

Regional $\dot{V}_A/\dot{Q}$ measured in these four subjects are shown in Fig. 32, which may be compared with the results of similar measurements in subjects with two normal lungs shown in Fig. 23. The curves of Fig. 32 vary: PB and GD, who showed zonal patterns of perfusion distribution, demonstrated relatively high apical $\dot{V}_A/\dot{Q}$ which decreased down the lung to a minimum some 15-20 cm. below the apex and then rose again as the base was approached. Patients AR and JC who showed relatively even perfusion distribution, also showed relatively small differences in regional $\dot{V}_A/\dot{Q}$; apical $\dot{V}_A/\dot{Q}$ were slightly lower than those at the base. The regional distribution of $\dot{V}_A/\dot{Q}$ in all four patients were consonant with their perfusion distribution if it was assumed that in each, regional ventilation increased down the lung. In any event, regional differences in $\dot{V}_A/\dot{Q}$ were less striking in the four patients studied after pneumonectomy than in normals with two lungs. This was largely due to decreased apical $\dot{V}_A/\dot{Q}$ relative to those of the remainder of the lung.

We may conclude, then, that when pulmonary blood flow was doubled, regional perfusion distribution became more even as did the regional distribution of $\dot{V}_A/\dot{Q}$. Regional gas tensions, therefore, showed less variation from apex to base in subjects after pneumonectomy than in subjects with two normal lungs. Since it has been said that ventilation distribution is dependent on regional gas tensions[81], we might expect that ventilation distribution would

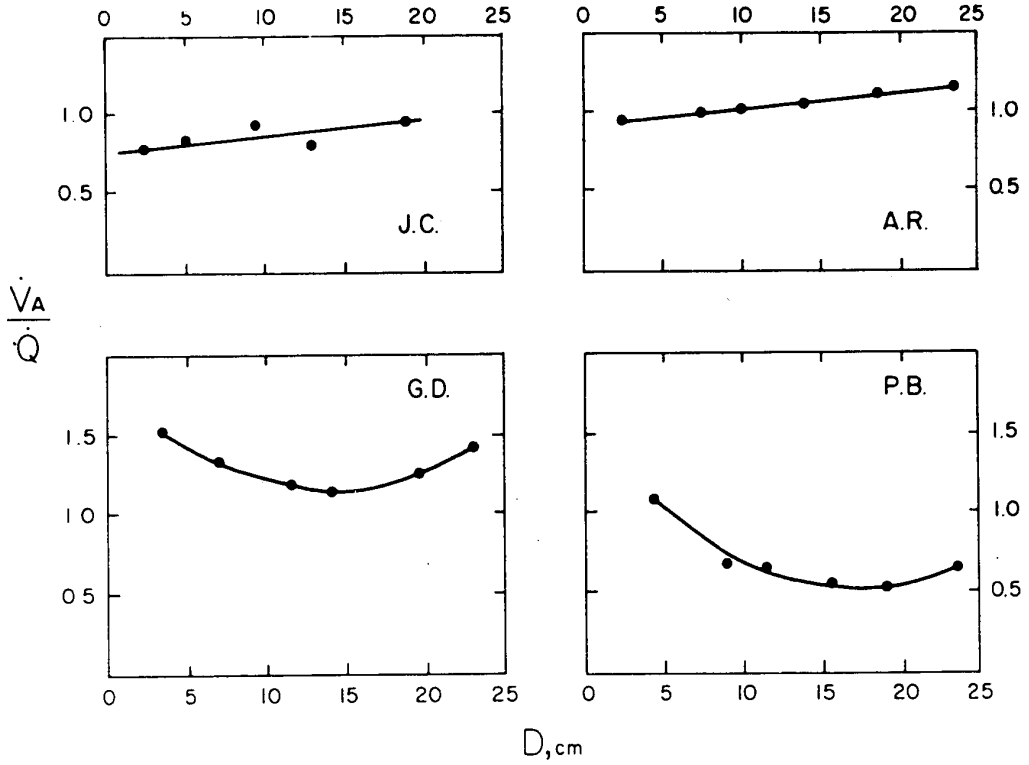


Fig. 32. Regional $\dot{V}_A/\dot{Q}$ in four erect subjects with one lung which was normal. Ordinates: regional $\dot{V}_A/\dot{Q}$ (eq III-7). Abscissae: distance from lung apex (0 cm) to base (25 cm). Compare these results with those of Fig. 23.

also become more even after pneumonectomy. Fig. 33 illustrates that such was not the case. Regional ventilation per unit volume (reciprocal of $T\frac{1}{2}$) from these four subjects were compared to similar data from subjects with two normal lungs. When allowance was made for the fact that there was a two-fold difference in FRC between the two groups, the regional distributions of ventilation appeared identical.

In summary, study of patients after pneumonectomy in whom the remaining lung was normal afforded an opportunity to examine the regional effect of a large increase in pulmonary blood flow. Such patients demonstrated decreased apex to base differences in perfusion, suggesting that pulmonary artery pressure was increased. In addition, apex to base variations of $\dot{V}_A/\dot{Q}$ and of respiratory gas tensions were reduced. In spite of these changes, the regional distribution of ventilation appeared to be unaffected by pneumonectomy. These results are entirely explicable on the basis of the mechanical models of Permutt[79] and West[80] which predict perfusion distribution and the mechanical model of Milic Emili et al[63] which predicts the regional distribution of ventilation.

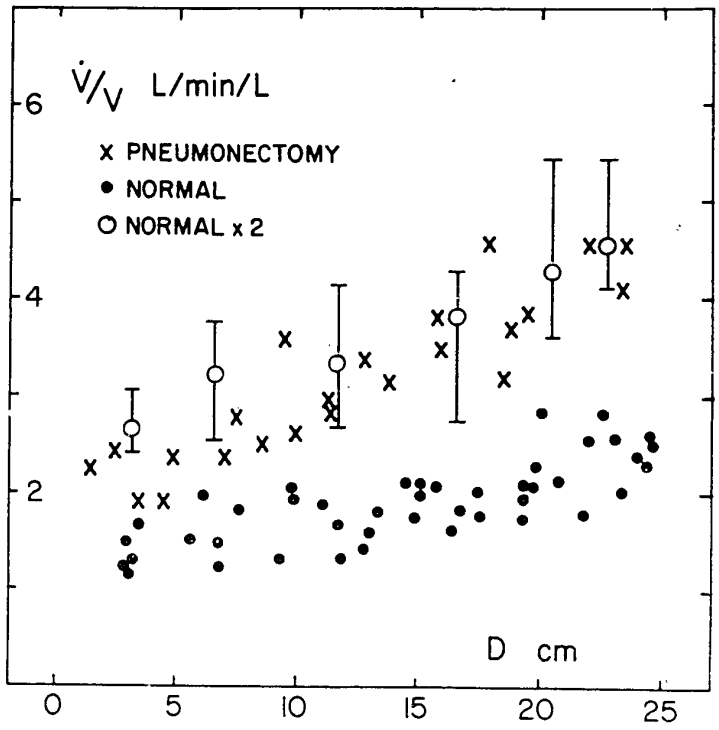


Fig. 33. Distribution of regional ventilation after pneumonectomy. Ordinate: regional ventilation per unit volume measured from regional washout curves. Abscissa: distance down the lung (top = 0 cm). Crosses (x) represent subjects with one normal lung. Dots (•) are subjects with two. In order to correct for differences in FRC, data from normals with two lungs were multiplied by two. Resulting mean values are shown by open circles (o); the brackets show the range of these values.

3. PULMONARY EMBOLISM

Gas exchange in patients with pulmonary embolism is, at present, imperfectly understood. This is, in large part, due to difficulties in establishing a diagnosis; it is common to diagnose embolic disease on the basis of fragmentary or equivocal evidence. Because of this, uncertainty exists regarding the incidence, natural history and pathophysiology of this disease. Though embolic disease would appear to lend itself to study with radioactive gases, very few studies of this type have been completed. Indeed, an alternate isotopic method for evaluating regional perfusion distribution has recently been developed and applied extensively in patients with pulmonary embolism, with gratifying results[82]. The method employs human serum albumin tagged with ^{131}I. By adjusting the pH of the albumin solution, the albumin can be made to form aggregates of a size such that they do not pass through the pulmonary circuit but will temporarily embolize the microcirculation. If a region receives no flow then it receives no albumin and shows decreased radioactivity when the lungs are scanned by radiation detectors. This technique is simple, does not require highly specialized equipment, and its importance as a diagnostic aid can hardly be overemphasized. It does, however, have drawbacks. It is difficult to quantitate the results of studies with macroaggregates; an area may be cold because it has relatively little perfusion or simply because there is relatively little lung tissue in the area. A second problem with ^{131}I tagged macroaggregates is that they do not assess ventilation. This is not usually important for clinical purposes, but ventilation distribution in pulmonary embolism is a question of considerable interest.

If the blood flow to a region is stopped completely, that region or part of it become dead space, and an alveolar-arterial CO_2 difference will develop[29]. Measurement of alveolar-arterial CO_2 difference has been proposed as a diagnostic test for pulmonary embolism,[28] but, in practice, this test has proved disappointing. It has been suggested that this is because lung regions which are embolized are also hypoventilated. Experiments using autologous blood clot emboli in animals have suggested that embolized areas of lung decrease their ventilation[27]. Temporary unilateral pulmonary artery obstruction may be induced with balloons introduced on the end of a cardiac catheter; normal subjects undergoing this procedure may decrease the ventilation on the obstructed side[83]. This hypoventilation may be relieved by having the affected lung inhale CO_2, suggesting that the initial hypoventilation was secondary to hypocapnia. Indeed, overall hypocapnia induced by hyperventilation has been shown to increase overall airway resistance[84]. Thus, there is considerable indirect evidence favoring the possibility that regions affected by pulmonary emboli decrease their ventilation; in terms of gas exchange this would be a helpful homeostatic mechanism.

Studies with ^{133}Xe were carried out to elucidate this problem as well as to demonstrate the efficacy of the method in locating pulmonary vascular obstructions.

Seven patients who had experienced pulmonary embolism two or more days previously were studied (Table 5). None of the patients were critically ill at the time of the study. ^{133}Xe study included measurement of regional perfusion distribution ($\dot{Q}_T$), regional ventilation distribution ($T_{\frac{1}{2}}$) and regional $\dot{V}_A/\dot{Q}$ (eq.III-7). Cardiac outputs were not measured, normal values for the

TABLE 5 - PATIENTS WITH PULMONARY EMBOLISM

Patient NO.	Age	Sex	Diagnosis on admission to hospital	Other conditions	Studies of regional lung perfusion
1	64	F	Fulmonary hypertension; right heart failure	Carcinoma of breast; radical mastectomy; metastases in bones	Pulmonary arteriography;
2	58	M	Pulmonary emboli	None	^{131}I lung scan;
3	45	M	Pulmonary emboli	None	^{131}I lung scan
4	70	F	Pulmonary emboli	Leiomyosarcoma of inferior vena cava	^{133}necropay
5	45	F	Carcinoma of vulva	(Postoperative state) Pulmonary infarction	^{131}I lung scan;
6	29	F	Fracture of right hip	(Postoperative state) Multiple sclerosis; chronic bronchitis	^{131}I lung scan;
7	57	M	Pulmonary emboli	Carcinoma of transverse colon; chronic bronchitis; phlebitis	

cardiac output being assumed. As noted earlier, absolute levels of $\dot{V}_A/\dot{Q}$ vary as different cardiac outputs are assumed, but this does not change relationships among regional $\dot{V}_A/\dot{Q}$.

Six of the seven patients underwent routine pulmonary function tests; such tests were impossible in one patient (no. 4) who died 48 hours after the ^{133}Xe studies. The routine function tests were completed within one week of the ^{133}Xe except in the case of patient 7 who was tested one month after the ^{133}Xe studies.

Confirmatory diagnostic studies of a specific nature were available in six of the seven patients (Table 5): four had lung scans after injections of albumin macroaggregates tagged with ^{131}I, one underwent pulmonary angiography, and the patient who died was autopsied. These confirmatory investigations were all carried out within 2 days of the ^{133}Xe studies. Patient 7 had phlebitis and his clinical picture and laboratory findings were typical of pulmonary embolism.

Unfortunately, pulmonary emboli commonly occur in patients who have other disease. The present series was no exception to this rule; Table 5 lists the other pathological conditions present in these patients. The problems introduced by associated disease are illustrated by the results of the routine pulmonary function tests, shown in Table 6. None of the patients demonstrated normal pulmonary function, but only in patients 2 and 3 could the results be ascribed to pulmonary embolism per se. Patient no. 1 was obese and had a radical mastectomy scar which may have limited ventilatory function. Patient no. 5 had pulmonary infarction with pleural effusion and pleuritic chest pain. Patient no. 6 had multiple sclerosis with muscular weakness.

TABLE 6 - ROUTINE PULMONARY FUNCTION TESTS IN PATIENTS WITH PULMONARY EMBOLISM
(Predicted normal values are in parentheses)

Patient	Vital capacity	Functional residual capacity	Residual volume	Mixing efficiency	Forced expiratory volume 0.75 sec	Maximal midexpiractory flow rate	Diffusing capacity
	(litres)	(litres)	(litres)	%	(litres)	(litres/sec)	(ml/min/mm Hg)
1	1.95 (2.87)	2.57 (2.67)	2.06 (1.65)	56 (50)	1.02 (1.68)	1.32 (2.40)	12.5 (11.8)
2	3.49 (3.10)	1.50 (2.98)	1.23 (1.87)	57 (50)	2.40 (2.03)	2.80 (2.77)	19.9 (13.0)
3	2.78 (4.05)	2.71 (3.48)	1.76 (2.01)	67 (55)	2.01 (2.68)	2.60 (3.39)	12.4 (16.5)
4[x]							
5	1.84 (3.05)	2.67 (2.41)	1.57 (1.57)	63 (55)	1.35 (1.88)	2.07 (2.80)	10.3 (14.3)
6	1.78 (3.15)	1.79 (2.43)	1.59 (1.28)	53 (65)	0.75 (2.20)	0.95 (3.40)	13.3 (18.9)
7	3.68 (4.70)	4.08 (4.25)	3.02 (2.62)	59 (50)	2.35 (2.58)	2.05 (3.72)	17.1 (14.8)

[x] Not studied

In addition, patient nos.6 and 7 were cigarette smokers with histories suggestive of chronic bronchitis; expiratory flow rates were grossly impaired in no. 6 and the maximum midexpiratory flow rate was depressed in patient no. 7.

In short, on the basis of these results, very little may be said regarding the effect of pulmonary embolism on overall pulmonary function. It can certainly be stated that embolism does not necessarily decrease the diffusing capacity for CO ($D_{L_{CO}}$), a test of (among other things) the integrity of the pulmonary capillary bed. A tentative conclusion also might be that pulmonary embolism depresses the vital capacity (VC), for this measurement produced subnormal results in all our patients. Both of these conclusions are supported by other data[9d].

The results of the ^{133}Xe studies are presented in Table 7. For the purposes of interpretation, we have defined $\dot{Q}_T = 75$ as the lower limit of normal and have designated lung regions normal or abnormal by this criterion. It should be pointed out that this limit is probably conservative; it may well be that regions with slightly higher $\dot{Q}_T$ were abnormally perfused. Changing the lower limit of normal to another value of $\dot{Q}_T$ would in no way alter the conclusions to be drawn from Table 7.

In general, 5 counters were positioned over each lung; in Table 7, counters are numbered from apex to base - counter R_1 was at the right apex, counter L_5 at the left base. Regional washouts are presented in terms of $T\frac{1}{2}$, the time necessary for regional count rates to fall to one-half of their pre-washout values. Since $T\frac{1}{2}$ measured after rebreathing did not differ from those measured after infusion, the $T\frac{1}{2}$ of Table 7 are the mean of the values obtained after both procedures.

TABLE 7. ^{133}Xe STUDIES IN PATIENTS WITH PULMONARY EMBOLISM

Patient	Time since embolism		Right Lung (apex) R_1	R_2	R_3	R_4	Right Lung (base) R_5	Left Lung (apex) L_1	L_2	L_3	L_4	Left Lung (base) L_5
1	3 months	$\dot{V}_A/\dot{Q}$	2.25	2.10	2.61	2.07	2.89	1.68	1.84	0.78	0.77	0.94
		$\dot{Q}_I$	31	69	40	68	41	50	43	111	176	131
		$T_{\frac{1}{2}}$	23	25	26	24	30	27	15	16	28	28
2	27 days	$\dot{V}_A/\dot{Q}$	0.98	0.84	0.91	0.89	0.98	1.00	0.84	1.36	2.68	2.61
		$\dot{Q}_I$	82	122	116	102	130	106	108	104	60	46
		$T_{\frac{1}{2}}$	34	24	32	20	38	38	38	32	20	40
3	2 months	$\dot{V}_A/\dot{Q}$	1.01	1.75	1.35	0.89	0.93	0.60	0.62	0.73	0.58	0.60
		$\dot{Q}_I$	42	29	34	48	48	87	84	79	81	79
		$T_{\frac{1}{2}}$	38	35	31	39	39	35	31	31	35	39
4	7 days	$\dot{V}_A/\dot{Q}$	1.03	1.08	1.51	0.82	n.s.*	1.28	1.08	1.63	1.98	1.72
		$\dot{Q}_I$	50	83	66	83		55	46	53	36	40
		$T_{\frac{1}{2}}$	24	20	20	18		22	28	20	12	18
5-A	3days	$\dot{V}_A/\dot{Q}$	1.34	1.34	1.00	1.26	n.s.	1.07	0.97	0.99	0.99	n.s.
		$\dot{Q}_I$	72	73	99	50		89	93	109	110	
		$T_{\frac{1}{2}}$	22	28	21	64		17	25	24	30	
5-B	22 days	$\dot{V}_A/\dot{Q}$	0.88	0.99	0.95	1.18	1.00	1.05	0.88	1.04	0.97	1.03
		$\dot{Q}_I$	80	93	76	48	24	85	107	92	127	90
		$T_{\frac{1}{2}}$	29	28	24	37	59	22	16	20	24	34
6	13 days	$\dot{V}_A/\dot{Q}$	0.89	0.98	1.03	0.98	0.63	0.95	0.96	0.94	0.86	1.28
		$\dot{Q}_I$	74	81	80	84	84	88	77	94	60	44
		$T_{\frac{1}{2}}$	57	33	29	42	88	33	35	31	65	47
7	2 days	$\dot{V}_A/\dot{Q}$	1.43	0.89	0.93	1.15	n.s.	2.46	1.95	1.40	1.53	1.78
		$\dot{Q}_I$	68	106	85	56		50	43	79	55	56
		$T_{\frac{1}{2}}$	24	24	59	54		16	30	54	82	52

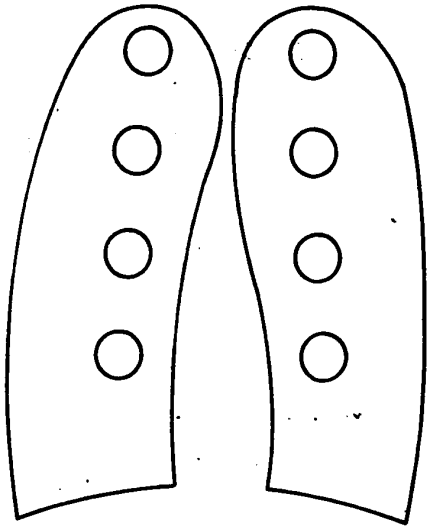
*not studied. Values from regions which were hypoperfused ($\dot{Q}_I$<75) are underlined

Patients nos. 1-4 demonstrated distinct areas of hypoperfusion which varied in extent from 2 regions (No. 2) to seven regions (No. 1). In patient no. 1 the left apex and the entire right lung were under-perfused; this finding was confirmed by pulmonary angiography. Patient no. 2 showed hypoperfusion at the left base both on ^{133}Xe studies and on ^{131}I lung scan. Perfusion of the entire right lung was curtailed in the case of patient no. 3, a finding also supported by ^{131}I scan. Patient no. 4 showed normal $\dot{Q}_I$ only in regions R_2 and R_4; at autopsy 48 hours after the ^{133}Xe study multiple emboli were found in the left lung but none in the right. In each of these patients, regional $\dot{V}_A/\dot{Q}$ were high in regions with $\dot{Q}_I > 75$, and $T\frac{1}{2}$ were short and did not appear to vary from region to region in the same patient. Ventilation per unit volume appeared to be unaffected by regional differences in blood flow per unit volume.

Patient no. 5 was studied twice (Fig. 34), once 3 days and again 22 days after her embolic episode. This patient had a pulmonary infarction at the right base (Table 7, study 5A, counter R_4; study 5B, counters R_4 and R_5) on both occasions. Infarcted regions showed decreased perfusion, prolonged $T\frac{1}{2}$ and high $\dot{V}_A/\dot{Q}$. At the time of the first study, apical regions of the right lung (R_1 and R_2) demonstrated decreased $\dot{Q}_I$ and high $\dot{V}_A/\dot{Q}$; $T\frac{1}{2}$, however, were similar to those measured in the normal opposite lung. At the time of the second study, blood flow to the right apex had increased to normal levels, $\dot{V}_A/\dot{Q}$ had decreased and $T\frac{1}{2}$ was unchanged. In this patient, it appeared that in the absence of infarction, ventilation distribution was independent of perfusion distribution.

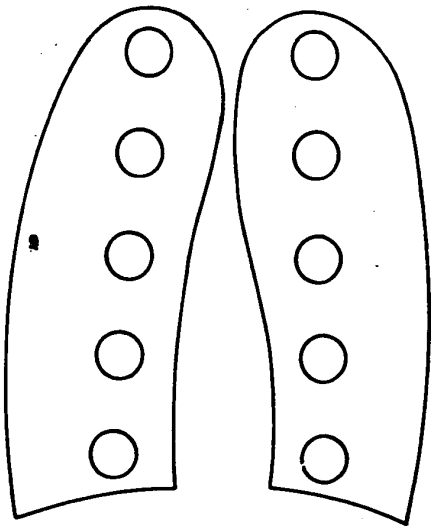
Fig. 34. Sequential ^{133}Xe studies in patient 5. The circles in each lung field are schematic representations of the counter positions, and figures relevant to each counter are shown beside it. The upper part of the figure shows data gathered 48 hours after clinical embolization, and the lower part of the figure shows data acquired two weeks later. See text for discussion.

$T_{1/2}$	$\dot{Q}_I$	$\dot{V}_A/\dot{Q}$
22	·72	1·34
28	·73	1·34
21	·99	1·00
64	·50	1·26



$\dot{V}_A/\dot{Q}$	$\dot{Q}_I$	$T_{1/2}$
1·07	·89	17
·97	·93	25
·99	1·09	24
·99	1·10	30

$T_{1/2}$	$\dot{Q}_I$	$\dot{V}_A/\dot{Q}$
29	·80	·88
28	·93	·99
24	·76	·95
37	·48	1·18
59	·24	1·00



$\dot{V}_A/\dot{Q}$	$\dot{Q}_I$	$T_{1/2}$
1·05	·85	22
·88	1·07	16
1·04	·92	20
·97	1·27	24
1·03	·90	34

Patients nos. 6 and 7 each had chronic airway disease in addition to pulmonary embolism. Patient no.6 demonstrated decreased perfusion at the right apex and left base on ^{131}I lung scan. On ^{133}Xe study, $T\frac{1}{2}$ was prolonged in R_1, R_5 and L_4 (Table 7). In region R_1 perfusion was slightly depressed and $\dot{V}_A/\dot{Q}$ normal, and it is not certain whether the borderline blood flow in this region was due to embolism or bronchitis. In region R_5, $T\frac{1}{2}$ was long, $\dot{Q}_I$ was normal and $\dot{V}_A/\dot{Q}$ low -- this region's malfunction may be ascribed to bronchitis. Perfusion was decreased in both L_4 and L_5, $T\frac{1}{2}$ was definitely prolonged in L_4 and questionably so in L_5. However, regional $\dot{V}_A/\dot{Q}$ was high in L_5. Regions showing more striking curtailment of perfusion than ventilation, i.e., regions with high $\dot{V}_A/\dot{Q}$ have not been encoutered in bronchitis per se (see below). At least some of the hypoperfusion present in L_4 and L_5 was therefore probably due to embolic obstruction. These regions, then, were likely the site of both bronchitis and pulmonary embolism. Patient no. 7 had prolonged $T\frac{1}{2}$ in R_3, R_4, L_3, L_4 and L_5. Not all of these regions were hypoperfused and three other regions (R_1, L_1, L_2) demonstrated low $\dot{Q}_I$ and normal $T\frac{1}{2}$. Thus, though these two patients demonstrated some regions with decreased ventilation and some regions with decreased perfusion, one phenomenon was not generally associated with the other; there was no evidence of a systematic shift in ventilation away from hypoperfused regions.

The ^{133}Xe method appeared to be an efficient one for locating pulmonary emboli. In this regard, the results of the ^{133}Xe studies were the same as those of other tests of blood flow distribution, except in patient no. 4. This patient showed no emboli in the right lung at autopsy 48 hours after ^{133}Xe studies demonstrated hypoperfusion in several areas on the right side.

These two results are not necessarily contradictory however. Resolution of pulmonary emboli within a 48 - hour period is known to occur [85,86].

This study indicated that there was no significant shift of ventilation away from embolized areas 48 hours after the embolic episode. As noted above, such a shift has been postulated on the basis of other studies and a variety of mechanisms for the shift suggested. Both humans and dogs develop bronchoconstriction after autologous thromboemboli[87,88]. It is very likely that this effect is due to circulating agents such as serotonin which are released by the embolic material[87]. However, this bronchoconstriction is too severe to be local, and is too transient to influence ventilation distribution 48 hours after the embolic episode. There is some rather equivocal evidence that extracts of embolized lungs have high surface tensions[89]. If this were the case, such areas would have decreased ventilation. The possibility of such changes in pulmonary surfactant awaits further investigation.

As discussed above, there is excellent evidence that hypocapnia has a bronchoconstrictor effect. Humans have been shown to reduce the ventilation of one lung when its artery is occluded and this shift in ventilation may be reversed by CO_2 inhalation[83]. These data are not necessarily in conflict with our results however. Bronchoconstriction has been demonstrated only in fairly severe hypocapnia-at $P_{A_{CO_2}} < 25$ mmHg[84]. When the $\dot{V}_A/\dot{Q}$ data of Table 7 were applied to the O_2-CO_2 diagram it became apparent that the P_{CO_2} of embolized regions were probably not less than 25 mmHg. This estimate required an assumption regarding absolute $\dot{V}_A/\dot{Q}$ which depended on cardiac output, not measured in these patients. However, given the interregional variation in $\dot{V}_A/\dot{Q}$ demonstrated by these patients, regional $P_{A_{CO_2}} < 25$ mmHg would have been possible only if $\dot{V}_A/\dot{Q}$ of non-embolized regions had been in excess of 2.0. This was most unlikely.

The above argument assumed that units within each single lung region behaved in nearly identical fashion. Obviously, this cannot have been the case in all instances. However, in some patients, notably nos. 1 and 2, the areas affected by emboli were considerably larger than the counter fields which observed their behavior. Further, if all the hypoperfused lung regions observed in this study were in fact composed of some units which were normally perfused and others with very little or no perfusion, then important segments of these regions must have had very high $\dot{V}_A/\dot{Q}$ indeed (> 5.0). Hypoventilation of such subregions on the basis of hypocapnia would then be expected, and this hypoventilation should have been reflected by prolonged regional washouts; such was not the case. In light of the above it was felt justifiable to treat embolized lung regions as if they were homogeneous.

The highest regional $\dot{V}_A/\dot{Q}$ noted were in the vicinity of 3.0, about three to four times the $\dot{V}_A/\dot{Q}$ of normal regions. These values were high but perhaps not as high as might have been anticipated. On the basis of these figures, it is unlikely that any of these patients would have developed an easily measurable alveolar-arterial CO_2 difference. This may be in part explained by arguing that the figures were in error, that because of inhomogeneities of function within single lung regions there were much larger $\dot{V}_A/\dot{Q}$ variations than those shown in Table 7. As discussed above, however, intraregional differences in function probably were not notable in this series, so other reasons must be sought for the relatively low $\dot{V}_A/\dot{Q}$ of embolized regions. One explanation might be that some perfusion was present distal to the embolic obstruction. It has been shown that distal perfusion may persist acutely[27] and the passage of time would tend to favor resolution of vascular obstruction. A second explanation is that these studies did not take into account the effect of reinspired

dead space gas. ^{133}Xe from the dead space was reinspired by all lung regions during both infusion and rebreathing. Because of this, differences among regional $\dot{V}_A/\dot{Q}$ are minimized unless the dead space effect can be quantitated. Such quantitation cannot be done with confidence in patients with lung disease, so the $\dot{V}_A/\dot{Q}$ of embolized regions must have been higher than the values recorded in Table 7. On the other hand, O_2 and CO_2 are reinspired from the dead space as well as ^{133}Xe. Indeed patients with pulmonary embolism characteristically have **tachypnea resulting in large amounts of dead space ventilation. If, for** example, one third to one half of the inspired ventilation originated in the dead space, gas concentrations in a single region could not approach those of room air, irrespective of the perfusion of the region. Thus, in embolized regions, gas concentrations consonant with very high $\dot{V}_A/\dot{Q}$ (as conventionally calculated) would not develop whether the gas considered were O_2, CO_2 or ^{133}Xe. This may account for the insensitivity of measurements of alveolar-arterial CO_2 differences in the diagnosis of pulmonary embolism.

It should also be pointed out that this study was not unique in failing to demonstrate that alterations in regional perfusion cause changes in regional ventilation. Both pneumonectomy (see above) and mitral stenosis[90] cause changes in regional perfusion distribution in humans; in both instances the regional distribution of ventilation is normal. Further, in the isolated dog lung, deliberate changes in perfusion distribution do not alter ventilation distribution[91].

To summarize, seven patients were studied with ^{133}Xe two or more days after an episode of pulmonary embolism. The ^{133}Xe method was efficient in locating emboli, detecting hypoperfusion in the same regions as did other studies of regional blood flow distribution. Embolized regions demonstrated

low $\dot{Q}_I$, high $\dot{V}_A/\dot{Q}$ and normal ventilation; there was no evidence favoring shifts of ventilation away from embolized regions. Regional differences in $\dot{V}_A/\dot{Q}$ were not extreme; the highest $\dot{V}_A/\dot{Q}$ in embolized regions being three to four times that of normal regions. These differences were such that shifts of ventilation on a hypocapneic basis would not have been expected. Persistence of some perfusion distal to embolic obstruction and the reinspiration of dead space gas were the probable explanations for the relatively minor changes in regional $\dot{V}_A/\dot{Q}$ which were observed.

4. BRONCHIECTASIS

Bronchiectasis, chronic pathological dilation of one or more bronchi, is diagnosed by bronchography which is essentially an examination of regional bronchial anatomy. Though the regional lesions of bronchiectasis have functional significance, their functional evaluation is rendered difficult by the fact that patients with bronchiectasis commonly have other lung disease[9e,92]. Thus, abnormalities in overall lung function tests are frequently difficult to attribute to bronchiectasis per se. Studies of regional function would be somewhat easier to interpret, and when combined with bronchography would allow correlation of regional structures with function.

We studied eight patients with proven bronchiectasis (Table 8). Five patients were female, three were male; the age range was from 19 to 61 years. All patients gave a history of chronic cough and sputum. In five instances, symptoms began after a childhood episode of pneumonia and another patient said his difficulties began when he aspirated a chicken bone (Table 8). Four subjects had been suspected of having other disease as indicated in Table 8.

All patients underwent an abbreviated battery of routine pulmonary function tests including: vital capacity (VC), the volume expired during the first second of a forced vital capacity ($FEV_{1.0}$), diffusing capacity (D_{LCO}) and, in some instances, mixing efficiency (ME).

^{133}Xe studies were performed as described in Section III. Regional $\dot{V}_A/\dot{Q}$ were computed without corrections for the effects of the dead space or recirculating ^{133}Xe. Cardiac output was measured except in patients 2, 3 and 7; normal values were assumed for these subjects. Regional $\dot{Q}_I$ were measured to evaluate perfusion and regional $T\frac{1}{2}$ were measured during washout from infusion

TABLE 8 - CLINICAL DATA IN PATIENTS WITH BRONCHIECTASIS

Patient Number	Sex & Age	Years Cough And Sputum	Predisposing Disease	Other Disease
1	Male 61	40	None	Chronic Bronchitis
2	Female 33	4	Bronchopneumonia Childhood. Recurrent lower respiratory tract infections.	None
3	Female 25	2	Pneumonia	None
4	Female 39	30	Cough and Wheezing since early childhood	"Bronchial Asthma" Otitis Media Latent Diabetes Mellitus
5	Male 26	20	Bronchitis and Pneumonia at Age 6.	None
6	Female 32	25	Pneumonia Age 7	None
7	Male 41	21	Aspiration Chicken bone, 1945	Chronic Bronchitis. Pulmonary Fibrosis. Old Pulmonary Tuberculosis. Post Left Lower Lobe Resection. Cor Pulmonale.
8	Female 19	19	Pneumonia Age 6 months	None

and again during washout from rebreathing. Washout results were expressed in terms of the reciprocal of $T\frac{1}{2}$, or ventilation per unit volume ($\dot{V}/V$).

Although values for $\dot{V}/V$ reflected regional differences for each patient, because of differences in overall ventilation and FRC, intersubject comparison using values of $\dot{V}/V$ alone is not valid. Therefore, for comparative purposes, in each patient the mean $\dot{V}/V$ of regions considered normal was calculated and all regional values of $\dot{V}/V$ in that patient were then expressed as a percent of this mean; these indices have been termed relative regional ventilation. For the purposes of comparing the distributions of ventilation and perfusion, relative regional perfusion was similarly computed by comparing in each patient all regional $\dot{Q}_I$ to the mean $\dot{Q}_I$ of normally ventilated regions. It should be pointed out that the selection of normal regions was arbitrary. In general regions which produced high values for $\dot{V}/V$ were designated normal and it is likely that some regions not designated normal were not in fact diseased. However, relative regional ventilation and relative regional perfusion were computed only for purposes of data presentation; a different approach to these computations would not have affected the results of these studies.

Within days of the ^{133}Xe studies, bronchography was carried out in each patient. Bilateral bronchograms were available in all patients except patient 7. The x-rays were evaluated region by region by an independent observer who was unaware of the results of the ^{133}Xe studies. The lung regions evaluated were chosen so that they coincided as much as possible with the regions studied with ^{133}Xe. On the basis of the collimation used in these studies, it was estimated that in the midcoronal plane the counting field of each scintillation counter was a circle of 5 cm. diameter. Accordingly, circles of 5 cm. diameter were

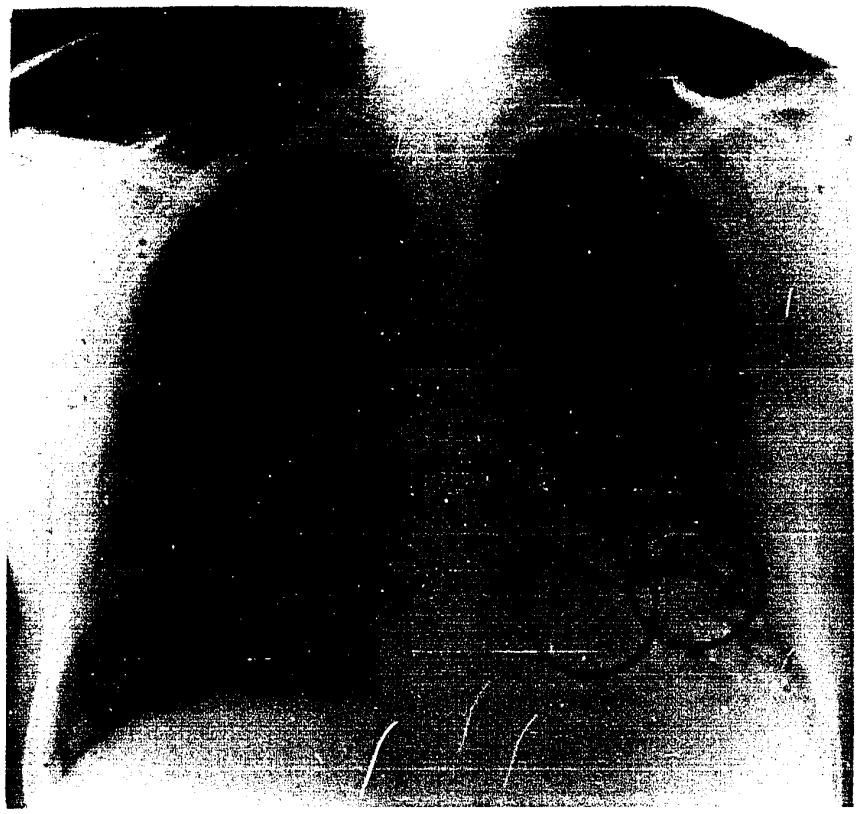


Fig. 35. Left bronchogram of patient 5, with 5 cm rings in place delineating the bronchographic regions assessed. The rings were placed to include the ^{133}Xe counter fields in the mid-coronal plane.

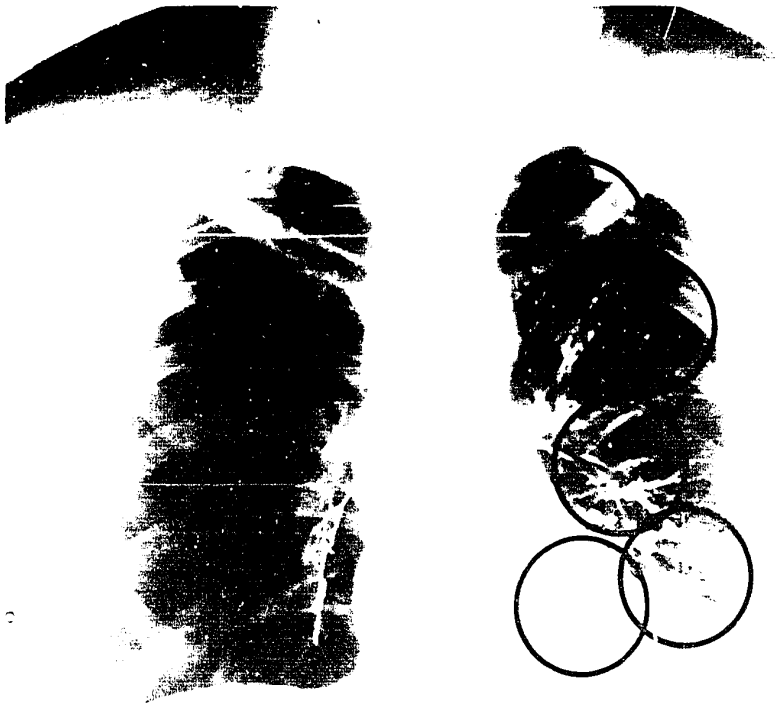


TABLE 9 - NUMERICAL SYSTEM USED IN EVALUATING BRONCHOGRAMS

Anatomical Lesion	Numerical Value
No Abnormality	1
Changes consistant with bronchitis. No diagnostic ebidence of bronchiectasis	1B
Cylindrical bronchiectasis	2
Cylindrical and varicose bronc-iectasis	3
Varicose bronchiectasis	4
Varicose and cystic bronch-iectasis	5
Cystic bronchiectasis	6

affixed to the bronchogram using the same coordinates that had been employed to set the scintillation counters for the ^{133}Xe studies. Evaluation of the bronchograms was confined to the portions which fell inside these circles (Fig. 35). These regions were then scored numerically according to the type of bronchiectasis which they contained. The numerical system used was adapted from the classification of Reid[93]. She separated bronchiectasis into three types, cylindrical, varicose and saccular, each of which could be recognized bronchographically. Each of these types was associated with loss of airway subdivisions distal to the bronchial lesion; this loss was least severe in cylindrical bronchiectasis and most severe in lesions of the saccular variety. The system we used is shown in Table 9 and is modified from that of Reid only in that it allows notation of regions which contained more than one type of bronchiectasis.

RESULTS

The results of routine lung function tests are shown in Table 10. As might be expected, the vital capacity (VC) and volume expired during the first second of a forced vital capacity expiration ($FEV_{1.0}$) were reduced; the amount of this reduction varied from severe (Patients 7 and 8) to very mild (Patient 5). Of greater interest was the fact that D_{LCO} was definitely abnormal in most patients -- only patients 1, 2b and 3 demonstrated D_{LCO} which were within normal limits. Mixing efficiency (ME) was reduced in the two patients in whom it was measured.

Table 11 contains the results of the ^{133}Xe studies together with the results of the bronchographic evaluation. Ventilation was assessed using both washout after rebreathing and washout after infusion; the mean of the $\dot{V}/V$

TABLE 10 - PULMONARY FUNCTION TESTS IN BRONCHIECTASIS
(Predicted Normal Values in Brackets)

Patient	VC (L)	$FEV_{1.0}$(L)	DL_{CO}(ml/min/mmHg)	ME(%)
1	2.65 (3.70)	1.11 (2.20)	17.4 (13.3)	
2a	2.81 (3.45)	1.88 (2.53)	13.6 (18.7)	
2b	3.60 (3.45)	2.52 (2.99)	15.0 (18.7)	
3	2.36 (3.68)	1.95 (1.98)	17.9 (19.7)	46 (65)
5	4.87 (4.95)	4.04 (4.04)	16.6 (23.3)	
6	2.00 (3.65)	1.44 (1.66)	11.6 (19.2)	
7	2.76 (4.28)	1.16 (2.29)	7.8 (19.3)	
8	2.15 (3.42)	1.13 (1.80)	9.4 (18.9)	21 (70)

derived from the two washouts is shown. Regions considered normal for the purpose of computing relative regional ventilation and relative regional perfusion are indicated. No regions containing pure saccular bronchiectasis (grade 6) were encountered in this series.

Comparison of bronchographic scores with regional $\dot{V}/V$ reveals good general agreement except in patient 1 (see below). Regions which showed abnormality on bronchogram were less well ventilated than those that did not. Bronchiectasis was present at the right base of patient 2 on two occasions (2a and 2b); $\dot{V}/V$ were low in these areas both times. Patients 3, 4 and 5 had left basilar bronchiectasis and these regions also demonstrated reduced ventilation. Patients 6 and 8 demonstrated bronchiectasis at both bases which were hypoventilated as was the right apex of patient 8 who had grade 5 (cystic and varicose) bronchiectasis in this area. Only the right lung of patient 7 was evaluated bronchographically, and the whole lung showed some bronchiectatic abnormality. While the base of this lung showed reduced ventilation, it is possible that the apex (region R_1) was functioning normally in spite of its bronchographic appearance. Patient 1 was atypical in that region R_4 demonstrated cylindrical bronchiectasis but its ventilation was not reduced. This patient also had radiographic evidence of bronchitis[94]; irregular bronchial margins and dilated mucous glands were seen in regions L_3, L_4 and L_5.

Almost all regions which were bronchiectatic were also hypoventilated, but low values of $\dot{V}/V$ were not confined to bronchiectatic regions. Indeed, adjacent to regions with bronchiectasis, bronchographically normal regions frequently demonstrated reduced $\dot{V}/V$. As a result, it commonly appeared that a larger area of lung was functionally abnormal than could be demonstrated by bronchogram.

TABLE 11. RESULTS OF BRONCHOGRAPHY AND ^{133}Xe STUDIES IN PATIENTS WITH BR

Patient		Right Lung (apex) R_1	R_2	R_3	R_4	(base) R_5	(apex) L_1	L_2	Le
1	$\dot{V}_A/\dot{Q}$	0.56	0.59	o.60	0.60	0.64	0.55	0.64	
	$\dot{Q}_I$	99	98	100	115	103	87	89	
	$\dot{V}/V$	2.29	2.63	2.36	2.47	1.60	2.23	2.22	
	BrS*	1	1	1	2	1B	1	1	
2a	$\dot{V}_A/\dot{Q}$	0.58	0.40	0.27	0.29	0.31	0.80	0.90	
	$\dot{Q}_I$	132	106	61	53	41	120	150	
	$\dot{V}/V$	3.14	2.48	0.53	0.39	0.46	4.58	4.76	
	BrS	1	1	2	3	4	1	1	
2b	$\dot{V}_A/\dot{Q}$	0.95	0.99	0.90	0.87	0.77	0.97	0.90	
	$\dot{Q}_I$	88	103	92	61	55	107	96	
	$\dot{V}/V$	4.50	5.00	3.42	2.08	1.01	4.72	4.26	
	BrS	1	1	1	1	2	1	1	
3	$\dot{V}_A/\dot{Q}$	0.99	1.04	0.99	0.96	0.95	1.00	1.03	
	$\dot{Q}_I$	117	118	110	91	87	103	95	
	$\dot{V}/V$	2.40	2.86	2.22	1.87	2.14	2.22	2.22	
	BrS	1	1	1	1	1	1	1	
4	$\dot{V}_A/\dot{Q}$	0.58	0.60	0.54	0.53	0.64	0.60	0.55	
	$\dot{Q}_I$	119	139	101	1o5	109	99	119	
	$\dot{V}/V$	1.84	1.97	1.69	1.86	1.91	1.75	2.14	
	BrS	1	1	1	1	1	1	1	
5	$\dot{V}_A/\dot{Q}$	0.55	0.57	0.55	0.51	0.50	0.57	0.39	
	$\dot{Q}_I$	85	96	118	112	121	101	117	
	$\dot{V}/V$	1.88	2.38	2.71	2.81	2.19	2.22	1.54	
	BrS	1	1	1	1	1	1	1	
6	$\dot{V}_A/\dot{Q}$	0.55	0.61	0.62	0.54	0.51	0.57	0.61	(
	$\dot{Q}_I$	74	94	95	97	52	85	110	
	$\dot{V}/V$	2.07	2.17	1.60	1.02	0.22	1.79	2.53	
	BrS	1	1	1	4	2	1	1	
7	$\dot{V}_A/\dot{Q}$	0.73	o.56	0.40	0.44	0.49	0.32	0.40	(
	$\dot{Q}_I$	117	99	90	67	68	33	41	
	$\dot{V}/V$	2.61	0.97	0.86	0.38	0.42	0.16	0.28	(
	BrS	2	2	3	4	5	n.s.‡	n.s.	(
8	$\dot{V}_A/\dot{Q}$	0.61	0.63	0.53	0.50	n.s.	0.77	0.65	(
	$\dot{Q}_I$	69	88	47	47		147	156	(
	$\dot{V}/V$	0.56	0.67	0.33	0.39		1.67	1.14	(
	BrS	5	5	4	4		1	1	

* BrS - Bronchographic score
\+ These regions contained bronchographic medium at the time of the ^{133}Xe study
‡ n.s. - Not studied

Regions which were considered normal for the purpose of calculating relative regional ve
regional perfusion are underlined.

11. RESULTS OF BRONCHOGRAPHY AND ^{133}Xe STUDIES IN PATIENTS WITH BRONCHIECTASIS

ex)		Right Lung		(base)	(apex)		Left Lung	
l	R_2	R_3	R_4	R_5	L_1	L_2	L_3	L_4
56	0.59	o.60	0.60	0.64	0.55	0.64	0.59	0.49
9	98	100	115	103	87	89	88	88
29	2.63	2.36	2.47	1.60	2.23	2.22	2.56	1.89
	1	1	2	1B	1	1	1B	1B
58	0.40	0.27	0.29	0.31	0.80	0.90	0.58	0.48
2	106	61	53	41	120	150	92	83
14	2.48	0.53	0.39	0.46	4.58	4.76	3.11	1.56
	1	2	3	4	1	1	1^+	$1^{\mp}$
95	0.99	0.90	0.87	0.77	0.97	0.90	0.89	0.94
3	103	92	61	55	107	96	95	84
50	5.00	3.42	2.08	1.01	4.72	4.26	4.23	3.17
	1	1	1	2	1	1	1	1
99	1.04	0.99	0.96	0.95	1.00	1.03	0.98	0.69
7	118	110	91	87	103	95	97	74
60	2.86	2.22	1.87	2.14	2.22	2.22	1.43	0.65
	1	1	1	1	1	1	1	3
68	0.60	0.54	0.53	0.64	0.60	0.55	0.44	0.25
9	139	101	1o5	109	99	119	67	37
64	1.97	1.69	1.86	1.91	1.75	2.14	0.66	0.13
	1	1	1	1	1	1	1B	2^+
65	0.57	0.55	0.51	0.50	0.57	0.39	0.26	0.34
6	96	118	112	121	101	117	90	41
68	2.38	2.71	2.81	2.19	2.22	1.54	0.50	0.24
	1	1	1	1	1	1	1	3
5	0.61	0.62	0.54	0.51	0.57	0.61	0.61	0.45
	94	95	97	52	85	110	115	64
7	2.17	1.60	1.02	0.22	1.79	2.53	1.86	0.21
	1	1	4	2	1	1	1	3
3	o.56	0.40	0.44	0.49	0.32	0.40	0.66	0.54
	99	90	67	68	33	41	48	77
1	0.97	0.86	0.38	0.42	0.16	0.28	0.82	0.75
	2	3	4	5	n.s.‡	n.s.	n.s.	n.s.
1	0.63	0.53	0.50	n.s.	0.77	0.65	0.54	0.40
	88	47	47		147	156	63	59
6	0.67	0.33	0.39		1.67	1.14	0.36	0.32
	5	4	4		1	1	5	5

ic score
ained bronchographic medium at the time of the ^{133}Xe study

onsidered normal for the purpose of calculating relative regional ventilation and rel
are underlined.

BLE 11. RESULTS OF BRONCHOGRAPHY AND ^{133}Xe STUDIES IN PATIENTS WITH BRONCHIECTASIS

(apex)		Right Lung		(base)	(apex)		Left Lung		(base)
R_1	R_2	R_3	R_4	R_5	L_1	L_2	L_3	L_4	L_5
0.56	0.59	o.60	0.60	0.64	0.55	0.64	0.59	0.49	0.59
99	98	100	115	103	87	89	88	88	97
2.29	2.63	2.36	2.47	1.60	2.23	2.22	2.56	1.89	0.98
1	1	1	2	1B	1	1	1B	1B	1B
0.58	0.40	0.27	0.29	0.31	0.80	0.90	0.58	0.48	0.40
132	106	61	53	41	120	150	92	83	59
3.14	2.48	0.53	0.39	0.46	4.58	4.76	3.11	1.56	1.62
1	1	2	3	4	1	1	1+	1+	1+
0.95	0.99	0.90	0.87	0.77	0.97	0.90	0.89	0.94	0.92
88	103	92	61	55	107	96	95	84	87
4.50	5.00	3.42	2.08	1.01	4.72	4.26	4.23	3.17	3.33
1	1	1	1	2	1	1	1	1	1
0.99	1.04	0.99	0.96	0.95	1.00	1.03	0.98	0.69	0.59
117	118	110	91	87	103	95	97	74	40
2.40	2.86	2.22	1.87	2.14	2.22	2.22	1.43	0.65	0.38
1	1	1	1	1	1	1	1	3	1
0.58	0.60	0.54	0.53	0.64	0.60	0.55	0.44	0.25	0.29
119	139	101	1o5	109	99	119	67	37	30
1.84	1.97	1.69	1.86	1.91	1.75	2.14	0.66	0.13	0.11
1	1	1	1	1	1	1	1B	2+	2
0.55	0.57	0.55	0.51	0.50	0.57	0.39	0.26	0.34	0.37
85	96	118	112	121	101	117	90	41	63
1.88	2.38	2.71	2.81	2.19	2.22	1.54	0.50	0.24	0.33
1	1	1	1	1	1	1	1	3	4
0.55	0.61	0.62	0.54	0.51	0.57	0.61	0.61	0.45	0.28
74	94	95	97	52	85	110	115	64	44
2.07	2.17	1.60	1.02	0.22	1.79	2.53	1.86	0.21	0.11
1	1	1	4	2	1	1	1	3	4
0.73	o.56	0.40	0.44	0.49	0.32	0.40	0.66	0.54	0.53
117	99	90	67	68	33	41	48	77	131
2.61	0.97	0.86	0.38	0.42	0.16	0.28	0.82	0.75	1.14
2	2	3	4	5	n.s.‡	n.s.	n.s.	n.s.	n.s.
0.61	0.63	0.53	0.50	n.s.	0.77	0.65	0.54	0.40	n.s.
69	88	47	47		147	156	63	59	
0.56	0.67	0.33	0.39		1.67	1.14	0.36	0.32	
5	5	4	4		1	1	5	5	

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ontained bronchographic medium at the time of the ^{133}Xe study
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e considered normal for the purpose of calculating relative regional ventilation and relative
ion are underlined.

In addition, as shown in Fig. 36, the first study of patient 2 (study 2a) showed reduced ventilation in regions L_3, L_4 and L_5 though these regions appeared normal on a bronchogram done 48 hrs. before. However, this may have been the trouble, since at the time of the ^{133}Xe study radio-opaque bronchographic medium was scattered through the left base. The medium itself may well have caused the dysfunction observed in this area. In any event, when the patient was re-studied 6 months later, the medium was gone and regions L_3, L_4 and L_5 functioned normally. Patient 4 also had some bronchographic medium retained at the left base at the time of her ^{133}Xe study, which may have contributed to the extremely low values $\dot{V}/V$ seen in these areas.

When the series was considered as a whole, regional function did not correlate well with the type of bronchiectasis noted. In Fig. 37, bronchographic score was plotted against relative regional ventilation. Regions with retained bronchographic medium are so indicated. In general bronchiectatic regions were less well ventilated than others. When cylindrical bronchiectasis (grade 2) was present, regional function was quite variable with instances of both normal and severely compromised ventilation being observed. More severe lesions were always associated with depressed $\dot{V}/V$ but the degree of hypoventilation appeared to be no worse than the majority of regions with cylindrical bronchiectasis (grade 2). $\dot{V}/V$ were independent of the anatomical findings once varicose (grade 3) bronchiectasis was present. Functionally, these patients tended to demonstrate two kinds of regions: those which were normally or nearly normally ventilated, a group including some regions with cylindrical bronchiectasis; and those which were very badly ventilated, a group including most regions with cylindrical bronchiectasis and all with varicose lesions. There were few regions which demonstrated an intermediate or moderate degree of hypoventilation.

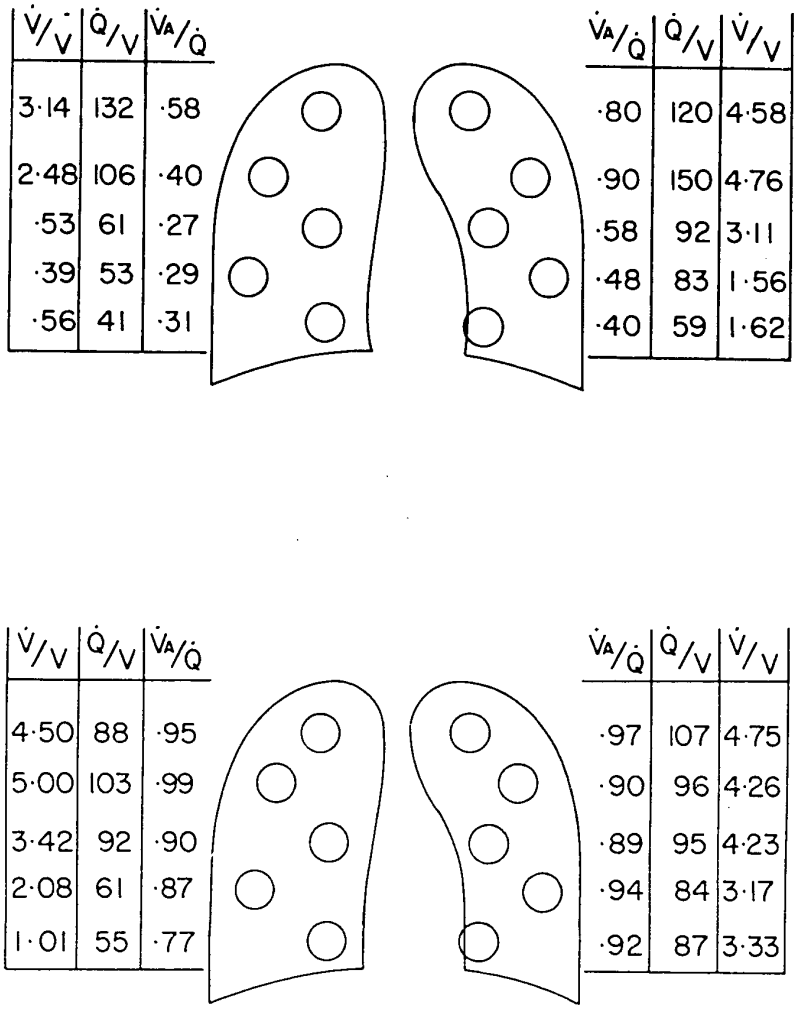


Fig. 36. Sequential studies in patient 2. At the top is the first study, below is the one performed six months later. Measured $\dot{V}_A/\dot{Q}$, $\dot{Q}/V$ and $\dot{V}/V$ are placed opposite schematic counter fields indicated by the circles.

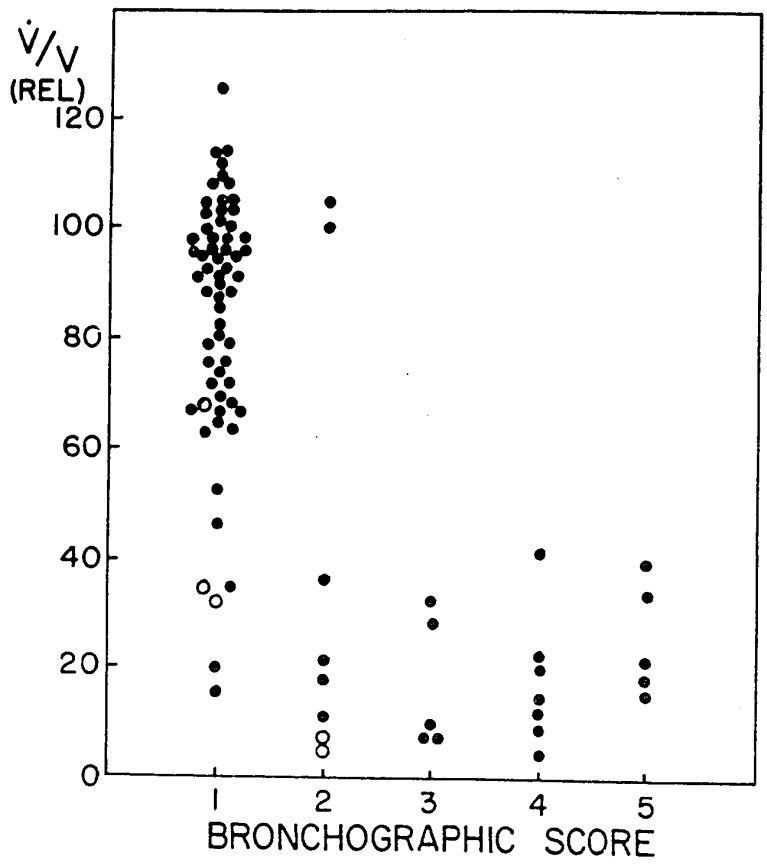


Fig. 37. Correlation of ^{133}Xe findings with bronchographic assessment. Ordinate: relative regional ventilation. Abscissa: bronchographic score. Each point represents a lung region. Open circles (o) are regions which contained bronchographic medium at the time of the ^{133}Xe study, and closed circles (●) are regions which did not.

Irrespective of bronchographic score, regions which displayed prolonged washout (low $\dot{V}/V$) also demonstrated low $\dot{V}_A/\dot{Q}$. Interregional variations of $\dot{V}_A/\dot{Q}$ were considerable but never as large as interregional variations in ventilation. This was in part explained by the fact that regional perfusion was also correlated with regional ventilation. Fig. 38 compares relative regional ventilation with relative regional perfusion for all patients. When relative regional ventilation was less than 60%, relative regional perfusion was almost uniformly decreased.

The dependence of regional perfusion on regional ventilation was strikingly illustrated by comparing the two studies of patient 2 (Fig. 36). On the first occasion ventilation in regions L_{1-2} was higher than any other region, and only R_1 was as well perfused as these regions. Six months later, after the patient had stopped smoking and followed a program of antibiotics and postural drainage, ventilatory function had improved so that only R_{4-5} appeared to exhibit significantly decreased ventilation and with the exception of these regions, perfusion distribution also appeared normal. In other words, successful therapy which was aimed at increasing the ventilation of abnormal regions also increased the perfusion of these regions.

In order to compare regional results with tests of overall function, mean values of relative regional $\dot{V}/V$ and mean values of regional bronchographic score were calculated for each patient. The first of these was thought to represent overall ventilatory impairment, the second to represent the extent of bronchiectasis. These indices did not correlate well with either VC or $FEV_{1.0}$, but did with each other and with D_{LCO} (Fig. 39). However, both D_{LCO} and mean relative regional $\dot{V}/V$ correlated as well with the number of regions involved by bronchiectasis in each patient (Fig. 39) as they did with mean

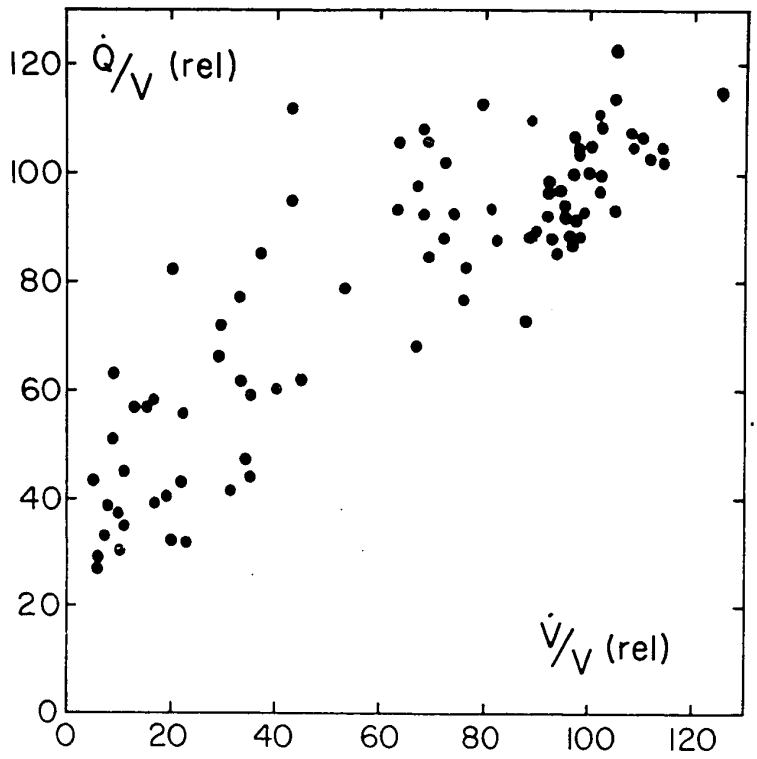


Fig. 38. Regional distribution of perfusion in bronchiectasis. Ordinate: relative regional perfusion. Abscissa: relative regional ventilation. Each point represents a lung region.

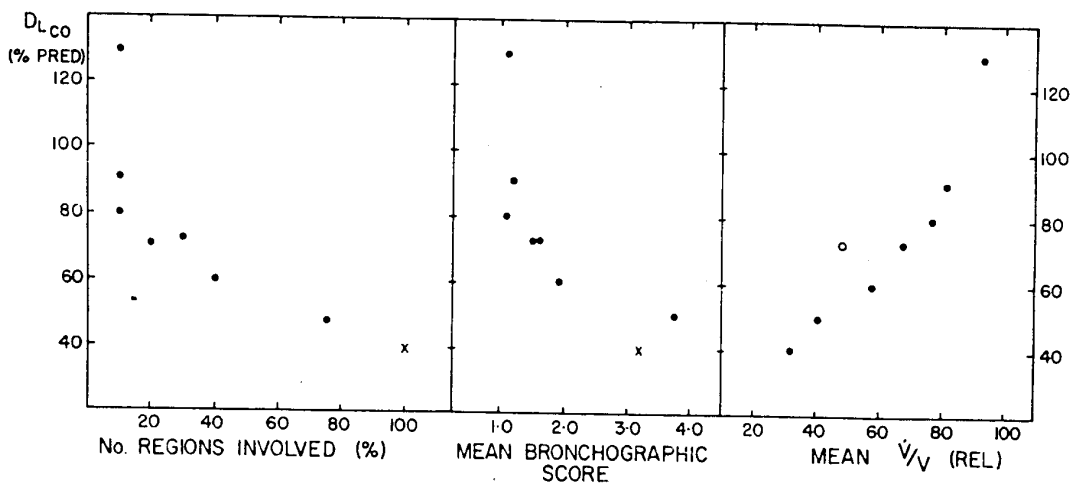


Fig. 39. Correlation of $D_{L\,CO}$ with ^{133}Xe and bronchographic results. Ordinate: steady state diffusing capacity of the lung for CO, expressed as a per cent of the predicted normal value. Abscissae: number of lung regions which demonstrated bronchiectasis, expressed as a percent of the total regions examined in each patient (left); mean bronchographic score for each patient (center); mean relative regional ventilation for each patient (right). Open circle (o) in the right hand panel indicates study 2a; bronchographic medium was present in the lung of this patient during the ^{133}Xe study but not when $D_{L\,CO}$ was measured. Crosses in the center and left panels are patient 7; bronchographic evaluation was carried out for the right lung only, while the $D_{L\,CO}$ presumably measured the function of both lungs.

bronchographic score. This was of course to be expected in light of Fig. 37 which indicated that the degree of regional ventilatory impairment was more dependent on the presence of bronchiectasis than its extent.

The results of the routine lung function tests shown in Table 10 are not greatly different from those reported in a larger series[95]. Figures for $D_{L_{CO}}$ are somewhat lower than those of Cherniack and Carton[95], but these authors used a single breath test which in the presence of obstructive lung disease is known to produce values which are more nearly normal than is the case with steady state methods[9f]. Our failure to find a correlation between bronchographic findings and either VC or $FEV_{1.0}$ are probably due to the smallness of the series; such correlations were found by Cherniack and Carton[95]. The striking correlation between $D_{L_{CO}}$ and results of both ^{133}Xe and bronchography was gratifying and may indicate that the steady state $D_{L_{CO}}$ is a particularly valuable test in patients with relatively uncomplicated bronchiectasis. We found that $D_{L_{CO}}$ correlated as well with the number of bronchiectatic regions (irrespective of the type of bronchiectasis) as it did with the mean bronchographic score, which took account of type or severity of bronchiectasis. This is precisely what has been found by Cherniack and Carton[95] who also related overall function to bronchographic findings. These data agree with the ^{133}Xe finding that relative regional ventilation was independent of the anatomical type of bronchiectasis (Fig. 37).

As expected, bronchiectatic regions generally showed functional abnormality when studied with ^{133}Xe. The pattern of functional abnormality (low $\dot{V}/V$, $\dot{V}_A/\dot{Q}$ and $\dot{Q}_I$) was also expected. There were, however, areas of poor agreement between the ^{133}Xe and bronchographic studies; these fall into three groups.

First, bronchographically normal regions adjacent to bronchiectatic regions frequently demonstrated abnormal function (e.g. patient 3). The most obvious explanation for this phenomenon is that the spatial resolution of the ^{133}Xe technique was less good than that afforded by bronchography. This was very likely the case, since lung regions as studied by ^{133}Xe were conical, not cylindrical and since contamination of regional count rates by radiation scattered from other regions could not be prevented. Differences in spatial resolution were not necessarily the only reason for the area of functional abnormality to exceed the area of anatomical bronchiectasis, however. Some regions bordering a lung region containing ectatic bronchi undoubtedly were supplied in part by these bronchi and, therefore, would have been expected to function badly. It was also possible that bronchial filling was incomplete and abnormal bronchi, therefore, not seen. Finally, parenchymal or pleural abnormalities might have affected regions adjacent to frank bronchiectasis. For example, patient 3 had bronchiectasis only in L_4 but also showed ventilatory abnormality in both L_3 and L_5. At surgery, this patient was found to have pleural adhesions involving the entire left lower lobe, which might have limited ventilation through much of the lower left lung field.

Second, though most bronchiectatic regions were hypoventilated, some which exhibited cylindrical bronchiectasis were not. Further, the type of bronchiectatic lesion did not seem to influence the degree of hypoventilation. Overall function was more sensitive to the amount of lung involved by bronchiectasis than to the type or intensity of bronchiectasis in any region. Again, these results may have been influenced by technical problems. Thus, patient 1 who had cylindrical bronchiectasis involving the right middle lobe (R_4) seemed to have normal function in this area. The anatomical lesion was situated

anteriorly; posteriorly placed counters are relatively insensitive to such lesions and it was possible that a minor degree of right middle lobe malfunction was simply not recorded. Only a minor degree of malfunction could be so overlooked however. Patient 6 demonstrated much better ventilation in R_4 which contained varicose bronchiectasis than she did in R_5 which had cylindrical disease. The explanation for this may be that the lesion in R_4 was well circumscribed and surrounded by presumably normal lung tissue, i.e., the bronchiectasis was subregional in R_4 while the entire counterfield of R_5 was involved by cylindrical bronchiectasis. Once again, however, it is not likely that all the variability of function demonstrated by bronchiectatic regions can be explained on the basis of such technical factors.[133] Xe washout may be importantly influenced by abnormalities not reflected on bronchography, such as the status of small airways. Mucous plugging of very small ($<$2mm) airways would produce functional but not necessarily bronchographic abnormality. It is of interest, then, that bronchiectatic lung regions near the apex (patient 7 and 8) tended to function better than those at the base irrespective of the type of bronchiectasis seen, perhaps because retention of secretions was more prominent in the dependent, basal areas. The presence or absence of lesions not apparent on the bronchogram would appear to be of crucial importance in determining the function of regions with cylindrical bronchiectasis. This is illustrated by the fact that some regions with cylindrical disease (patient 1, region R_5, patient 7, region R_1) showed good preservation of function, while other regions with similar bronchographic appearance (patient 6, region R_5) showed grossly decreased ventilatory function.

Third and finally, in two patients (1 and 2a) there was evidence of hypoventilation in regions which neither contained nor were adjacent to areas of bronchiectasis. These patients will be discussed individually below.

The sequential studies of patient 2 (Fig. 36) present several interesting aspects. In the 6 months between studies, bronchograms, routine function tests and the results of study with ^{133}Xe all showed improvement. Part of this improvement was probably because the initial studies were completed four weeks after an episode of right lower lobe pneumonia. Some of the bronchographic findings at the right base and their attendant functional abnormalities may have been due to post pneumonic bronchiectasis which was partially reversible. The functional abnormalities at the left base in study 2a were likely secondary to retained bronchographic medium. It is known that overall lung function is reversibly depressed by bronchography[96], so that regional retention of radiopaque material might be expected to cause reversible regional malfunction; this may also have been the case in region L_4 of patient 5 which showed striking hypoventilation. On the first study patient 2 showed major washout discrepancies at both the left base and right apex; washout of infused isotope was slower than that of inhaled isotope. This indicated that these regions were not functioning in homogenous fashion; units with low $\dot{V}_A/\dot{Q}$ and $\dot{V}/V$ co-existed with other units having high $\dot{V}_A/\dot{Q}$ and $\dot{V}/V$. (See the section on bronchitis for a full discussion of this phenomenon). Such an effect might have been produced by an uneven distribution of contrast medium at the left base, but the explanation for the findings at the right apex was not so apparent. These right apical regions may also have been recovering from uneven involvement by bronchitis or bronchopneumonia at the time of the first study. In any event, six months later (Fig. 36B) no washout discrepancies were apparent.

Patient 1 had chronic bronchitis as well as mild right middle lobe bronchiectasis. Bronchitis probably played the most important role in determining this patient's overall and regional function. This patient showed

some restriction of ventilation at both bases with slight depression of $\dot{V}_A/\dot{Q}$ at the left base. Also, at the left base, ventilation as derived from washout after infusion was less than that computed after rebreathing. It will be shown (see section on bronchitis) that this finding implied regional inhomogeneity of function, something commonly found in regions affected by chronic bronchitis.

Thus, in both patients 1 and 2, there is evidence that some regional abnormality might have been expected on the basis of disease other than bronchiectasis; these patients showed such abnormalities.

While Table 11 shows distinct differences in regional function, the variation in regional $\dot{V}_A/\dot{Q}$ are not large enough to imply significant impairment of overall gas exchange. Regional $\dot{V}_A/\dot{Q}$ can be interpreted literally, however, only when there are no functional differences within lung regions. In patients 1 and 2 discrepancies in regional washout clearly indicated that functional inhomogeneities did exist in some lung regions, but these were not regions in which bronchiectasis was demonstrated. In addition to these patients regional washouts after rebreathing could be compared to washouts after infusion in patients 5, 7 and 8. No significant washout discrepancies were noted in these subjects. For technical reasons, the records of patients 3, 4 and 6 were not suitable for such comparison. Thus, there was no evidence that bronchiectatic regions functioned in non-homogenous fashion. It should be noted, however, that the series was small and that discrepancies in regional washout are evident only when intraregional functional differences are large. All of these patients exhibited normal arterial blood gases; these results would be expected if the values of Table 11 were interpreted literally.

Blood flow was not evenly distributed in these patients, but was decreased in regions which were hypoventilated, i.e., in bronchiectatic regions. This, of course, was expected since obliteration of the microvasculature has been well documented in areas of bronchiectasis[93]. On the other hand, functional mechanisms may play a role in determining blood flow distribution. Hypoventilated regions had low $\dot{V}_A/\dot{Q}$ and were, therefore, relatively hypoxic. Since alveolar hypoxia is a known pressor agent for the pulmonary circulation[97], regional hypoxia might shift flow away from hypoventilated regions. The striking increase in flow to bronchiectatic regions shown by sequential study of patient 2 indicates that such functional factors may have been important in determining flow distribution, though the nature of these factors was not demonstrated. It should be noted that the technique used in these experiments examined the distribution of only the pulmonary arterial blood flow, and thereby may have underestimated total regional flow since bronchial artery flow to bronchiectatic areas may be considerable[98].

Because of their experimental nature, no therapeutic decisions were based on the results of these ^{133}Xe studies. However, some evaluation of ^{133}Xe methods as a clinical tool in the management of bronchiectasis is possible. Patients 3 and 5 were clear cut cases of left lower lobe bronchiectasis, treated by resection; the results of their ^{133}Xe studies were in large part irrelevant to their management. Patient 6, on the other hand, had bilateral basal bronchiectasis. Though it has been initially decided to treat this patient medically, should resectional surgery be advised, it is clear that the left side should be attacked first, since function on this side was considerably worse than on the right side. Patient 8 was also treated medically, but in her case as well, the course of resectional therapy was indicated by the ^{133}Xe studies. This

patient had varicose bronchiectasis of the right upper lung field, but function in this area was better preserved than in the right lower zones, though these areas demonstrated less abnormality on bronchography. Thus, should surgery be carried out, the right lower lobe should be excised and the right upper preserved. Thus ^{133}Xe studies may be helpful in cases with bilateral disease and abnormal overall function, in whom care must be taken to preserve a maximum amount of functional tissue.

In summary, eight patients with bronchiectasis were studied using ^{133}Xe and the results compared with a semi-quantitative assessment of their bronchograms. There was good agreement between the results of the two studies; bronchiectatic regions showed reduced ventilation, reduced perfusion and low $\dot{V}_A/\dot{Q}$. The reduction in ventilation tended to be sizable; few regions with moderately depressed ventilation were seen. The degree of ventilatory depression was not related to the type of bronchiectasis observed. Some regions with cylindrical bronchiectasis showed normal or nearly normal function, others demonstrated sharply reduced ventilation, similar to regions with more severe anatomical bronchiectasis. The presence of bronchiectasis, as opposed to its anatomical type was the most important determinant of both regional function and overall function.

Though there were distinct differences in regional function, regional $\dot{V}_A/\dot{Q}$ did not differ enough to indicate significant abnormality of overall gas exchange, and there was no definite evidence for variations of $\dot{V}_A/\dot{Q}$ within single lung regions affected by bronchiectasis.

5. ASTHMA

Asthma is characterized by an increase in airway resistance, presumably due to spasm of the bronchial smooth muscle and/or increased bronchial secretions[9g]. If the distribution of the airways resistance were even, patients with asthma would develop abnormalities of pulmonary gas exchange only when the resistance represented an overwhelming mechanical load, i.e., only when the minute ventilation became abnormally low. Of course, this is not the case: patients with asthma frequently have hypoxemia in the absence of overall hypoventilation[99, 100], and even asymptomatic asthmatics have been shown to have abnormal ventilation distribution[101].

Previous studies with ^{133}Xe[102] have shown that these abnormalities may have a regional basis. Asthmatics in remission were studied in the seated position. Some lung regions were noted to exhibit delayed washin of the isotope and, since perfusion distribution appeared to be normal, it was concluded that the $\dot{V}_A/\dot{Q}$ of these regions were low. It was also noted that the extent of regional abnormality was correlated with the degree of overall airway obstruction as assessed by the maximum mid-expiratory flow rate (MMFR).

In an effort to document the presence of regions with low $\dot{V}_A/\dot{Q}$, we studied 10 asthmatics, 8 of whom had been subjects of the previous study. The subjects were 2 women and eight men ranging in age from 21 to 51 (Table 12). They were selected by the Allergy Department of the Royal Victoria Hospital according to strict criteria. All patients had been observed for several years and gave a history of recurrent episodes of bronchospasm, not necessarily related to respiratory infection. None had cough or produced sputum between episodes, and all thought they were physically fit at the time of study. All were on desensitization programs with vaccines; 5 were taking bronchodilator

TABLE 12 - CLINICAL DATA IN SUBJECTS WITH ASTHMA

	Sex	Age, yr	MMFR	FEV
			% of predicted value	
DA	F	36	55	93
GA	M	46	63	84
AG*	M	22	56	68
NT*	M	36	41	66
SL*	M	32	27	49
PT*	M	34	43	67
KS*	M	38	55	78
MR*	F	51	54	64
WA*	M	39	39	65
GW*	M	31	7	24

*Subject of previous study (2).

substances and 1 was taking corticosteroids at the time of study. None were hospitalized at the time of study.

Routine pulmonary function tests and the ^{133}Xe study were performed the same day. The maximal mid-expiratory flow rate (MMFR) and forced expiratory volume (FEV) were measured and were compared with predicted normal values. The functional residual capacity (FRC) was measured with the patient supine.

Cardiac output was measured by dye-dilution techniques several times during each ^{133}Xe study.

^{133}Xe studies were carried out with the patients in the supine position. Five counters were positioned posteriorly to each lung, ranging from apex to base. Regional $\dot{V}_A/\dot{Q}$ were computed from steady state count rates during infusion and rebreathing (eq. III-7). Regional perfusion distribution was assessed on the basis of bolus injections of ^{133}Xe; both conventional perfusion indices ($\dot{Q}_I$) and steady state perfusion indices ($\dot{Q}_i$) were computed. Regional ventilation was assessed by examining ^{133}Xe washout after both infusion and rebreathing. The washout half-times ($T\frac{1}{2}$) were measured and were standardized according to eq. III-25 yielding regional ventilation per unit volume ($\tilde{V}$). $\tilde{V} < 50$ were defined as abnormal; $\tilde{V} > 60$ as normal and $\tilde{V}$ between 50 and 60 as borderline. Results of routine pulmonary function tests are presented in Table 12. The MMFR was more depressed than the FEV, and was abnormal in all patients; the degree of abnormality was variable, reflecting relatively mild obstruction of air flow (GH) to severe obstruction (GW).

Results of the ^{133}Xe studies are shown in Table 13. The recorded $\tilde{V}$ is the mean of values determined from washout after infusion and after rebreathing. Abnormal ($\tilde{V} < 50$) and borderline ($50 < \tilde{V} < 60$) regions are underlined in Table 13. On this basis, the patients may be separated into three groups. In 4 patients (DA, GH, AG, and NT) the findings were normal, in that $\tilde{V} > 60$ in all regions.

TABLE 13. RESULTS OF ^{133}Xe STUDIES IN PATIENTS WITH ASTHMA

Patient		(apex) R_1	R_2	Right Lung R_3	R_4	(base) R_5	(apex) L_1	L_2	Left Lung L_3	
DA	$\dot{V}_A/\dot{Q}$	0.70	0.73	0.74	0.75	0.75	0.70	0.72	0.75	0
	$\dot{Q}_I/\dot{Q}_i$	100/82	105/87	99/81	99/81	100/82	102/82	106/86	106/87	86
	$\tilde{\dot{V}}$	71	88	73	81	88	73	74	83	
GH	$\dot{V}_A/\dot{Q}$	1.12	1.01	1.09	1.10	1.16	1.08	1.09	1.08	0
	$\dot{Q}_I/\dot{Q}_i$	75/65	105/81	97/82	99/85	108/93	102/87	108/92	92/78	107
	$\tilde{\dot{V}}$	82	87	72	94	127	100	112	95	
NT	$\dot{V}_A/\dot{Q}$	0.69	0.69	0.68	0.59	0.67	0.69	0.61	0.65	0
	$\dot{Q}_I/\dot{Q}_i$	73/59	95/77	106/86	112/87	115/93	77/63	108/85	117/94	114
	$\tilde{\dot{V}}$	70	76	73	65	74	68	74	74	
AG	$\dot{V}_A/\dot{Q}$	0.47	0.52	0.44	0.52	0.53	0.50	0.49	0.52	0
	$\dot{Q}_I/\dot{Q}_i$	110/81	106/81	108/78	122/93	114/87	108/81	106/80	88/67	96
	$\tilde{\dot{V}}$	83	95	63	91	70	75	70	74	
SW	$\dot{V}_A/\dot{Q}$	0.70	0.76	0.74	0.65	0.74	0.68	0.74	0.74	0
	$\dot{Q}_I/\dot{Q}_i$	125/101	109/90	126/103	96/77	103/84	89/72	118/97	108/89	77
	$\tilde{\dot{V}}$	82	71	73	58	75	70	76	79	
PT	$\dot{V}_A/\dot{Q}$	0.45	0.61	0.68	0.71	0.67	0.50	0.50	0.58	0
	$\dot{Q}_I/\dot{Q}_i$	71/52	83/66	98/79	90/73	49/39	70/55	82/62	93/73	115
	$\tilde{\dot{V}}$	33	71	67	60	25	38	46	81	
KS	$\dot{V}_A/\dot{Q}$	1.29	1.15	1.13	1.09	0.91	1.07	1.05	1.11	1
	$\dot{Q}_I/\dot{Q}_i$	78/77	91/80	97/84	64/56	56/48	81/76	93/81	100/87	88
	$\tilde{\dot{V}}$	107	111	105	64	38	76	104	117	1
MR	$\dot{V}_A/\dot{Q}$	0.62	0.70	0.65	0.63	0.54	0.60	0.68	0.54	0
	$\dot{Q}_I/\dot{Q}_i$	102/81	98/80	110/88	107/85	86/66	109/86	119/96	122/97	127
	$\tilde{\dot{V}}$	50	63	69	52	29	62	81	57	3
WA	$\dot{V}_A/\dot{Q}$	0.66	0.64	0.65	0.63	0.54	0.52	0.60	0.82	0
	$\dot{Q}_I/\dot{Q}_i$	n.s.+	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n
	$\tilde{\dot{V}}$*	40	39	50	38	37	34	39	61	
GW	$\dot{V}_A/\dot{Q}$	0.67	0.65	0.66	0.66	0.68	0.72	0.68	0.73	0
	$\dot{Q}_I/\dot{Q}_i$	72/58	66/53	70/56	67/54	59/48	73/60	62/50	64/53	69
	$\tilde{\dot{V}}$	39	30	35	29	35	59	34	52	

* Values represent washout after infusion only
\+ n.s., not studied

Results from regions which had abnormally low or borderline values of $\tilde{\dot{V}}$ are underlined

TABLE 13. RESULTS OF ^{133}Xe STUDIES IN PATIENTS WITH ASTHMA

(apex)		Right Lung		(base)	(apex)		Left Lung		(base)
R_1	R_2	R_3	R_4	R_5	L_1	L_2	L_3	L_4	L_5
0.70	0.73	0.74	0.75	0.75	0.70	0.72	0.75	0.83	0.74
0/82	105/87	99/81	99/81	100/82	102/82	106/86	106/87	86/72	104/86
71	88	73	81	88	73	74	83	62	67
1.12	1.01	1.09	1.10	1.16	1.08	1.09	1.08	0.99	1.10
5/65	105/81	97/82	99/85	108/93	102/87	108/92	92/78	107/91	113/97
82	87	72	94	127	100	112	95	75	104
0.69	0.69	0.68	0.59	0.67	0.69	0.61	0.65	0.61	0.59
3/59	95/77	106/86	112/87	115/93	77/63	108/85	117/94	114/90	117/91
70	76	73	65	74	68	74	74	60	63
0.47	0.52	0.44	0.52	0.53	0.50	0.49	0.52	0.53	0.62
0/81	106/81	108/78	122/93	114/87	108/81	106/80	88/67	96/74	86/68
83	95	63	91	70	75	70	74	61	76
0.70	0.76	0.74	0.65	0.74	0.68	0.74	0.74	0.60	0.63
5/101	109/90	126/103	96/77	103/84	89/72	118/97	108/89	77/60	93/74
82	71	73	58	75	70	76	79	35	42
0.45	0.61	0.68	0.71	0.67	0.50	0.50	0.58	0.59	0.50
1/52	83/66	98/79	90/73	49/39	70/55	82/62	93/73	115/88	66/50
33	71	67	60	25	38	46	81	61	31
1.29	1.15	1.13	1.09	0.91	1.07	1.05	1.11	1.17	1.12
8/77	91/80	97/84	64/56	56/48	81/76	93/81	100/87	88/78	74/64
107	111	105	64	38	76	104	117	110	97
0.62	0.70	0.65	0.63	0.54	0.60	0.68	0.54	0.52	0.46
2/81	98/80	110/88	107/85	86/66	109/86	119/96	122/97	127/103	101/74
50	63	69	52	29	62	81	57	36	25
0.66	0.64	0.65	0.63	0.54	0.52	0.60	0.82	0.78	0.65
n.s.+	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
40	39	50	38	37	34	39	61	51	47
0.67	0.65	0.66	0.66	0.68	0.72	0.68	0.73	0.65	0.57
2/58	66/53	70/56	67/54	59/48	73/60	62/50	64/53	69/55	66/51
39	30	35	29	35	59	34	52	37	26

washout after infusion only

d

ns which had abnormally low or borderline values of $\dot{V}$ are underlined

Four patients (SW, PT, KS, and MR) had some regions with normal ^{133}Xe washout and some with borderline or abnormal $\tilde{V}$ values; the number of regions affected varied from 1 (KS) to 6 (MR). Finally, in 2 patients (WA and GW), $\tilde{V}$ was low in all or almost all regions, although the degree of abnormality varied. Regional $\dot{V}_A/\dot{Q}$ correlated with regional $\tilde{V}$: depression of one measurement was associated with depression of the other. Examples of each of the three groups are shown in Fig. 40. Patient DA was entirely normal; regional $\tilde{V} > 60$, and regional $\dot{V}_A/\dot{Q}$ and $\dot{Q}_I$ were similar in all regions. Patient SW showed sharp reduction of $\tilde{V}$ at the left base and borderline $\tilde{V}$ in one region near the left base. Regional $\dot{V}_A/\dot{Q}$ were low in these regions and $\dot{Q}_I$ in these regions also tended to be low. Patient GW did not demonstrate any normal lung regions; everywhere $\tilde{V} < 60$. However, $\tilde{V}$ did vary from region to region and, in general, correlated with regional $\dot{V}_A/\dot{Q}$.

Considering the series as a whole, some regions were involved more frequently than others. As shown in Fig. 41, the lung bases were most commonly affected and the middle zones least commonly, and definitely abnormal values ($\tilde{V} < 50$) were recorded significantly less often ($\underline{P} < 0.05$) by counter 3 than by any other[103].

Regional $\tilde{V}$ were averaged to determine mean $\tilde{V}$ in each patient, giving an index of overall ventilatory abnormality as assessed by ^{133}Xe. There was significant correlation ($\underline{r} = 0.71$, $P < 0.05$) between MMFR and mean $\tilde{V}$ (Fig.42).

The distribution of perfusion was not uniform and was related to the distribution of ventilation. If perfusion distribution were dependant upon ventilation distribution, shifts in perfusion from area to area would be determined by the relative degrees of ventilation of the areas involved. Thus, in patient SW (Fig. 40) the borderline $\tilde{V}$ in region R_4 reflected one of his most severely underventilated regions, which might then be underperfused; by

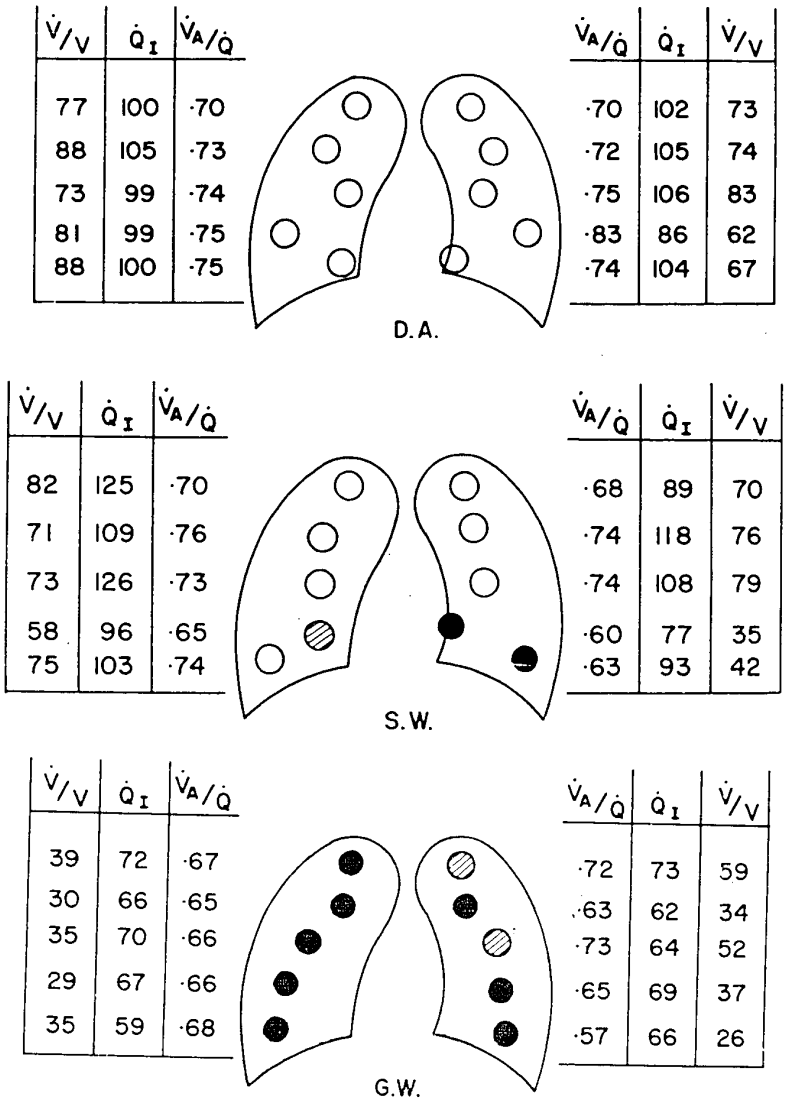


Fig. 40. Results of ^{133}Xe studies in three asthmatics. Regional $\dot{V}_A/\dot{Q}$, $\dot{Q}_I$ and ventilation per unit volume ($\dot{V}/V = \bar{\dot{V}}$) are shown next to the counter fields where they were measured. Regions which were normally ventilated are represented by open circles, regions with abnormal ventilation are indicated by filled (black) circles, and regions with borderline ventilation are represented by shaded circles. See text for discussion.

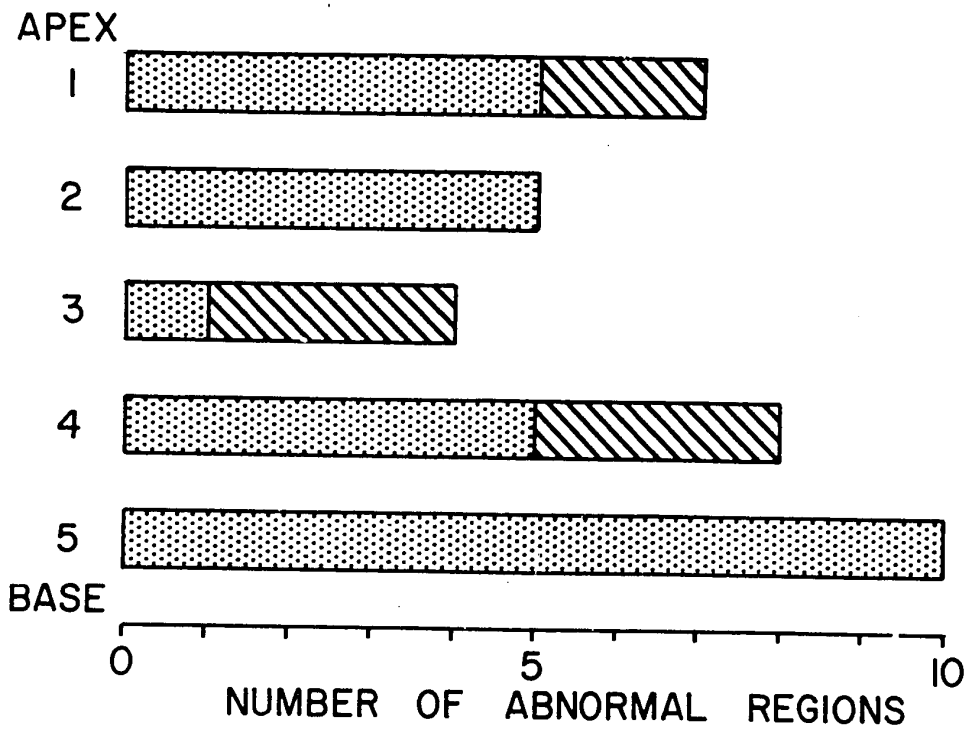


Fig. 41. Regional incidence of ventilation impairment. Ascissa shows number of regions which were abnormal (stippled) or borderline (hatched). Ordinate shows lung regions from apex to base, designated as counter fields. Data from right and left lungs were combined in this figure.

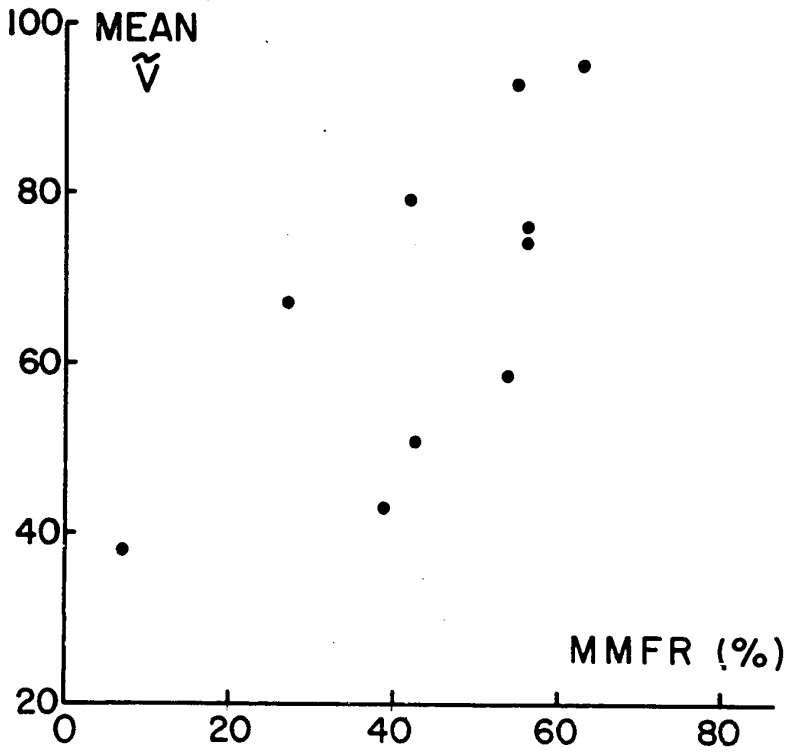


Fig. 42. Correlation of over-all ventilation impairment as assessed by ^{133}Xe with maximum mid-expiratory flow rate (MMFR). Over-all impairment as measured with ^{133}Xe was obtained by averaging all regional values of $\tilde{V}$ in each patient (ordinate). Figures for MMFR are percentages of predicted normal values.

contrast, a similar borderline value $\tilde{V}$ in patient GW (Fig. 40) represented this patient's best-ventilated region, which might then be overperfused. To take account of this, relative regional ventilation was computed in each patient by comparing individual regional $\tilde{V}$ with the mean $\tilde{V}$ of well-ventilated regions ($\tilde{V} > 60$). Similarly, relative regional perfusion was calculated in each patient by relating regional $\dot{Q}_I$ to the mean $\dot{Q}_I$ of normally ventilated regions. In the case of GW in whom no region exhibited $\tilde{V} > 60$, region L_3 ($\tilde{V} = 59$) was used as the standard for computation of relative regional ventilation and relative regional perfusion. Use of relative regional ventilation and relative regional perfusion allows inclusion of all patients studied in a single comparison of ventilation distribution with perfusion distribution. The resulting plot is shown in Fig. 43 ($r = 0.43$ and $P < 0.01$): when regional $\tilde{V}$ was < 70% of normal, regional perfusion also was decreased. Relative perfusion per unit volume appeared to be independent of $\tilde{V}$ when the latter exceeded 70% of normal.

Comparison of the results obtained during ^{133}Xe studies with these obtained five years previously[102] showed changes in most cases, generally with parallel change in the MMFR. (Although three counters were used in the first study and five in the second, the total area covered was the same.) During the present study, abnormal ventilation was found in a smaller area of the lungs in three patients (SW, KS, and AG) and in a greater area in four (PT, GW, WA, and MR); only one (NT) showed no abnormality on either occasion. Fig. 44 shows comparisons of findings in three patients. The greatest degree of improvement occurred in AG (Fig. 44), and deterioration was most marked in WA (Fig. 44). Finally, PT (Fig. 44) had clearing of one region while others became involved: this was the only clear-cut example of this phenomenon.

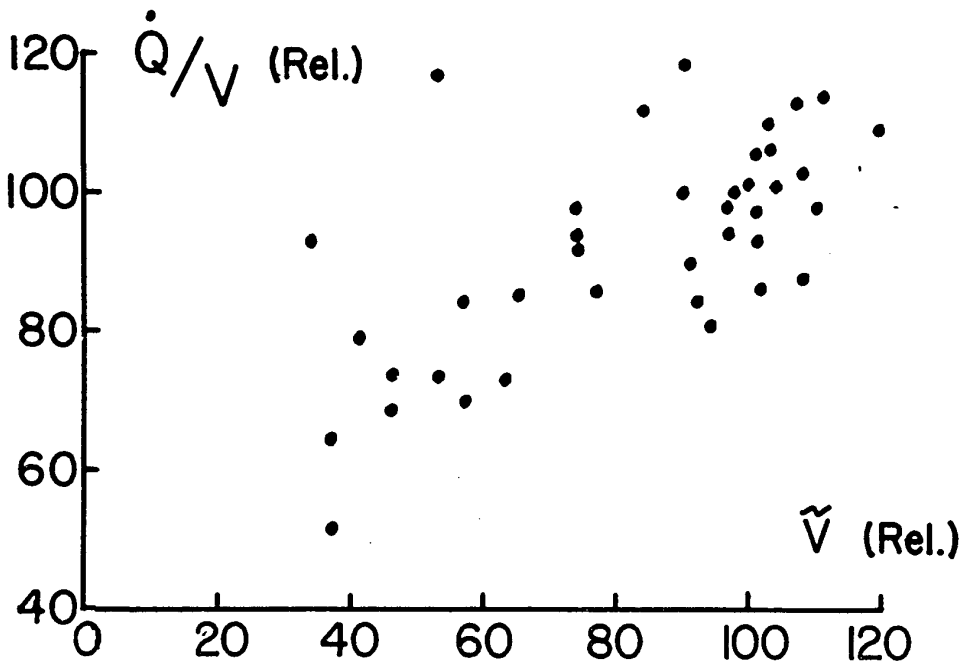


Fig. 45. Correlation of relative regional blood flow per unit volume ($\dot{Q}/V$, ordinate) with relative regional ventilation per unit volume ($\tilde{V}$, abscissa). Data from all lung regions of nine patients are shown. ($r = 0.45$, $P < 0.01$).

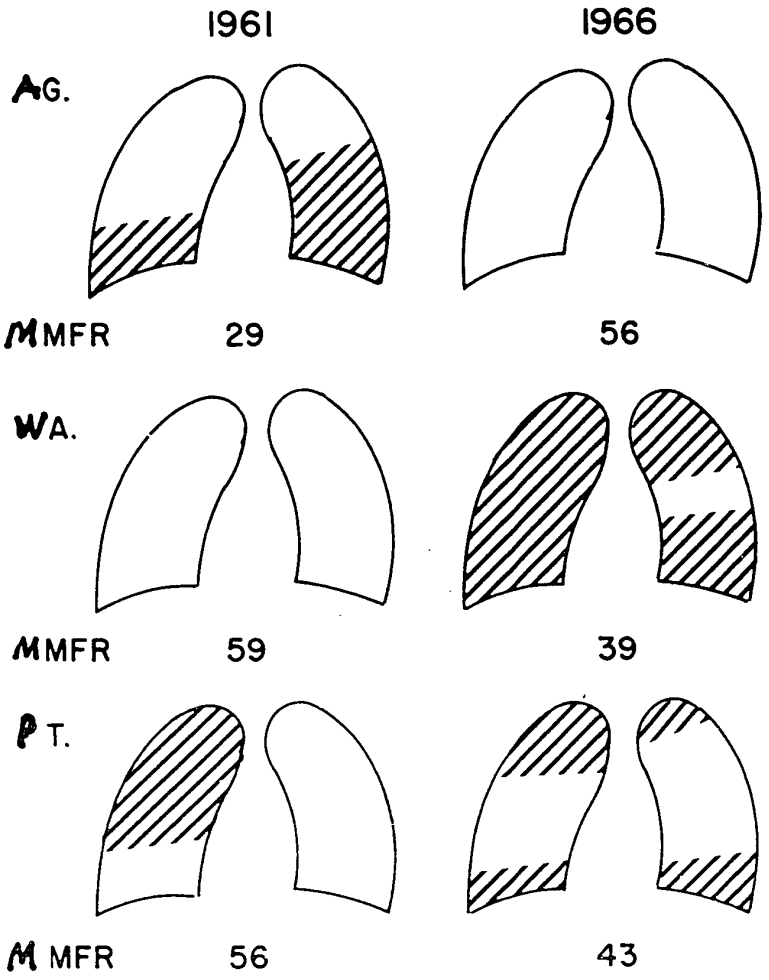


Fig. 44. Changes in regional distribution of abnormality of pulmonary function. Regions in which function was abnormal are hatched. Figures for MMFR are percentages of predicted normal values.

These patients present a spectrum. Four were normal, four showed both normal regions and regions with depressed $\tilde{V}$ and $\dot{V}_A/\dot{Q}$, and two patients demonstrated abnormal $\tilde{V}$ in virtually all lung regions. Of these, the patients who had both normal and abnormal regions are of the most immediate interest. These patients showed clear-cut regional differences in $\dot{V}_A/\dot{Q}$ and $\tilde{V}$, and therefore must have had abnormalities of overall gas exchange. To assess this, reasonable assumptions were made regarding the composition of mixed venous blood, and, using the $\dot{V}_A/\dot{Q}$ of Table 13 plus the $O_2 - CO_2$ and $CO_2 - N_2$ diagrams, regional gas tensions were computed. Then, assuming that each lung region was equal in volume, that no lung tissue existed outside the regions examined, and that regional perfusion per unit volume was distributed according to regional $\dot{Q}_i$, the contribution of each region to mixed alveolar gas and arterial blood was computed. The results, of course, were values for the overall arterial-alveolar differences which would have been present had the figures of Table 13 accurately represented all gas exchange. The results indicated trivial embarrassment of overall gas exchange - D_{N_2} = 1-2 mmHg and D_{O_2} = 2-3 mmHg.

Comparison of the above values with D_{O_2} and D_{N_2} measured in comparable patients would be of interest. If the measured values exceeded those predicted on the basis of ^{133}Xe studies, then regional $\dot{V}_A/\dot{Q}$ measurements must have underestimated $\dot{V}_A/\dot{Q}$ differences which, in fact, existed. The most obvious reason for such a discrepancy would be regional inhomogeneity, i.e., variation of $\dot{V}_A/\dot{Q}$ within single lung regions; in the presence of such inhomogeneity, the value of regional measurement is reduced.

Measurement of D_{O_2} and D_{N_2} are usually carried out in patients with greater abnormality of pulmonary function than that shown by SW, PT, KS and MR. However, Valabhji[104] examined D_{O_2} in patients with slight depression of the FEV_1 with essentially normal results, agreeing with our predictions.

Also, D_{N_2} may be calculated from data reported by Ledbetter, Bruck and Farhi[41] who used an N_2 washout technique in studying children with asthma. The D_{N_2} were 2-4 mmHg in the children with the least severe airway obstruction. If a D_{N_2} of 1-2 mmHg is allowed for normal non-regional $\dot{V}_A/\dot{Q}$ inhomogeneities[32], then it may be said that these results agree with our predictions. Thus, it may be that in our patients showing an admixture of normal and abnormal regions, the ^{133}Xe results were accurate representations of gas exchange.

If, as suggested by the above, intraregional inhomogeneities of function were not important in these patients, we would expect that ventilation per unit volume computed after infusion ($\tilde{V}_p$) would be similar to that computed after rebreathing ($\tilde{V}_i$). As shown in Fig. 45, this was indeed the case. It must be remembered, however, that this evidence for intraregional homogeneity of function is limited. Discrepancies between $\tilde{V}_p$ and $\tilde{V}_i$ are seen only in the presence of certain kinds of inhomogeneities of both $\dot{V}_A/\dot{Q}$ and ventilation. Further, as noted previously, assessment of regional ventilation by regional $T\frac{1}{2}$ is a relatively crude procedure. Had more rigorous analysis of washout curves been possible, evidence for intraregional inhomogeneity of function might have emerged. On the other hand, the importance of inhomogeneities detected this way would probably be less than those indicated by differences between $\tilde{V}_p$ and $\tilde{V}_i$.

However, some absolutely quantitative interpretation of regional $\tilde{V}$ must be attempted in two cases (WA and GW). These patients had grossly decreased $\tilde{V}$ in virtually all lung regions. If the regional washouts had reflected the state of all of the lung units, the only possible explanation for the gross prolongation of all of the regional washouts would have been that these

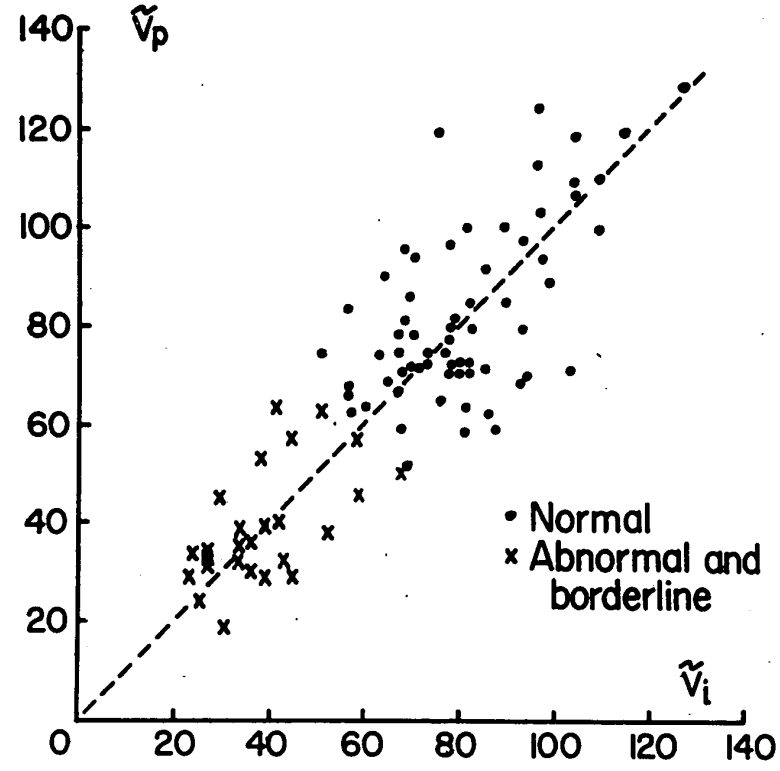


Fig. 45. Comparison of regional washout of infused ^{133}Xe ($\tilde{V}_p$) and inspired ^{133}Xe ($\tilde{V}_i$). Dashed line is the line of identity. Figures for $\tilde{V}_i$ were not obtained for WA, so the number of abnormal regions is less than in Fig. 41.

patients either were not ventilating adequately or had extraordinarily large FRC. Since neither was the case, regional washouts did not reflect the state of all lung units. Therefore, relatively well-ventilated units, although not detected in these studies, must have existed; presumably such units had high $\dot{V}_A/\dot{Q}$. Since these well-ventilated units had no regional representation, and since $T\frac{1}{2}$ after rebreathing and after infusion were similar in GW, it is likely that these units were relatively evenly distributed throughout the lungs and amounted to a small volume. There can be no question that important degrees of intraregional inhomogeneity of function existed in these two patients, who were the most severely affected in the series.

Regions with decreased ventilation were underperfused (Fig. 43). The normal blood-flow distribution found in patients with asthma in a previous study[102] probably was due to their upright posture; since blood-flow distribution in the erect normal subject is uneven[56], abnormalities are difficult to detect. Since it is likely that the lung parenchyma was morphologically normal in these patients, regional decreases in flow probably were functional in origin. This hypothesis is supported by the findings of Woolcock, McRae, Morris and Read[105], who showed that abnormalities of blood-flow distribution may occur temporarily during exacerbations of asthma. Hypoventilated regions have low $\dot{V}_A/\dot{Q}$ and, therefore, have relatively low $P_{A_{O_2}}$; and since alveolar hypoxia is a known pressor agent for the pulmonary circulation[97], regional hypoxic vasoconstriction may divert flow from hypoventilated regions. This hypothesis does not necessarily explain the severe degree of underperfusion of the right lung base in patient KS; though the $\dot{V}_A/\dot{Q}$ was lower in the hypoventilated region than elsewhere in the lung, the overall $\dot{V}_A/\dot{Q}$ was high, and

the hypoventilated, underperfused region may have had a PO_2 of about 100 mmHg. This value is considerably higher than that which has been shown to influence hemodynamics[97].

The positive correlation between MMFR and the overall ventilatory impairment is of interest. Theoretically, there is no need for such a correlation, regional washouts being more analogous to tests involving inert-gas washout or washin. It is apparent that both tests, though dissimilar, are sensitive to the regional and overall increases in airway resistance that presumably constitute the major physiologic pulmonary abnormality in asthma. The correlation between mean $\tilde{V}$ and MMFR (Fig. 42) would be greater if NT and SW were excluded: these patients had lower MMFR values than might be expected on the basis of their mean $\tilde{V}$. These patients also had unusually slow, regular breathing patterns, with a frequency of 3/min. in SW and 5-6/min. in NT. Such low respiratory frequencies could result in normal values by ^{133}Xe testing, by minimizing inequalities in ventilation distribution that were due to inequalities in regional time constants (regional resistance X regional compliance).

The four subjects who showed no abnormality of regional lung function had reduced MMFR and, therefore, some degree of airway obstruction. This could mean that the obstruction was of similar, mild degree throughout the lungs. Since our methods are more sensitive to interregional differences in function than to deviations from "absolute normal," evenly distributed minor abnormalities of function could go undetected.

If the present small series may be taken as a representative cross-section of patients with asthma, a sequence is suggested. A relatively mild

degree of obstruction (MMFR > 50% predicted) tends to be distributed evenly throughout the lungs. Progression of the condition appears to be uneven, resulting in greater degrees of obstruction in some regions than in others and greater decreases in function in the regions most affected. Fig. 41 indicates that there may be a regional sequence of involvement, function deteriorating most often, and perhaps earliest, at the lung bases, and then at the apices, with a tendency for the middle zones to be spared; however, the findings shown in Fig. 44 suggest that a sequence may change with time. As implied above, severe airway obstruction involves all lung zones, though to different degrees in different regions. Although the reasons for these findings are not apparent, the findings themselves may be important to a consideration of the pathogenesis of asthma.

In summary, the regional distribution of pulmonary ventilation and perfusion, and regional alveolar ventilation/perfusion ratios, were measured in 10 patients with asthma in remission. Four subjects had normal ventilation distribution, 4 had hypoventilation in some regions and normal ventilation in others, and 2 patients had abnormal ventilation in almost all lung regions. The lung bases were involved most frequently and the middle zones least frequently. Correlation was good between the degree of over-all ventilatory impairment calculated from ^{133}xenon values and measurement of the maximal mid-expiratory flow rate the same day. In the 8 subjects who had been studied similarly 5 years previously, changes in regional function correlated in general with changes in over-all function.

Regions which were hypoventilated had low $\dot{V}_A/\dot{Q}$ and also tended to be hypoperfused. There was evidence of intraregional inhomogeneity of function in the two most severely affected patients. However, this was not true of

other subjects; no systematic differences between $\tilde{V}_p$ and $\tilde{V}_i$ were seen and predicted values for D_{O_2} and D_{N_2}, though small, were similar to those derived from the literature.

6. BRONCHITIS

Chronic bronchitis has been defined as the occurrence of cough and expectoration "on most days for at least three months in the year during at least two years"[106]. Such broad criteria may apply equally to both an otherwise asymptomatic cigarette-smoker and a patient in florid respiratory failure, and it follows that extreme variations in pulmonary function and morbid anatomy must exist within such a definition. Furthermore, chronic bronchitis is known to be commonly associated with various degrees of pulmonary emphysema, a lesion which in itself causes respiratory dysfunction. Many studies of the physiology of "chronic bronchitis" have been concerned with severely disabled patients in whom the probability of co-existent widespread emphysema was high. Consequently, the meaning of a clinical diagnosis of chronic bronchitis in a patient with little or no disability is not clear. Relatively minor abnormalities of the usual tests of pulmonary function are commonly found in such patients and their significance is not well understood.

We studied 10 patients with chronic bronchitis in whom the probability of widespread pulmonary emphysema was believed to be low. The subjects were drawn from a larger group of selected, well-studied patients with bronchitis who were participants in a prospective study by the Canadian Department of Veterans' Affairs of the natural history of chronic bronchitis[107, 108].

The subjects for this study were selected on the basis of results of pulmonary function tests conducted during the previous five years. Detailed information was available concerning the patients' histories in regard to occupation, smoking, clinical symptoms, daily sputum volume, and the appearance of plain films of the chest (Table 14); these particulars were known not to

TABLE 14. PARTICULARS OF BRONCHITICS STUDIED. THE SUBJECTS ARE LISTED IN ORDER OF SEVERITY OF DISEASE EFFECT AS JUDGED BY ROUTINE FUNCTION TESTS

Occupation	Age at which smoking began	Cigarettes per week	Age at which cough began	Daily sputum vol (ml)	Hemoptysis	Dyspnea*	Past history of pneumonia or pleurisy	Chest roentgenogram
Orderly		110	26	1	0	+	0	Lung fields overinflated; abnormal vasculature
Clerk	15	105	24	2	+	++	+	Increased lung markings
Bartender	18	140	34	2	0	+	0	Lung fields overinflated; increased lung markings
Inspector	18	140	21	2	0	+	+	Lung fields overinflated; bronchial walls visible
Machinist (metal)	14	35	31	4	+	++	+	Lung fields overinflated
Salesman	116	130	26	2	+	+	+	Lung fields overinflated; increased markings
Launderer	17	140	21	3	+	+	0	small bullae Lung fields overinflated
Machine tester	20	175	34	3	+	+	+	Lung fields overinflated
Cook	28	10	34	Varies	0	0	0	Bronchial walls visible
Orderly	12	70	30	2	0	+	0	Lung fields overinflated small bullae

nly occasionally
f dyspnea, has to walk slower than his peers on the level
of dyspnea, has to stop for breath when walking at his own pace on the level

TABLE 14. PARTICULARS OF BRONCHITICS STUDIED. THE SUBJECTS ARE LISTED IN ORDER OF SEVERITY OF DISEASE EFFECT AS JUDGED BY ROUTINE FUNCTION TESTS

Patient	Age	Occupation	Age at which smoking began	Cigarettes per week	Age at which cough began	Daily sputum vol (ml)	Hemoptysis	Dyspnea*	Past history of pneumonia or pleurisy	Chest roentgeno
1	45	Orderly		110	26	1	0	+	0	Lung fields ove abnormal vas
2	48	Clerk	15	105	24	2	+	++	+	Increased lung
3	49	Bartender	18	140	34	2	0	+	0	Lung fields ove increased lung
4	46	Inspector	18	140	21	2	0	+	+	Lung fields ove bronchial walls
5	53	Machinist (metal)	14	35	31	4	+	++	+	Lung fields ove
6	48	Salesman	116	130	26	2	+	+	+	Lung fields ove increased markir
7	44	Launderer	17	140	21	3	+	+	0	small bullae Lung fields ove
8	58	Machine tester	20	175	34	3	+	+	+	Lung fields over
9	56	Cook	28	10	34	Varies	0	0	0	Bronchial walls
10	54	Orderly	12	70	30	2	0	+	0	Lung fields over small bullae

* 0 Dyspnes only occasionally
\+ Because of dyspnea, has to walk slower than his peers on the level
++ Because of dyspnea, has to stop for breath when walking at his own pace on the level

have changed significantly during the five-year observation period[108]. The patients' ages ranged from 44 to 58 years, none was employed in a particularly dusty job. All had smoked cigarettes for at least 20 years, although two (no. 5 and 9) could be termed light smokers. All patients gave a history of chronic productive cough of at least 15 years' duration and five had experienced hemoptysis. Five patients had past histories suggestive of pneumonia or pleurisy. All 10 subjects had experienced dyspnea, and with one exception (no. 9) stated that because of this symptom they had to walk more slowly on the level than their peers. In addition two patients stated that at times they had to stop for breath when walking at their own pace on the level. The chest roentgenogram was interpreted as showing overinflation in 8 of the 10 patients, with some increased in lung markings in 5. Small bullae were believed to be visible in two patients. It was the opinion of an independent radiologist that no patient demonstrated x-ray evidence for widespread pulmonary emphysema.

During the five-year period the subjects had undergone serial pulmonary function tests[107]; only one had been tested less than 10 times and the mean for the group was 13. Lung volumes were measured by spirometry and helium dilution and included total lung capacity (TLC), vital capacity (VC), functional residual capacity (FRC), and residual volume (RV). Two measurements of expiratory flow were made, the maximal mid-expiratory flow rate (MMFR) and the forced expired volume during the first 0.75 sec. of expiration ($FEV_{0.75}$). The helium mixing index (mixing efficiency, ME), fractional uptake of CO, and steady-state CO-diffusing capacity also were measured. On the day of the ^{133}Xe study, flow rates were measured and lung volumes and ME (%) were determined

with the patients supine. On another occasion, within one year of the ^{133}Xe study, fractional CO uptake and diffusing capacity were measured and the lung volumes were determined with the patient in the conventional position (sitting).

Cardiac output was measured several times during the ^{133}Xe study using indicator dilution technique[70]; Coomassie blue was the indicator and it was measured with an ear oximeter[68, 69].

The ^{133}Xe techniques and calculations were identical to those employed in the study of asthmatics. The patients were studied in the supine position with 5 counters positioned posterior to each lung. Each patient underwent a 10 minute intravenous infusion of ^{133}Xe, a 10 minute period of ^{133}Xe rebreathing and 2-4 bolus injections of ^{133}Xe. Regional $\dot{V}_A/Q$ were calculated using count rates from rebreathing and infusion (eq. III-7). Regional $\dot{Q}_I$ and $\dot{Q}_i$ were computed from count rates measured after bolus injection combined with those measured during rebreathing. Regional ventilation was assessed by measuring regional $T\frac{1}{2}$; these were converted to regional $\tilde{V}$. $\tilde{V}$ were measured twice in each region, once during washout after infusion ($\tilde{V}_p$) and once during washout after rebreathing ($\tilde{V}_i$). Regional $\tilde{V} > 60$ were defined as normal, $\tilde{V} < 50$ were designated abnormal and $\tilde{V}$ between 50 and 60 were designated borderline.

Table 15 shows the results of pulmonary function tests contemporary with the ^{133}Xe studies. Subjective evaluation of these tests was made by an independent observer before the results of the ^{133}Xe studies were available. The patients were numbered according to this assessment; patient no. 1 was thought to demonstrate the least abnormality of function and no. 10 the greatest. Values for diffusing capacity are not shown since the significance of this test is similar to that of CO extraction ratio and, in these patients, the latter was more reproducible.

TABLE 15. PULMONARY FUNCTION TESTS IN PATIENTS WITH BRONCHITIS

(Predicted normal values are shown in parentheses)

Patient	Vital Capacity (L)	Residual Volume (L)	Total Lung Capacity (L)	Maximal Midexpiratory Flow Rate (L/sec)	Forced Expiratory Volume, 0.75sec (L)	Mixing Efficiency * (%)	CO Extraction Ratio
1	2.99 (3.71)	2.33 (1.64)	5.32 (5.46)	4.50 (3.57)	2.84 (2.70)	n.s.	.476 (.465)
2	2.99 (3.58)	1.80 (1.56)	4.79 (5.24)	3.75 (3.56)	2.35 (2.80)	84 (63)	.480 (.472)
3	2.89 (3.52)	1.98 (1.59)	4.88 (5.21)	1.78 (3.48)	1.45 (2.75)	82 (62)	.466 (.465)
4	3.18 (4.25)	2.33 (1.81)	5.51 (6.20)	3.05 (3.81)	2.50 (2.84)	81 (64)	.460 (.462)
5	3.09 (4.23)	2.91 (1.98)	6.00 (6.34)	2.87 (3.61)	2.65 (3.13)	61 (61)	.549 (.438)
6	3.12 (4.16)	3.47 (1.86)	6.15 (6.92)	2.50 (3.68)	2.62 (2.72)	46 (65)	.408 (.452)
7	2.86 (3.81)	2.72 (1.59)	5.58 (5.51)	1.80 (3.69)	1.85 (2.97)	71 (65)	.438 (.475)
8	2.90 (4.36)	4.17 (2.21)	6.70 (7.07)	0.95 (3.47)	1.38 (2.50)	60 (57)	.334 (.412)
9	2.63 (3.43)	1.77 (1.79)	4.39 (5.33)	2.10 (3.20)	1.72 (2.47)	71 (58)	.539 (.434)
10	1.31 (3.53)	3.06 (1.74)	4.37 (5.37)	0.75 (3.32)	0.72 (2.38)	57 (59)	.388 (.444)

* patients supine

1	2.99 (3.71)	2.33 (1.64)	5.32 (5.46)	4.50 (3.57)	2.84 (2.70)	n.s.	.476 (.465)
2	2.99 (3.58)	1.80 (1.56)	4.79 (5.24)	3.75 (3.56)	2.35 (2.80)	84 (63)	.480 (.472)
3	2.89 (3.52)	1.98 (1.59)	4.88 (5.21)	1.78 (3.48)	1.45 (2.75)	82 (62)	.466 (.465)
4	3.18 (4.25)	2.33 (1.81)	5.51 (6.20)	3.05 (3.81)	2.50 (2.84)	81 (64)	.460 (.462)
5	3.09 (4.23)	2.91 (1.98)	6.00 (6.34)	2.87 (3.61)	2.65 (3.13)	61 (61)	.549 (.438)
6	3.12 (4.16)	3.47 (1.86)	6.15 (6.92)	2.50 (3.68)	2.62 (2.72)	46 (65)	.408 (.452)
7	2.86 (3.81)	2.72 (1.59)	5.58 (5.51)	1.80 (3.69)	1.85 (2.97)	71 (65)	.438 (.475)
8	2.90 (4.36)	4.17 (2.21)	6.70 (7.07)	0.95 (3.47)	1.38 (2.50)	60 (57)	.334 (.412)
9	2.63 (3.43)	1.77 (1.79)	4.39 (5.33)	2.10 (3.20)	1.72 (2.47)	71 (58)	.539 (.434)
10	1.31 (3.53)	3.06 (1.74)	4.37 (5.37)	0.75 (3.32)	0.72 (2.38)	57 (59)	.388 (.444)

* patients supine

n.s. not studied

The results were similar in all of the subjects. VC was reduced to about 75% of normal and the ratio of RV to TLC indicated the presence of slight to moderate hyperinflation. Mixing efficiency and CO extraction were virtually normal in all cases. Expiratory flow rates varied from normal or slightly depressed to markedly abnormal (patients no. 7, 8, 10).

In general, it will be noted that the results of these function tests are similar and not grossly abnormal; indeed, the results obtained in patient no. 2 are within normal limits. An exception was patient no. 10 who had very abnormal lung volumes and sharply decreased flow rates.

Table 16 contains the results of the ^{133}Xe studies and Fig. 46 shows results in three patients. Both $\tilde{V}_p$ and $\tilde{V}_i$ are presented because in many cases they differed. In most patients, regional $\tilde{V}_p$ correlated better with regional $\dot{V}_A/\dot{Q}$ than did regional $\tilde{V}_i$; because of this regions were designated normal, borderline, or abnormal, according to $\tilde{V}_p$. Abnormal regions of variable extent were detected in every patient. Only one region with markedly decreased ventilation was detected in patient no. 9. Mild involvement of two regions was apparent in patient no. 4 (Fig. 46). The most severely affected was patient no. 6 (Fig. 46) in whom only one region (left apex) demonstrated $\tilde{V}_p > 60$ and in whom ventilation was severely compromised at both bases. It is of considerable interest that in spite of the striking differences in regional function evident when patients no. 4 and no. 6 were compared (Fig. 46), very little difference was apparent when results of routine pulmonary function tests were compared (Table 15). In contrast, patient no. 10, whose routine function tests were the worst of the series, demonstrated regional function which was intermediate between patients no. 4 and no. 6 (Fig. 46).

1	$\dot{V}_A/\dot{Q}$	0.68	0.54	0.56	0.61	0.60	0.68	0.63	0.61	
	$\dot{Q}_I/\dot{Q}_i$	169/138	188/157	184/142	179/141	101/89	197/160	228/192	216/168	1
	$\tilde{V}_p$	122	54	49	85	23	99	107	87	
	$\tilde{V}_i$	99	51	47	72	36	70	1o2	64	
2	$\dot{V}_A/\dot{Q}$	0.60	0.60	0.50	0.57	0.45	0.62	0.66	0.64	
	$\dot{Q}_I/\dot{Q}_i$	101/80	129/102	124/93	134/104	98/72	114/90	110/88	125/100	
	$\tilde{V}_p$	60	75	36	65	26	90	90	69	
	$\tilde{V}_i$	60	75	33	65	30	60	65	56	
3	$\dot{V}_A/\dot{Q}$	0.69	0.79	0.73	0.65	0.55	0.73	0.77	0.55	
	$\dot{Q}_I/\dot{Q}_i$	87/70	93/76	105/84	84/66	60/45	70/56	91/74	93/70	
	$\tilde{V}_p$	65	65	65	45	31	65	65	33	
	$\tilde{V}_i$	65	59	72	46	37	62	65	62	
4	$\dot{V}_A/\dot{Q}$	0.79	0.77	0.57	0.59	0.66	0.79	0.83	0.82	
	$\dot{Q}_I/\dot{Q}_i$	101/84	93/77	87/67	93/73	90/71	92/76	97/81	85/73	
	$\tilde{V}_p$	88	85	50	58	62	75	75	73	
	$\tilde{V}_i$	78	86	58	64	78	86	76	72	
5	$\dot{V}_A/\dot{Q}$	o.75	0.69	0.70	0.66	0.75	0.72	0.67	0.51	
	$\dot{Q}_I/\dot{Q}_i$	119/98	126/102	110/89	108/88	109/85	101/83	128/102	110/82	1
	$\tilde{V}_p$	106	98	98	106	80	101	98	84	
	$\tilde{V}_i$	98	98	98	106	98	81	87	94	
6	$\dot{V}_A/\dot{Q}$	0.63	0.47	0.37	0.41	0.51	0.63	0.52	0.50	
	$\dot{Q}_I/\dot{Q}_i$	121/96	98/74	52/35	92/65	84/63	120/96	113/86	113/84	
	$\tilde{V}_p$	53	23	8	12	12	62	32	27	
	$\tilde{V}_i$	59	22	11	35	32	64	37	22	
7	$\dot{V}_A/\dot{Q}$	0.39	0.44	0.45	0.40	0.45	0.27	0.33	0.41	
	$\dot{Q}_I/\dot{Q}_i$	85/60	101/63	102/71	120/85	80/58	101/62	87/58	109/78	1
	$\tilde{V}_p$	45	56	61	58	24	n.s.	25	58	
	$\tilde{V}_i$	42	55	74	84	33	28	28	61	
8	$\dot{V}_A/\dot{Q}$	0.65	0.67	0.63	0.49	0.53	0.86	0.68	0.63	
	$\dot{Q}_I/\dot{Q}_i$	138/119	130/105	102/80	108/81	116/87	155/130	159/129	101/80	1
	$\tilde{V}_p$	45	54	43	33	45	82	68	35	
	$\tilde{V}_i$	54	49	45	31	40	51	34	40	
9	$\dot{V}_A/\dot{Q}$	o.68	0.66	0.58	0.66	0.58	0.58	0.65	0.60	
	$\dot{Q}_I/\dot{Q}_i$	93/73	94/84	117/91	109/87	94/73	80/62	90/73	96/76	1
	$\tilde{V}_p$	108	100	100	100	80	86	101	84	
	$\tilde{V}_i$	76	100	92	76	78	54	74	76	
10	$\dot{V}_A/\dot{Q}$	0.64	0.60	0.56	0.50	0.44	0.64	0.63	0.57	
	$\dot{Q}_I/\dot{Q}_i$	102/83	97/78	95/74	103/77	76/55	119/95	119/95	119/91	
	$\tilde{V}_p$	84	64	55	32	26	94	80	59	
	$\tilde{V}_i$	84	60	59	47	39	106	100	94	

* n.s. - not studied

Results from regions with abnormal or borderline $\tilde{V}_p$ ($<$ 60) are underlined.

TABLE 16. RESULTS OF ^{133}Xe STUDIES IN PATIENTS WITH CHRONIC BRONCHITIS

Patient		Right Lung (apex) R_1	R_2	R_3	R_4	(base) R_5	Left Lung (apex) L_1	L_2	L_3	
1	$\dot{V}_A/\dot{Q}$	0.68	0.54	0.56	0.61	0.60	0.68	0.63	0.61	
	$\dot{Q}_I/\dot{Q}_i$	169/138	188/157	184/142	179/141	101/89	197/160	228/192	216/168	1
	$\dot{V}_P$	122	54	49	85	23	99	107	87	
	$\dot{V}_i$	99	51	47	72	36	70	1o2	64	
2	$\dot{V}_A/\dot{Q}$	0.60	0.60	0.50	0.57	0.45	0.62	0.66	0.64	
	$\dot{Q}_I/\dot{Q}_i$	101/80	129/102	124/93	134/104	98/72	114/90	110/88	125/100	
	$\dot{V}_P$	60	75	36	65	26	90	90	69	
	$\dot{V}_i$	60	75	33	65	30	60	65	56	
3	$\dot{V}_A/\dot{Q}$	0.69	0.79	0.73	0.65	0.55	0.73	0.77	0.55	
	$\dot{Q}_I/\dot{Q}_i$	87/70	93/76	105/84	84/66	6θ/45	70/56	91/74	93/70	
	$\dot{V}_P$	65	65	65	45	31	65	65	33	
	$\dot{V}_i$	65	59	72	46	37	62	65	62	
4	$\dot{V}_A/\dot{Q}$	0.79	0.77	0.57	0.59	0.66	0.79	0.83	0.82	
	$\dot{Q}_I/\dot{Q}_i$	101/84	93/77	87/67	93/73	90/71	92/76	97/81	85/73	
	$\dot{V}_P$	88	85	50	58	62	75	75	73	
	$\dot{V}_i$	78	86	58	64	78	86	76	72	
5	$\dot{V}_A/\dot{Q}$	o.75	0.69	0.70	0.66	0.75	0.72	0.67	0.51	
	$\dot{Q}_I/\dot{Q}_i$	119/98	126/102	110/89	108/88	109/85	101/83	128/102	110/82	1
	$\dot{V}_P$	106	98	98	106	80	101	98	84	
	$\dot{V}_i$	98	98	98	106	98	81	87	94	
6	$\dot{V}_A/\dot{Q}$	0.63	0.47	0.37	0.41	0.51	0.63	0.52	0.50	
	$\dot{Q}_I/\dot{Q}_i$	121/96	98/74	52/35	92/65	84/63	120/96	113/86	113/84	
	$\dot{V}_P$	53	23	8	12	12	62	32	27	
	$\dot{V}_i$	59	22	11	35	32	64	37	22	
7	$\dot{V}_A/\dot{Q}$	0.39	0.44	0.45	0.40	0.45	0.27	0.33	0.41	
	$\dot{Q}_I/\dot{Q}_i$	85/60	101/63	102/71	120/85	80/58	101/62	87/58	109/78	1
	$\dot{V}_P$	45	56	61	58	24	n.s.	25	58	
	$\dot{V}_i$	42	55	74	84	33	28	28	61	
8	$\dot{V}_A/\dot{Q}$	0.65	0.67	0.63	0.49	0.53	0.86	0.68	0.63	
	$\dot{Q}_I/\dot{Q}_i$	138/119	130/105	102/80	108/81	116/87	155/130	159/129	101/80	1
	$\dot{V}_P$	45	54	43	33	45	82	68	35	
	$\dot{V}_i$	54	49	45	31	40	51	34	40	
9	$\dot{V}_A/\dot{Q}$	o.68	0.66	0.58	0.66	0.58	0.58	0.65	0.60	
	$\dot{Q}_I/\dot{Q}_i$	93/73	94/84	117/91	109/87	94/73	80/62	90/73	96/76	1
	$\dot{V}_P$	108	100	100	100	80	86	101	84	
	$\dot{V}_i$	76	100	92	76	78	54	74	76	
10	$\dot{V}_A/\dot{Q}$	0.64	0.60	0.56	0.50	0.44	0,64	0.63	0.57	
	$\dot{Q}_I/\dot{Q}_i$	102/83	97/78	95/74	103/77	76/55	119/95	119/95	119/91	
	$\dot{V}_P$	84	64	55	32	26	94	80	59	
	$\dot{V}_i$	84	60	59	47	39	106	100	94	

3 38	0.54 188/157 54 51	0.56 184/142 49 47	0.61 179/141 85 72	0.60 101/89 23 36	0.68 197/160 99 70	0.63 228/192 107 1o2	0.61 216/168 87 64	0.55 199/153 43 43	0.63 149/110 51 n.s.*
) 30	0.60 129/102 75 75	0.50 124/93 36 33	0.57 134/104 65 65	0.45 98/72 26 30	0.62 114/90 90 60	0.66 110/88 90 65	0.64 125/100 69 56	0.48 76/56 21 20	0.43 93/66 16 22
9)	0.79 93/76 65 59	0.73 105/84 65 72	0.65 84/66 45 46	0.55 60/45 31 37	0.73 70/56 65 62	0.77 91/74 65 65	0.55 93/70 33 62	0.61 92/71 36 52	0.81 87/73 65 72
9 4	0.77 93/77 85 86	0.57 87/67 50 58	0.59 93/73 58 64	0.66 90/71 62 78	0.79 92/76 75 86	0.83 97/81 75 76	0.82 85/73 73 72	0.66 95/75 69 78	0.90 89/76 94 86
5 3 6	0.69 126/102 98 98	0.70 110/89 98 98	0.66 108/88 106 106	0.75 109/85 80 98	0.72 101/83 101 81	0.67 128/102 98 87	0.51 110/82 84 94	0.42 111/79 49 63	0.45 134/98 56 90
3 6	0.47 98/74 23 22	0.37 52/35 8 11	0.41 92/65 12 35	0.51 84/63 12 32	0.63 120/96 62 64	0.52 113/86 32 37	0.50 113/84 27 22	0.43 60/42 10 12	0.30 53/34 8 13
9)	0.44 101/63 56 55	0.45 102/71 61 74	0.40 120/85 58 84	0.45 80/58 24 33	0.27 101/62 n.s. 28	0.33 87/58 25 28	0.41 109/78 58 61	0.47 116/86 58 56	0.43 116/83 41 43
5 19	0.67 130/105 54 49	0.63 102/80 43 45	0.49 108/81 33 31	0.53 116/87 45 40	0.86 155/130 82 51	0.68 159/129 68 34	0.63 101/80 35 40	0.46 105/77 25 20	0.44 116/84 25 23
3 3	0.66 94/84 100 100	0.58 117/91 100 92	0.66 109/87 100 76	0.58 94/73 80 78	0.58 80/62 86 54	0.65 90/73 101 74	0.60 96/76 84 76	0.53 115/88 65 64	0.44 102/74 29 39
4 3	0.60 97/78 64 60	0.56 95/74 55 59	0.50 103/77 32 47	0.44 76/55 26 39	0.64 119/95 94 106	0.63 119/95 80 100	0.57 119/91 59 94	0.55 86/66 40 67	0.55 105/81 34 76

with abnormal or borderline $\bar{v}_p$ (< 60) are underlined.

TABLE 16. RESULTS OF ^{133}Xe STUDIES IN PATIENTS WITH CHRONIC BRONCHITIS

ex)	Right Lung		(base)	(apex)		Left Lung		(base)
R_2	R_3	R_4	R_5	L_1	L_2	L_3	L_4	L_5
0.54	0.56	0.61	o.60	0.68	0.63	0.61	0.55	0.63
188/157	184/142	179/141	101/89	197/160	228/192	216/168	199/153	149/110
54	49	85	23	99	107	87	43	51
51	47	72	36	70	1o2	64	43	n.s.*
0.60	0.50	0.57	0.45	0.62	0.66	0.64	0.48	0.43
129/102	124/93	134/104	98/72	114/90	110/88	125/100	76/56	93/66
75	36	65	26	90	90	69	21	16
75	33	65	30	60	65	56	20	22
0.79	0.73	0.65	0.55	0.73	0.77	0.55	0.61	0.81
93/76	105/84	84/66	60/45	70/56	91/74	93/70	92/71	87/73
65	65	45	31	65	65	33	36	65
59	72	46	37	62	65	62	52	72
0.77	0.57	0.59	0.66	0.79	0.83	0.82	0.66	0.90
93/77	87/67	93/73	90/71	92/76	97/81	85/73	95/75	89/76
85	50	58	62	75	75	73	69	94
86	58	64	78	86	76	72	78	86
0.69	0.70	0.66	0.75	0.72	0.67	0.51	0.42	0.45
126/102	110/89	108/88	109/85	101/83	128/102	110/82	111/79	134/98
98	98	106	80	101	98	84	49	56
98	98	106	98	81	87	94	63	90
0.47	0.37	0.41	0.51	0.63	0.52	0.50	0.43	0.30
98/74	52/35	92/65	84/63	120/96	113/86	113/84	60/42	53/34
23	8	12	12	62	32	27	10	8
22	11	35	32	64	37	22	12	13
0.44	0.45	0.40	0.45	0.27	0.33	0.41	0.47	0.43
101/63	102/71	120/85	80/58	101/62	87/58	109/78	116/86	116/83
56	61	58	24	n.s.	25	58	58	41
55	74	84	33	28	28	61	56	43
0.67	0.63	0.49	0.53	0.86	0.68	0.63	0.46	0.44
130/105	102/80	108/81	116/87	155/130	159/129	101/80	105/77	116/84
54	43	33	45	82	68	35	25	25
49	45	31	40	51	34	40	20	23
0.66	0.58	0.66	0.58	0.58	0.65	0.60	0.53	0.44
94/84	117/91	109/87	94/73	80/62	90/73	96/76	115/88	102/74
100	100	100	80	86	101	84	65	29
100	92	76	78	54	74	76	64	39

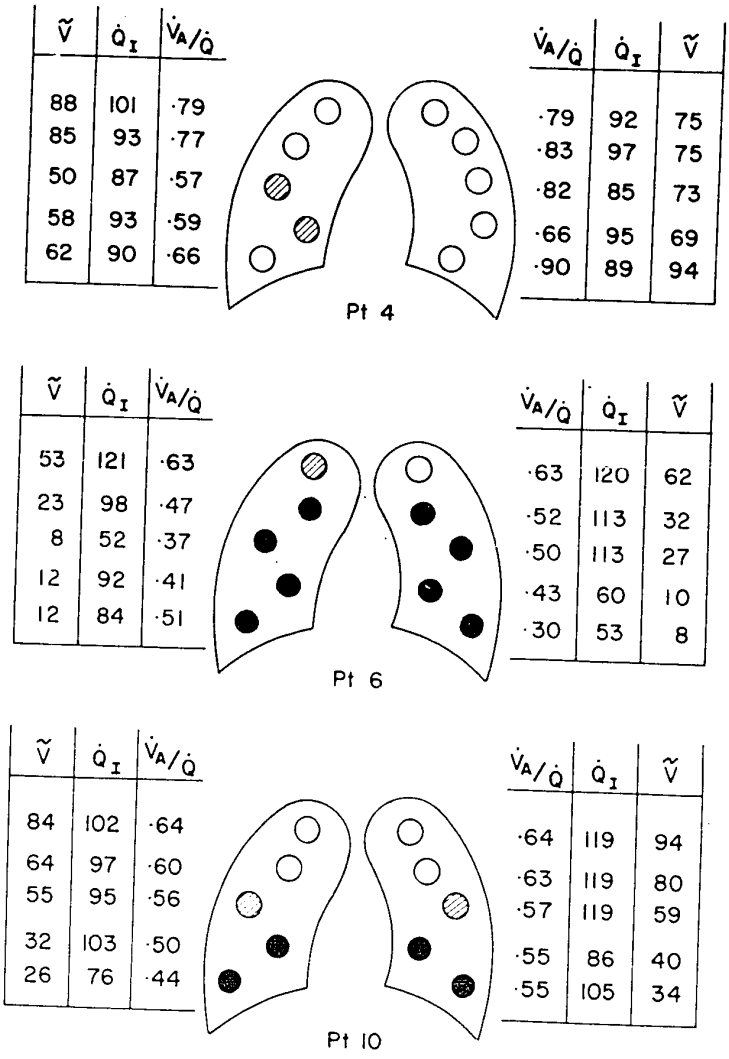


Fig. 46. Results of ^{133}Xe studies in three patients with chronic bronchitis. Counter positions are shown schematically in the lung fields and beside each are the values of $\dot{V}_A/\dot{Q}$, $\dot{Q}_I$ and ventilation per unit volume generated by that counter. Ventilation, signified here by V, was actually computed from washout after infusion and is therefore the same as V_p of Table 16. As in Fig. 40, normally ventilated regions are indicated by open circles, abnormal regions by filled circles, and regions with borderline ventilation are indicated by shaded circles.

The differences between $\tilde{V}_p$ and $\tilde{V}_i$ showed a consistent pattern: when $\tilde{V}_p$ was normal ($>$ 60) it agreed well with $\tilde{V}_i$ (Fig. 47), but when $\tilde{V}_p$ was low, $\tilde{V}_i$ was often higher and sometimes was normal (Fig. 48). Thus, in poorly ventilated regions, washout of infused isotope was slower than that of inhaled isotope. An example of this phenomenon is shown in Fig. 49.

Poorly ventilated regions exhibited lower $\dot{V}_A/\dot{Q}$ than did well ventilated regions in the same patient; when each patient was considered individually, regional $\dot{V}_A/\dot{Q}$ were found to correlate with regional $\tilde{V}_p$ and also usually with regional $\tilde{V}_i$. Differences in regional $\dot{V}_A/\dot{Q}$ tended to reflect the extent of disease; in patient no. 6, for example, $\dot{V}_A/\dot{Q}$ varied twofold, whereas patients with less severe ventilatory defects had smaller regional variations of $\dot{V}_A/\dot{Q}$.

Regional perfusion was related to regional ventilation. In several patients (nos. 1, 6-8, 10), regions with prolonged washout were clearly underperfused. In examining this relationship for the series as a whole, it is invalid to compare $\tilde{V}_p$ (or $\tilde{V}_i$) with the $\dot{Q}_I$ values in Table 16. If perfusion were related to ventilation, regions exhibiting borderline $\tilde{V}_p$ would be underperfused in patient no. 4 and overperfused in patient no. 6 (Fig. 46) since $\tilde{V}_p$ values between 50 and 60 represent poorly ventilated regions in the former and relatively well ventilated regions in the latter. To take account of this, the relative regional ventilation of each patient was obtained by comparing all of his regional $\tilde{V}_p$ with the mean $\tilde{V}_p$ of normal regions ($\tilde{V}_p > 60$), which was set equal to 100. Relative regional perfusion was obtained similarly for each patient by comparing regional $\dot{Q}_I$ to the mean $\dot{Q}_I$ of normally ventilated regions. The resulting plot for all subjects, shown in Fig. 50 ($r = 0.65$; $P < 0.001$), indicated that when $\tilde{V}_p$ was decreased to $<$ 70% of normal, regional perfusion also was decreased.

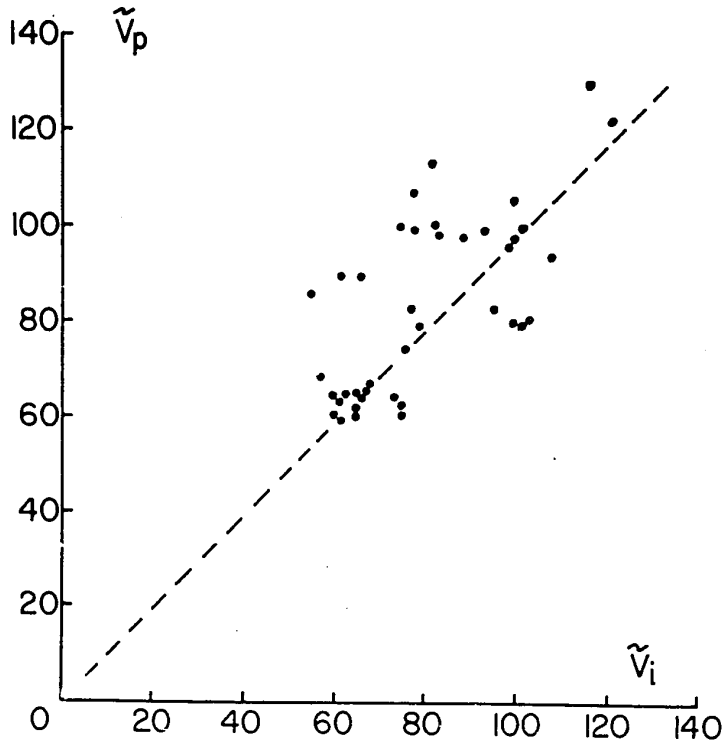


Fig.47. Regional washout after rebreathing ($\tilde{V}_i$) compared with regional washout after infusion ($\tilde{V}_p$) in normal regions ($\tilde{V}_p > 60$). The dashed line is the line of identity.

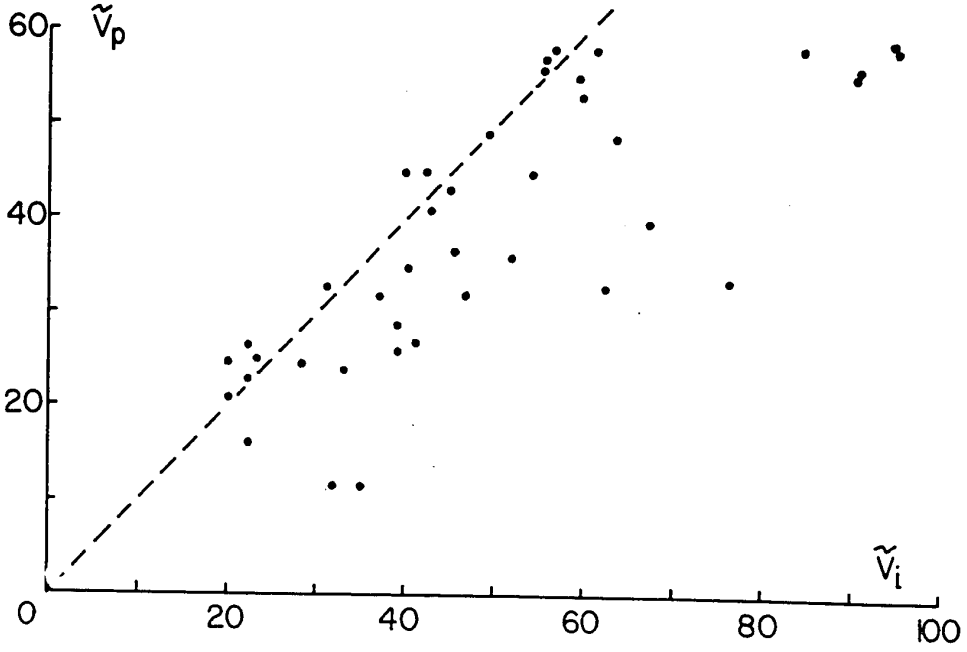


Fig. 48. Regional washout after rebreathing ($\tilde{V}_i$) compared with regional washout after infusion ($\tilde{V}_p$) in abnormal and borderline regions ($\tilde{V}_p < 60$). The dashed line is the line of identity.

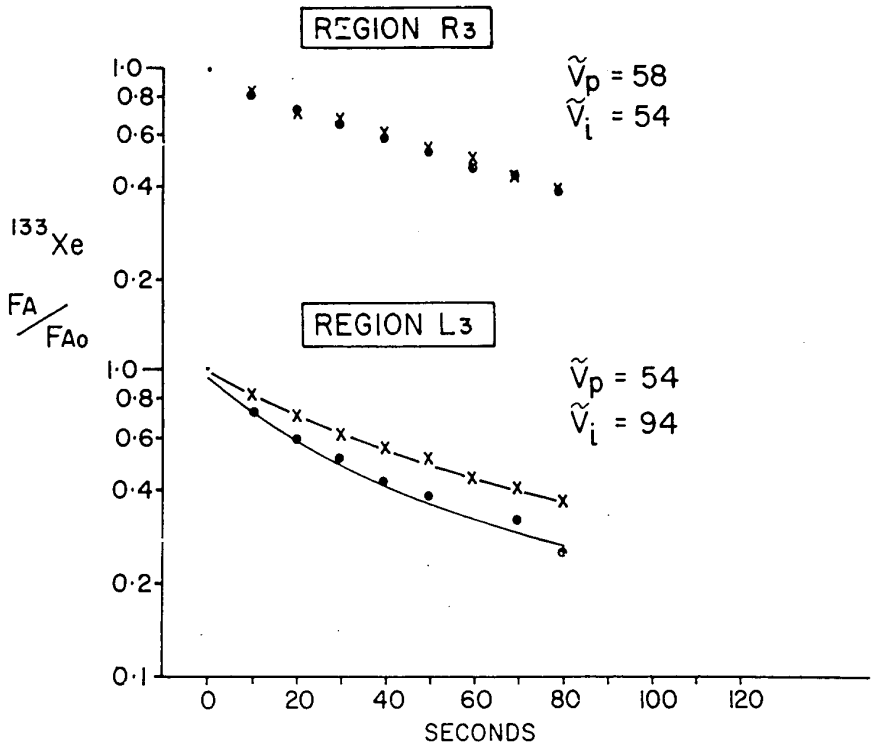


Fig. 49. Semilog plots of the washouts of regions R_3 and L_3 in patient No. 10. Ordinate: regional ^{133}Xe concentration expressed as a fraction of pre-washout concentration. Abscissa: time in seconds. Filled circles represent washout after rebreathing, x's represent washout after infusion. Minute ventilation did not differ during the two washouts.

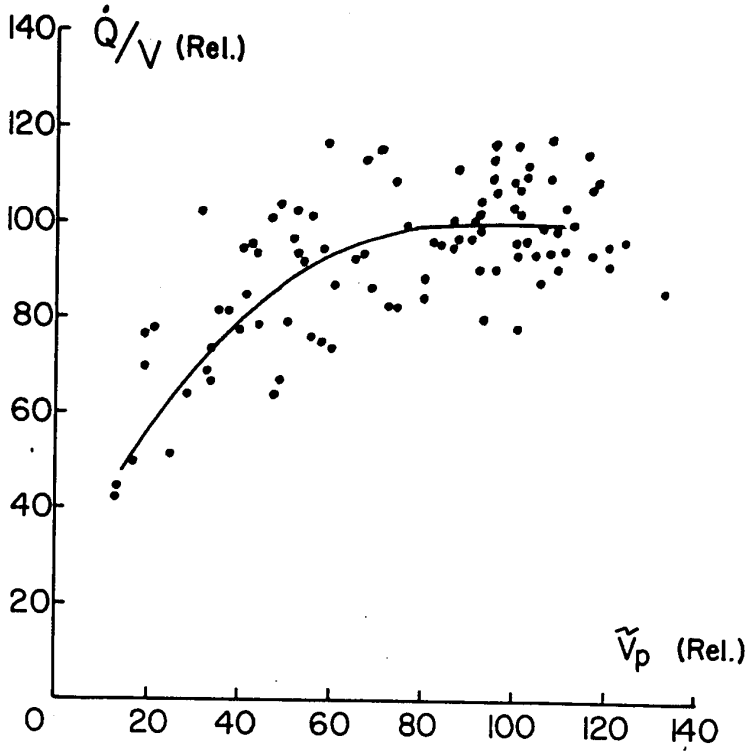


Fig. 50. Relationship of regional perfusion to regional ventilation. Ordinate: relative regional perfusion. Abscissa: relative regional ventilation. The curve was drawn by eye.

Five counters were used over each lung, from apex to base. If it is assumed that the arrangement of the counters did not vary a great deal, five comparable counter positions were examined for each lung of each patient. Data were, therefore, obtained from a total of 20 counters at the lung apex and a similar number at each of four positions progressing to the lung base. $\tilde{V}_p$ values were abnormal in 75% of the basal counters and were borderline or abnormal in 20% of apical counters. Thus, the frequency distribution of abnormal or borderline counters increased from apex to base (Fig. 51). The number of regions involved was significantly less ($P < 0.05$) at the apex (counter 1) than in the mid-zone (counter 3), and the mid-zones were involved less frequently ($P < 0.05$) than were the bases (counter 5). This significance held when either abnormal regions ($\tilde{V}_p < 50$) were considered or when both abnormal and borderline regions ($50 < \tilde{V}_p < 60$) were considered[103].

To compare ^{133}Xe results with tests of over-all function, all regional $\tilde{V}_p$ were averaged in each patient. The resulting mean $\tilde{V}_p$ was thought to represent an index of over-all ventilatory impairment. No correlation existed between each patient's mean $\tilde{V}_p$ and his VC, RV/TLC, MMFR, or FEV or between his mean $\tilde{V}_p$ and his rank in Table 15 (which represented the degree of abnormality of routine function as assessed before ^{133}Xe results were known). There was a suggestive but not significant correlation between mean $\tilde{V}_p$ and mixing efficiency and there was a highly significant correlation between mean $\tilde{V}_p$ and fractional CO uptake (Fig. 52, $r = 0.81$; $P < 0.01$).

It is unlikely that the differences noted between $\tilde{V}_p$ and $\tilde{V}_i$ were due to artifact. As noted previously, there are two major difficulties with the interpretation of regional washout in terms of regional ventilation per unit volume:

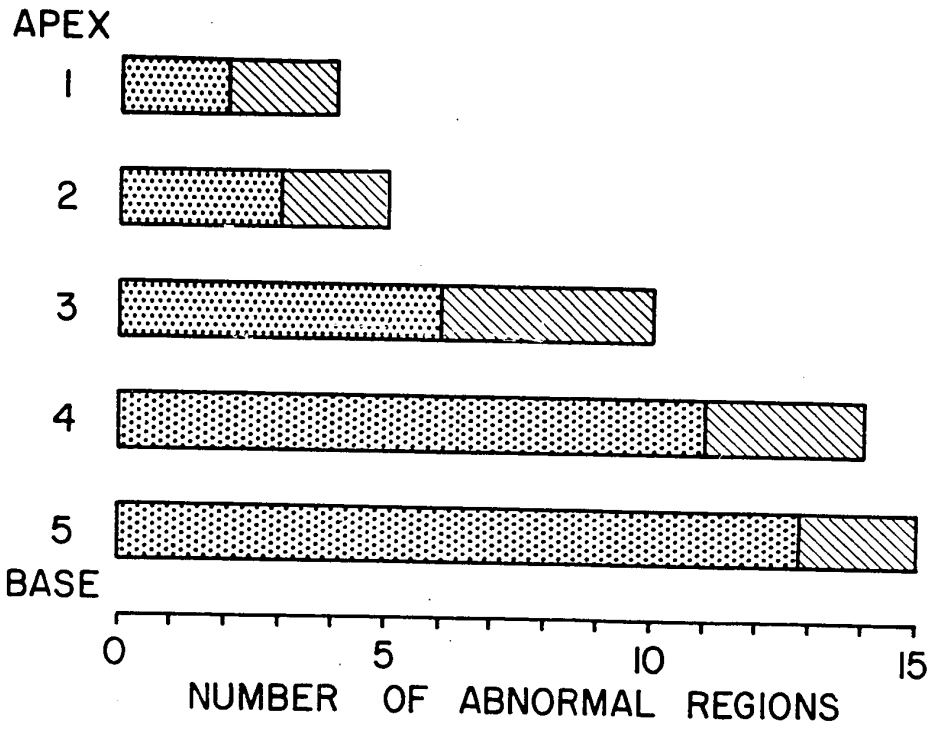


Fig. 51. Incidence of abnormally ventilated regions in patients with bronchitis. Ordinate: counter position from apex to base. Abscissa: number of regions which wer hypoventilated. Stippled bars represent abnormal ($\tilde{V}_p < 50$) regions, and hatched bars represent borderline ($50 < \tilde{V}_p < 60$) regions. No distinction was made between right and left lungs.

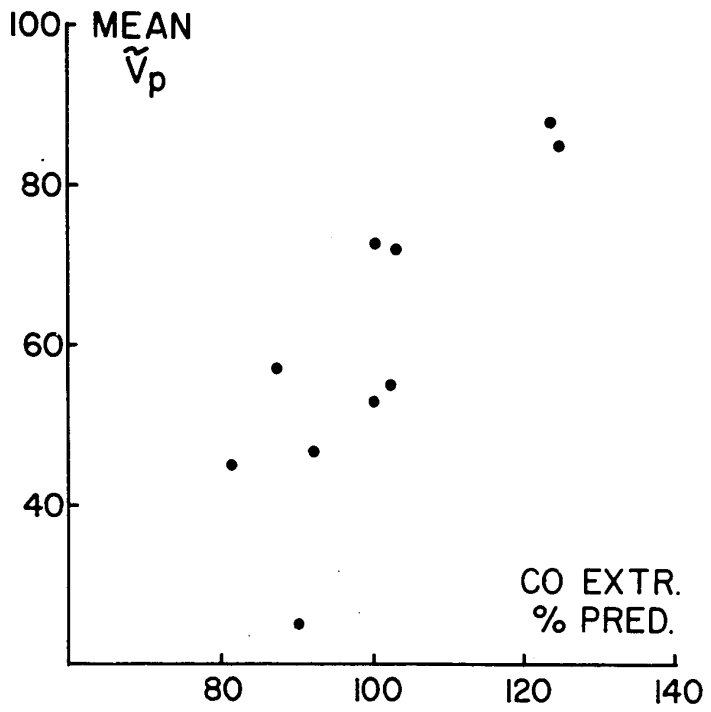


Fig. 52. Relationship between overall ventilatory impairment (mean $\tilde{V}_p$) and CO extraction in bronchitis. Ordinate: mean $\tilde{V}_p$, obtained by averaging all regional $\tilde{V}_p$ in each patient. Abscissa: CO extraction expressed as percent of the predicted normal value. Each point represents a different patient.

1) exchange of ^{133}Xe between regional gas and blood entering and leaving the region during washout, and 2) changes in radiation from the chest wall. If discrepancies between $\tilde{V}_p$ and $\tilde{V}_i$ were artefactual, the artefact should arise from one of these sources.

In regard to circulatory ^{133}Xe exchange, the equation representing the process of regional washout could be written:

$$dF_A/dt = F_{A_0} - \dot{V}_A/V \; F_A - \dot{Q}/V \alpha F_A + \dot{Q}/V \; C_{\bar{v}}$$

where F_{A_0} is regional ^{133}Xe concentration at the onset of washout, $\dot{V}_A/V \; F_A$ is a term representing ^{133}Xe leaving the region via ventilation, $\dot{Q}/V \; F_A\alpha$ represents ^{133}Xe leaving the region via the pulmonary venous blood and $\dot{Q}/V \; C_{\bar{v}}$ is isotope entering the region as it is washout out of the peripheral tissues. This equation is the differentiated form of eq. III-22.

Obviously, the effect of circulatory ^{133}Xe exchange on regional washout depends on the relative magnitude and time courses of $C_{\bar{v}}$ and $F_A\alpha$. The decay function of recirculating Xe concentration ($C_{\bar{v}}$) is independent of lung function and relatively slow[61]. Thus, if $C_{\bar{v}}$ exceeds $F_A\alpha$, washout is prolonged and if $F_A\alpha$ exceeds $C_{\bar{v}}$, washout is shortened. Therefore, for $\tilde{V}_i > \tilde{V}_p$, recirculating Xe concentrations must be higher, relative to regional concentrations, after infusion than after rebreathing. This could not have been the case because the regions in which washout discrepancies were apparent were those with low $\dot{V}_A/\dot{Q}$. These regions must have had relatively high regional concentrations at the end of infusion and relatively low regional concentrations at the end of rebreathing. As noted in section III, recirculating Xe levels at the end of infusion and rebreathing are 50 - 70% of the arterial Xe

concentrations. Arterial Xe concentrations represent the whole lung and, therefore, contain contributions from regions with high $\dot{V}_A/\dot{Q}$ as well as those from regions with low $\dot{V}_A/\dot{Q}$. Thus, at the end of infusion, mixed arterial ^{133}Xe concentrations must be lower than those present in the blood of regions with low $\dot{V}_A/\dot{Q}$, because high $\dot{V}_A/\dot{Q}$ regions are characterized by low ^{133}Xe concentrations. Conversely, at the end of rebreathing arterial ^{133}Xe concentrations must be higher than those in the blood of low $\dot{V}_A/\dot{Q}$ regions, since regions with high $\dot{V}_A/\dot{Q}$ have high ^{133}Xe concentrations during rebreathing. This analysis, then, leads to the conclusion that, when low $\dot{V}_A/\dot{Q}$ regions are considered, at the onset of washout from infusion, mixed arterial ^{133}Xe levels (Ca) are smaller in relation to regional concentrations (F_A) than is the case in the same regions at the end of rebreathing. Since recirculating Xe at the onset of washout is determined by Ca, and since the time course of peripheral washout is the same after both infusion and rebreathing, recirculating ^{133}Xe concentrations may be substituted for Ca in the above conclusion. Thus, in low $\dot{V}_A/\dot{Q}$ regions circulatory ^{133}Xe exchange would tend to make $\tilde{V}_p > \tilde{V}_i$, the opposite of what we found.

The second source of difficulty in the interpretation of regional $T\frac{1}{2}$ is the question of washout of the chest wall. If radiation from the chest wall was a more significant part of the total regional count rate during infusion than during rebreathing and if the level of background changed significantly during washout, $\tilde{V}_p$ might be lengthened more than $\tilde{V}_i$. Such was probably not the case. As noted earlier, isolated chest wall washout is quite slow, and could influence regional washouts only if chest wall radiation amounted to a major part of total regional radiation. In these patients, chest wall radiation exceeded 10% of total radiation only at the lung apices; it was precisely these regions which showed the fewest washout discrepancies.

Finally, in the preceding sections we have seen that neither asthmatics nor patients with bronchiectasis demonstrated washout discrepancies though these patients had regions which functioned as badly as many of those noted in bronchitis. Since the techniques involved were identical in all three sets of patients, it is most improbable that the washout discrepancies observed in bronchitis were due to artefact.

These differences are best explained on the basis of functional inhomogeneity within single lung regions. With one exception (discussed later) washout discrepancies followed a uniform pattern: differences occurred in areas with low $\dot{V}_A/\dot{Q}$ and abnormal $\tilde{V}_p$; washout of infused isotope was slower than that of inhaled isotope; ($\tilde{V}_p < \tilde{V}_i$) and though $\tilde{V}_i$ were higher than $\tilde{V}_p$ they were seldom normal. These findings indicated a consistent pattern of regional inhomogeneity. Regions in which $\tilde{V}_p < \tilde{V}_i$ contained (at least) two groups of units, one of which had lower values of $\dot{V}_A/\dot{Q}$ and ventilation per unit volume than did the other. During infusion, regional ^{133}Xe concentrations and, therefore, regional count rates, are inversely related to $\dot{V}_A/\dot{Q}$, so that at the end of this procedure the units with lower $\dot{V}_A/\dot{Q}$ contribute more to total regional count rate than would be predicted on the basis of their volume. Conversely, during rebreathing, ^{133}Xe concentration is directly related to $\dot{V}_A/\dot{Q}$, so that at the end of this procedure the units with lower $\dot{V}_A/\dot{Q}$ contribute somewhat smaller amount to the over-all regional count rate than would be predicted on the basis of their volume. Regional washout is dominated by the washout of the group of units within the region which have the greatest initial count rate. Regional washout after infusion reflects relatively low $\dot{V}_A/\dot{Q}$ units and is long when such units are badly ventilated; the washout of the same

region after rebreathing is importantly influenced by units with high $\dot{V}_A/\dot{Q}$ and if these units are well ventilated, $\tilde{V}_p < \tilde{V}_i$.

These principles are illustrated in Fig. 53 which shows washout after rebreathing and infusion from a region composed of two compartments with equal volume and blood flow but a three-fold difference in $\dot{V}_A/\dot{Q}$ and ventilation. A distinct difference between $\tilde{V}_p$ and $\tilde{V}_i$ is apparent.

Pertinent regional washouts have been simulated in the manner of Fig. 53, computing washout from regions consisting of two compartments with equal volumes and perfusions but with different $\dot{V}_A/\dot{Q}$ and ventilations. In such a model we have found that a two-fold difference in compartmental ventilation and $\dot{V}_A/\dot{Q}$ produced rather small (10%) difference between regional $\tilde{V}_p$ and $\tilde{V}_i$. Smaller intraregional differences in ventilation and $\dot{V}_A/\dot{Q}$ would thus not be detected easily. Regional washouts similar to those observed in this study (Table 16) were also simulated; the results showed that Fig. 53 was not an extreme example. Examples of some regions which demonstrated washout discrepancies are shown in Table 17 together with the characteristics of two equal volume, equally perfused compartments compatible with the $\dot{V}_A/\dot{Q}$, $\tilde{V}_p$ and $\tilde{V}_i$ of each of these regions. Compartmental differences in $\dot{V}_A/\dot{Q}$ and ventilation are larger than the differences between regions in the same patient noted in Table 16. Most examples shown contain a compartment with higher $\dot{V}_A/\dot{Q}$ than that observed in any region in that patient; all examples shown contain a compartment with lower $\dot{V}_A/\dot{Q}$ than that observed in any region in that patient. According to this analysis at least 10% of the lung of patient no. 6 (who had a normal $FEV_{0.75}$) was exchanging gas at $\dot{V}_A/\dot{Q} < 0.20$. While the figures of Table 17 may give a clue to the magnitude of intraregional homogeneity which may be present, it must be recalled that these figures are based on an artificial model. Each region was assumed

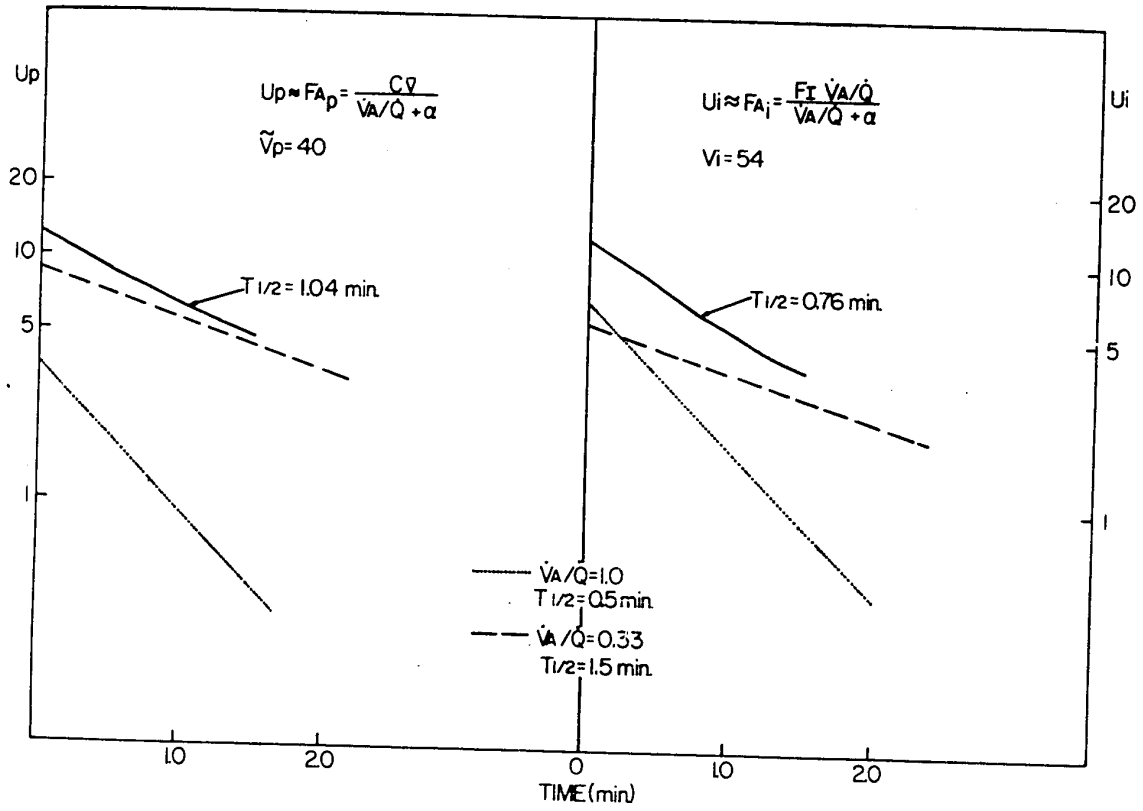


Fig. 55. Washout from a hypothetical region made up of two compartments with different function. Ordinate: count rate in kilocounts per minute on a logarhythmic scale. Abscissa: time in minutes. The two compartments are homogenous and of equal volume, one (dotted line) with $\dot{V}_A/\dot{Q} = 1.0$ and $T_{\frac{1}{2}} = 30$sec, the other (dashed line) with $\dot{V}_A/\dot{Q} = 0.33$ and $T_{\frac{1}{2}} = 90$ sec. The solid lines represent overall regional washout and are simply the sums of compartmental washouts. The equations indicate the factors governing the pre-washout ($t = 0$) compartmental concentrations and count rate. $\tilde{V}_p$ and $\tilde{V}_i$ were computed assuming an FRC of 2.5 L and an overall ventilation of 6.0 L/min.

TABLE 17 - CHARACTERISTICS OF TWO HYPOTHETICAL EQUAL VOLUME, EQUALLY PERFUSED COMPARTMENTS (A,B)
Compatible with observed regional $\dot{V}A/\dot{Q}$, $\tilde{V}p$, and $\tilde{V}i$

		Regional			Compartments A		Compartments B	
Patient	Region	$\dot{V}A/\dot{Q}$	$\tilde{V}p$	$\tilde{V}i$	$\dot{V}A/\dot{Q}$	$\tilde{V}$	$\dot{V}A/\dot{Q}$	$\tilde{V}$
5	L_4	.42	49	63	.28	36	.68	88
6	R_4	.41	12	35	.20	9	1.17	54
	L_5	.30	8	13	.17	6	.61	21
9	L_5	.44	29	39	.29	21	.78	58
10	L_3	.57	54	94	.34	42	1.21	150
	L_4	.55	40	67	.34	30	1.08	94

to consist of only two compartments which had equal volumes and perfusions. These assumptions may minimize true differences in compartmental $\dot{V}_A/\dot{Q}$ and ventilation. If the number, volume and perfusion of compartments were allowed to vary, compartmental differences in $\dot{V}_A/\dot{Q}$ and ventilation much larger than those shown in Table 17 would still be compatible with the regional values of Table 16.

The variations in regional $\dot{V}_A/\dot{Q}$ shown in Table 16 are not large - they are less than those seen in an erect normal - and would not indicate significant inefficiencies in overall gas exchange. However, in the presence of functional differences within lung regions, functional differences between lung regions represent the minimal differences in function which exist throughout the lung. In this series there was evidence that differences in function within single regions did exist; all our patients except no. 8 (see below) showed regions in which $\tilde{V}_p < \tilde{V}_i$. Crude analysis of these discrepancies (Table 17) indicated that these intraregional variations in function were not small and, therefore, probably caused significant inefficiencies of overall gas exchange. Though ventilatory function was generally well preserved in these patients, it is likely that measurement of alveolar-arterial gas tension differences would have yielded significantly abnormal results in most, if not all of them.

In two patients (no. 8 and 9) $\tilde{V}_p$ clearly exceeded $\tilde{V}_i$ regions considered to be normal. In patient no. 9 this occurred in a relatively large number of regions and probably was due to the fact that the alveolar ventilation was greater in relation to minute ventilation after infusion than after rebreathing. However, this explanation was not tenable in the case of patient no. 8, in whom two regions (L_1 and L_2) showed "normal" $\tilde{V}_p$ and grossly depressed $\tilde{V}_i$.

Regional $\dot{V}_A/\dot{Q}$ was relatively high in each of these regions. This may be interpreted as indication of high $\dot{V}_A/\dot{Q}$ badly ventilated subregions plus low $\dot{V}_A/\dot{Q}$ well ventilated subregions, but also could be in part due to artefact.

The results of the ^{133}Xe studies showed considerable variation from patient to patient. This allowed correlations to be drawn between these results and those of routine pulmonary function tests though variations in the latter from subject to subject were not large. A positive correlation between mixing efficiency (ME) and mean $\tilde{V}_p$ might be expected, since one is derived from inert-gas washin and the other from inert-gas washout. However, ME is a measure of the unevenness of ventilation, which is not necessarily the most important determinant of mean $\tilde{V}_p$. An index of the interregional variation of ventilation was calculated; using statistical techniques, the standard deviation of mean $\tilde{V}$ was derived for each patient and was compared with ME (Fig. 54). Correlation was good when either $\tilde{V}_p$ or $\tilde{V}_i$ was considered, indicating that interregional differences in ventilation may have been important determinants of overall mixing, or, alternatively, that interregional differences are simply indices of more important intraregional differences in ventilation.

Mean $\tilde{V}_p$ was correlated with the CO extraction ratio, which is an expression of that fraction of CO presented to the lung under "steady-state" conditions which is taken up by the blood. In obstructive disease, this ratio reflects, among other things, variations in $\dot{V}_A/\dot{Q}$ within the lung. Whereas mean $\tilde{V}_p$ could relate to regional variations in $\dot{V}_A/\dot{Q}$, the CO extraction ratio appeared not to relate to interregional variation of $\dot{V}_A/\dot{Q}$ (calculated in a manner analogous to that used for ventilation). Therefore, it is reasonable to postulate that intraregional variations in $\dot{V}_A/\dot{Q}$ were an important determinant of overall exchange as tested by CO uptake.

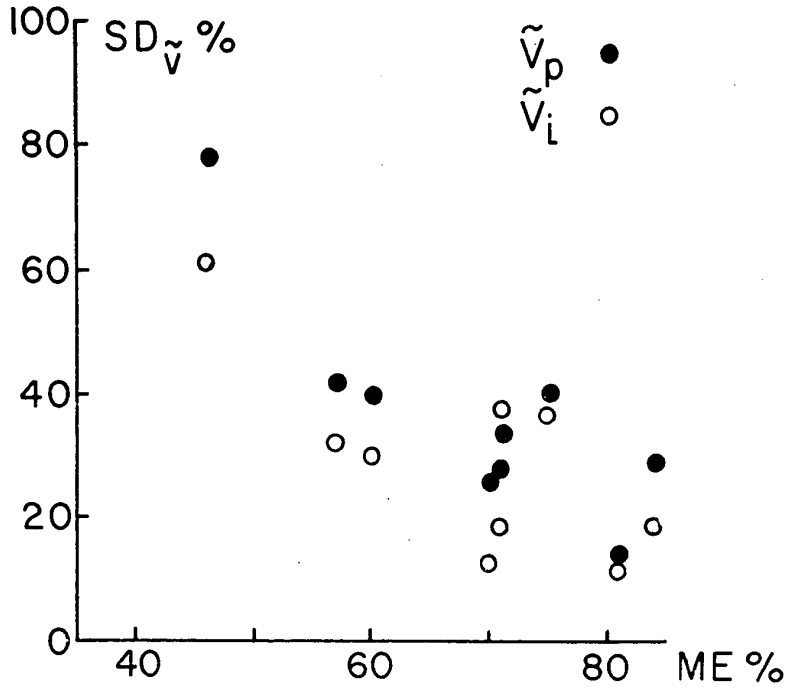


Fig. 54. Inter-regional variations in ventilation compared to mixing efficiency in chronic bronchitis. Ordinate: inter-regional variations in ventilation, which was calculated by taking, in each patient, the standard deviation of all regional $\tilde{V}_p$ (closed circles) or $\tilde{V}_i$ (open circles) and expressing these as a per cent of the mean $\tilde{V}_p$ or $\tilde{V}_i$. Abscissa: mixing efficiency expressed as a per cent of the predicted normal value. Each point represents a patient. As mixing efficiency increased, inter-regional variation of ventilation declined.

Whatever the interpretation placed on the correlations shown in Fig. 52 and 54, it is important to note that they demonstrate a wide range in function as assessed by ^{133}Xe studies are, therefore, to be interpreted as indicating that there may be considerable regional function impairment in chronic bronchitis when the bronchitis is clinically mild and accompanied only by minor abnormalities of overall pulmonary function.

Many epidemological studies of chronic bronchitis have been based on tests of expiratory flow rate[109], but in the present group of patients there was no correlation between the results of ^{133}Xe studies and the MMFR or FEV. Furthermore, in all of the subjects, ^{133}Xe revealed abnormalities of regional gas exchange, although MMFR was normal in three and FEV was within normal limits in four (including patient no. 6). It seems clear, therefore, that chronic bronchitis may be associated with severe regional abnormalities in pulmonary function without significant decrease of the forced expiratory flow rate and that the latter measurement may not relate to the severity of chronic bronchitis.

Were the abnormalities detected by these ^{133}Xe studies in fact related to chronic bronchitis and not due to co-existent emphysema? It cannot be denied that lungs of patients such as these demonstrate some emphysema on morphological study. If, however, all ^{133}Xe regional abnormalities are attributed to morphological emphysema, the emphysema must have involved about 50% of the lung tissue of all patients except nos. 4 and 5. Studies correlating routine function tests and pathologic anatomy[110] indicate that such extensive emphysema would be most unusual in patients such as these. Further, several of these patients have undergone measurement of the mechanical properties of their lungs, and in each case, static pressure volume curves were within normal limits. One of

the important characteristics of pulmonary emphysema is hyperdistensibility as demonstrated by the static pressure-volume curve; the presence of a normal static pressure-volume relationship is then evidence against widespread emphysema. Perhaps of particular significance is the fact that patient no. 6, who demonstrated the most extensive regional abnormalities noted in this series, had an entirely normal pressure-volume curve.

If the static elastic properties of these patient's lungs were normal, then abnormalities of regional ventilation distribution must be attributed to abnormalities in airway resistance. Significant airway obstruction would appear to have been present in some patients (nos. 1, 2, 6) in whom tests of expiratory flow rate did not indicate airway obstruction. These findings are compatible with the major site of obstruction being in the lung periphery. The resistance of peripheral airways ($<$ 2 mm internal diameter) constitutes only a small fraction of total airway resistance[112] which then may be little affected by major changes in the state of the peripheral airways. If over-all airway resistance were only slightly abnormal and static elastic properties of the lung were normal, little or no depression of expiratory flow rates would occur. However, the distribution of peripheral-airway resistance obviously is an important determinant of ventilation distribution. Therefore, expiratory flow rates may remain normal despite gross maldistribution of ventilation due to disease in small airways.

The studies of these patients lung mechanics supported this hypothesis. In general, static pressure volume curves of the lungs were normal. In those patients with well-preserved expiratory flow rates, the total airway resistance was normal or only slightly increased. In all subjects, however, dynamic

compliance fell very distinctly as respiratory frequency increased, implying that the distribution of ventilation was frequency dependent. These findings are probably typical of small airway disease.

Chronic bronchitis is often considered to be primarily a disease of major airways, since it is in these that the abnormalities thought to be typical of the disease are seen anatomically and roentgenographically[9h]. Obstructive lesions in the peripheral airways have been described[113] but their frequency, extent and importance have not. Peripheral-airway resistance is elevated in the lungs of patients with both bronchitis and emphysema[114] but there are no similar studies of the airways of patients such as those presented here. It seems very probable that the functionally important lesions were exclusively in the peripheral airways in some of our patients (no. 1, 2 and 6). However, if all of the abnormalities in all of our subjects were due to disease in peripheral (or central) airways, the expiratory flow rates and ^{133}Xe results would have shown significant correlation. The absence of this correlation suggests that there may be more than one site of airway obstruction in chronic bronchitis, as has been shown to be the case in more severe disease[115].

Regional perfusion was not distributed evenly, in that regions which were underventilated tended to be underperfused, i.e., regions with low $\dot{V}_A/\dot{Q}$ were hypoperfused. If these patients did not have extensive destruction of lung parenchyma, it must be concluded that the abnormal flow distribution was functional in origin. Similar decreases in regional perfusion of a functional nature were observed in patients with asthma. If the mechanisms responsible for regional hypoperfusion were common to both diseases, it might be anticipated that similar relationships would obtain between relative regional ventilation

and relative regional perfusion. Comparison of Fig. 43 with Fig. 50 appeared to show that badly ventilated regions were somewhat better perfused in bronchitis than in asthma, which may indicate either that different factors were responsible for regional hypoperfusion or that common factors were operative but there was greater intraregional variation of function in bronchitis. Relative regional ventilation (Fig. 50) was based on $\tilde{V}_p$ which tended to represent units with low $\dot{V}_A/\dot{Q}$ and relatively poor ventilation, whereas relative regional perfusion was based on $\dot{Q}_I$ which more closely represented mean regional blood flow. The use of $\tilde{V}_p$ to derive relative regional ventilation caused underestimation of the true (mean) relative regional ventilation in regions with $\tilde{V}_p < 60$. Such an underestimate of ventilation would cause badly ventilated regions to appear relatively overperfused. Generally, in asthmatics, $\tilde{V}_p = \tilde{V}_i$ so the error noted above could account for the observed differences in the relative perfusion of badly ventilated regions. Thus, a mechanism common to both diseases, such as regional hypoxia, which would tend to adjust regional perfusion to regional ventilation, is not excluded by the present data.

The striking tendency for the lung bases to be affected most frequently and the apices least frequently is compatible with the concept that bronchitis is dependent chiefly upon personal and environmental air pollution. Most exposure to cigarettes and atmospheric pollutants occurs while humans are seated or standing. Since ventilation increases steadily from apex to base in these postures[63], inhaled pollutants would attain highest concentration at the bases and lowest at the apices, and, when pathogenic, might give rise to disease most often at the lung bases.

Asthma and chronic bronchitis sometimes are very similar clinically and often bronchitis is diagnosed as asthma. However, comparison of the results

obtained during the present studies with those obtained in patients with asthma reveals greater differences than similarities, although admittedly both series were small in number. The regional distribution of the disease was different: in bronchitis the apices were relatively spared, whereas in asthma the mid-zones were found to be least often affected. Regional zones of malfunction were found in chronic bronchitis even when total pulmonary function was normal or nearly so, whereas in patients with spasmodic asthma the regional differences were found only when the MMFR was depressed to 50% or less of its predicted normal value. Significant inhomogeneity of function within single regions or counter fields was found repeatedly in bronchitis but not in asthma. These findings are consistent with the hypothesis that bronchitis is primarily a local or regional process whereas, particularly in its milder stages, asthma tends to be a more general process. Because of the regional and subregional character of chronic bronchitis, significant abnormalities of overall gas exchange may well exist in such patients with only minor ventilatory impairment, but this is not likely to be the case in patients with spasmodic asthma.

In summary, ten patients with chronic bronchitis were studied; these patients were of a type commonly encountered but little understood. Although overall pulmonary function was nearly normal in several patients, all had decreased ventilation and depressed $\dot{V}_A/\dot{Q}$ in some lung regions. Basal regions were most commonly affected. Differences between $\tilde{V}_p$ and $\tilde{V}_i$ gave evidence of inhomogeneity of function within single regions, so that recorded function differences between regions represented minimal values for actual differences throughout the lung. Analysis of washout discrepancies indicated that important differences in $\dot{V}_A/\dot{Q}$ and ventilation were probably present in most of these

patients. The presence of abnormal regional function without significant depression of expiratory flow rates suggested that significant peripheral-airway disease was present in these patients. Thus, in bronchitis overall gas-exchange efficiency may be compromised even when severe ventilatory disability is absent.

7. EMPHYSEMA

All agree that one of the most common and important diseases primarily affecting the lungs is emphysema. Unfortunately, it has become clear that emphysema is a diagnosis that can be made with certainty only on the basis of morbid anatomy. This has rendered physiological investigation of this disease somewhat problematical and has lead to studies of emphysematous patients under diagnostic headings such as "diffuse obstructive pulmonary syndrome" and "chronic bronchitis." The latter of these terms is particularly bothersome since chronic bronchitis may be precisely defined in terms of clinical symptoms and since a distinct majority of patients with emphysema have these symptoms, considerable confusion has arisen.

However, recent studies have correlated pathological findings with the results of pulmonary function tests and reasonable working criteria for the diagnosis of emphysema have emerged[110]. Patients with emphysema usually have at least a moderate degree of limitation of activity due to their disease. They tend to have considerable limitation of expiratory air flow with a high RV. Mixing efficiency tends to be poor and the FRC large. The most consistant and important abnormalities of function are a depression of steady state D_{LCO} and hyperdistensibility of the lungs as measured by the static pressure-volume curve[116]. It should be noted that patients with these abnormalities usually also have chronic cough and sputum so that it is difficult to ascribe all the above abnormalities of function to the lesions of emphysema per se. It can be stated, however, that patients with pure chronic bronchitis usually do not display grossly decreased D_{LCO} or pulmonary hyperdistensibility.

As noted earlier in this thesis, it has been demonstrated repeatedly that patients with emphysema have gross maldistribution of $\dot{V}_A/\dot{Q}$ throughout their lungs; this maldistribution causes marked inefficiency of overall gas exchange and outright respiratory failure frequently ensues. Of several approaches to the distribution of $\dot{V}_A/\dot{Q}$ in patients with emphysema, one of the most productive has been that of Briscoe[38], who combined inert gas washout with measurement of arterial blood gas tensions. He concluded that the emphysematous lung could be represented by a two compartment model: a small well ventilated well perfused compartment with high $\dot{V}_A/\dot{Q}$ existing in parallel with a larger very badly ventilated slightly underperfused compartment with low $\dot{V}_A/\dot{Q}$. Subsequent analyses of other data from such patients have supported this concept[42].

Radiological examinations of the lungs of patients with emphysema show regional inhomogeneity in regard to the distribution of blebs, pulmonary parenchyma and large and small pulmonary blood vessels[117]. Further, previous studies with ^{133}Xe[118] have shown that distinct regional differences of ventilation and perfusion exist in the lungs of many patients with emphysema. On the basis of such studies various surgical approaches to the emphysematous lung have been suggested and implemented. These have included excision, exclusion and obliteration of lung regions which have been thought to function poorly.

In light of these data, it is of interest to assess regional gas exchange in emphysema. It would be of considerable interest if the wide variations in $\dot{V}_A/\dot{Q}$ seen in this disease had a regional basis; such a finding would lend great support to those espousing surgical approaches to this disease.

It is unlikely, however, that many students of emphysema would expect that differences in regional gas exchange are of critical importance. Indeed, it has been postulated by two authorities [119, 9i] that important differences in gas concentrations exist within the emphysematous secondary lobule. Thus, it is likely that important intraregional variations in function exist in the emphysematous lung. Since the most significant limitation to the study of regional lung function is the presence of intraregional inhomogeneity, studies of patients with emphysema could yield important information about the methods, if not the subjects.

Twenty patients were studied: 5 females and 15 males, who ranged from 34 to 67 years of age; only three were less than 45. All had either been followed for some time in the outpatient clinic of the Royal Victoria Hospital or were studied while in-patients. None were acutely ill and all were clinically stable at the time of study. They were selected for the study on the basis of clinical history, x-rays of the chest and routine lung function tests, all of which were thought typical of pulmonary emphysema[110]. All patients were dyspneic on mild or moderate exertion and some were under treatment for right heart failure. Almost all gave a history of chronic productive cough.

Pathological support for the diagnosis of emphysema was available in four patients; three underwent resection of emphysematous lobes and one came to autopsy some months after these ^{133}Xe studies.

Pulmonary function tests were carried out within three months of the ^{133}Xe studies. Lung volumes, including vital capacity (VC), functional residual capacity (FRC) and residual volume (RV) were measured by spirometry and helium dilution. Mixing efficiency (ME) was also measured by closed circuit helium dilution. Expiratory flow rate was assessed in two ways: the maximum

mid-expiratory flow rate (MMFR) was measured as was the volume produced in the first 0.75 sec. of forced expiration ($FEV_{0.75}$). Steady-state diffusing capacity for CO ($D_{L_{CO}}$) was also estimated. Arterial oxygen saturations (Sa_{O_2}) were measured spectophotometrically and arterial carbon dioxide tensions (Pa_{CO_2}) were measured with Severinghaus electrodes.

In addition to these studies, in 10 patients measurements of lung mechanics were available. These were carried out using an esophageal balloon to measure pleural pressure and included static lung compliance (C_{st}), total lung resistance (R_L) and the maximum elastic recoil pressure (max P_{el}) which is the pleural pressure measured during open glottis breath-hold at maximum inspiration[116]. If max Pel is very negative (less than -25 cm H_2O) lung recoil is normal; less negative pressures (more than -15 cm H_2O) indicate loss of lung elasticity.

Dye dilution cardiac outputs were measured during the ^{133}Xe study in all patients. In 13 patients indocyanin green dye was used and arterial blood sampled to inscribe the dye curve. In the remaining 7 patients Coomassie blue dye was used and the dye curve inscribed by an ear oximeter.

Xe studies were conducted with the patients supine with 5 scintillation counters positioned behind each lung from apex to base. Each patient rebreathed ^{133}Xe for 10 min., received a 10 min. intravenous infusion of ^{133}Xe and received two or more slug injections of ^{133}Xe while breath-holding at FRC. Arterial ^{133}Xe concentration were measured during the rebreathing and infusion procedures in most patients who had an arterial catheter in place for cardiac output measurements.

Regional ventilation was assessed by taking the reciprocal of regional $T\frac{i}{2}$ measured after infusion ($\dot{V}_p/V$) and after rebreathing ($\dot{V}_i/V$). Because this method utilized the early part of the washout curve, it may have neglected badly ventilated (slow washout) units.

The computation of regional $\dot{V}_A/\dot{Q}$ depended on whether or not the patient underwent measurement of arterial ^{133}Xe concentrations. In subjects who had not, regional $\dot{V}_A/\dot{Q}$ were computed according to eq. III-7. In the majority of patients arterial ^{133}Xe concentrations were measured and these measurements allowed recirculating ^{133}Xe to be considered in the calculation of regional $\dot{V}_A/\dot{Q}$ according to eq. III-13. The effect of this correction for recirculating ^{133}Xe was to increase differences among regional $\dot{V}_A/\dot{Q}$ in each patient.

Calculations of regional $\dot{V}_A/\dot{Q}$ assumed that steady states regarding ^{133}Xe exchange were attained in lung regions during 10 min. of infusion and rebreathing. As noted, the speed of approach to regional steady state depends on regional $\dot{V}_A/V$ and $\dot{Q}/V$; if these fractions are small the steady state is not attained rapidly. In emphysema these fractions may be small and the validity of steady state analysis may be questioned. Failure to establish steady state conditions is theoretically more likely during ^{133}Xe infusion than during rebreathing. This is because input concentration during infusion ($C_{\bar{v}}$) needs a finite time to rise to steady state levels, while input concentration during rebreathing (F_I) is always high. The respiratory ^{133}Xe output ($\dot{V}_{Xe}$), the product of the minute ventilation and the mixed expired ^{133}Xe concentration was compared to the ^{133}Xe injection rate during infusion. If one allowed for the overall $\dot{V}_A/\dot{Q}$ of the patients and the solubility of ^{133}Xe, the results were consonant with steady state conditions (Table 20). In all patients mixed expired ^{133}Xe levels appeared constant over the latter part of infusion. Thus, it is probable that overall steady states were established by the ^{133}Xe infusion in these studies. This was not true in all lung regions examined, however; in a number of very badly ventilated regions, which presumably contributed little to mixed expired gas, count rate was still increasing at the end of the infusion time.

This tendency was less pronounced when the rebreathing period was considered. Thus, in spite of overall steady state conditions regional steady state count rates were in some instances underestimated. Because the degree of underestimation of U_p was greater than that of U_i, resulting regional $\dot{V}_A/\dot{Q}$ were probably overestimated.

Another error which may have caused overestimation of regional $\dot{V}_A/\dot{Q}$ was the assumption that $\dot{V}_I = \dot{V}_A$, which was made in deriving both eq. III-7 and eq. III-13. As discussed previously, this assumption is reasonable in most instances but when $\dot{V}_A/\dot{Q}$ are very low $\dot{V}_I$ may significantly exceed $\dot{V}_A$.

Perfusion distribution was assessed in the usual manner; steady state perfusion indices ($\dot{Q}_i$) were calculated for each lung region according to eq. III-24. In this series, regional $\dot{Q}_i$ tended to be low. The reasons for this are probably twofold: 1. FRC was very likely underestimated in many cases. Plethysmographic lung volumes commonly exceed those determined by helium dilution in our laboratory. 2. Many patients were unable to breath-hold the requisite time and exhaled significant amounts of the injected isotope. This would have the effects of preferentially reducing $\dot{Q}_i$ in well-ventilated regions, and underestimating interregional differences in perfusion.

Results of pulmonary function tests and arterial gas analysis are shown in Table 18. They are typical of emphysema. The VC was reduced in all but two patients (1, 17), FRC was generally increased and all patients except No. 13 (who had undergone pulmonary resection) demonstrated increased RV. Mixing was reduced as was $D_{L_{CO}}$. The MMF was less than 1.0 L/sec. in all subjects. Seven patients had normal blood gases; in the remainder either Sa_{O_2} was decreased ($< 94\%$) or Pa_{CO_2} was increased (> 46 mmHg). For the sake of simplicity, pulmonary function tests in 5 selected patients are shown in Table 18-A.

TABLE 18 - A. RESULTS OF PULMONARY FUNCTION TESTS IN 5 PATIENTS WITH EMPHYS

(Predicted Normal Values in parenthesis)

Patient	Age	Sex	VC (L)	FRC (L)	RV (L)	RE %	MMFR L/sec	FEV 0.75 L	D_{LCO} (ml/min/mmHg)	Pa_{CO_2} (mmHg
1	53	M	3.08	5.44	4.50	37	0.69	0.70	10.2	41
			(4.01)	(4.21)	(2.54)	(53)	(3.53)	(2.92)	(16.7)	
3	67	M	2.06	4.01	3.51	24	0.22	0.45	9.9	47
			(3.76)	(3.74)	(2.47)	(45)	(2.66)	(1.98)	(11.3)	
6	36	F	1.30	4.28	3.86	39	0.30	0.35	10.4	70
			(3.15)	(2.43)	(1.28)	(65)	(3.43)	(2.20)	(18.9)	
10	48	F	2.23	3.14	2.71	35	0.30	0.53	5.2	38
			(3.23)	(2.78)	(1.74)	(56)	(2.69)	(2.00)	(14.7)	
13*	45	F	1.41	2.68	2.08	25	0.25	0.43	5.9	44
			(4.57)	(3.82)	(2.18)	(57)	(3.70)	(0.65)	(16.2)	

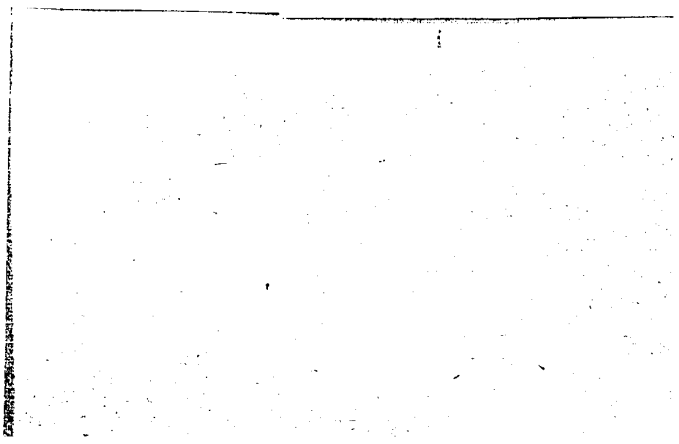
* Previously had lobectomy

ONARY FUNCTION TESTS IN 5 PATIENTS WITH EMPHYSEMA

Normal Values in parenthesis)

	ME %	MMFR L/sec	FEV 0.75 L	D_{LCO} (ml/min/mmHg)	Pa_{CO_2} (mmHg	Sa_{O_2} %	C_{st} L/cmH_2O	R_L cmH_2O/L/S	maxPel cmH_2O
0	37	0.69	0.70	10.2	41	94	.25	7.0	-9.0
4)	(53)	(3.53)	(2.92)	(16.7)				(<2.0)	(<-20)
1	24	0.22	0.45	9.9	47	88	---	---	---
7)	(45)	(2.66)	(1.98)	(11.3)					
5	39	0.30	0.35	10.4	70	79	.12	33.0	-14.0
3)	(65)	(3.43)	(2.20)	(18.9)				(<2.0)	(<-20)
-	35	0.30	0.53	5.2	38	93	.36	4.5	-12.5
.)	(56)	(2.69)	(2.00)	(14.7)				(<2.0)	(<-20)
	29	0.29	0.43	5.9	44	89	.44	7.3	-7.5
)	(57)	(3.70)	(0.09)	(16.2)				(<2.0)	(<-20)

0



Results of the ^{133}Xe studies are presented in Table 19, and five representative patients are presented in Table 19-A. Most patients showed considerable interregional variation in ventilation with ten-fold differences in $\dot{V}_p/V$ being not uncommon. However, interregional differences in $\dot{V}_A/\dot{Q}$ were less striking with only a few patients showing variations in regional $\dot{V}_A/\dot{Q}$ that exceeded 2:1. Further, regional $\dot{V}_A/\dot{Q}$ were low. In the majority of patients only a few regions exhibited $\dot{V}_A/\dot{Q} > 0.5$; $\dot{V}_A/\dot{Q} < 0.10$ were not rare and in no patient was a regional $\dot{V}_A/\dot{Q} > 1.0$ measured. These regional $\dot{V}_A/\dot{Q}$ cannot be entirely representative of pulmonary gas exchange in these patients, as they imply that the overall alveolar ventilation was a small fraction of the cardiac output. Minute ventilation was measured during these studies and values of $\dot{V}_E$ are shown in Table 20.

There was no reason to believe that these patients had greatly enlarged anatomical dead spaces, and the respiratory rate ranged from 15 - 25 breaths/min. It is, therefore, most difficult to believe that the figures representing $\dot{V}_E$ in Table 20 are consonant with $\dot{V}_A$ which were less than half the cardiac outputs also shown in Table 20. Reasons for this inconsistancy will be discussed.

In Tables 19 and 19-A, both $\dot{V}_p/V$, calculated from washout after infusion, and $\dot{V}_i/V$, calculated from washout after rebreathing are shown for each region since these values frequently did not coincide. $\dot{V}_p/V$ was less than 80% of $\dot{V}_i/V$ in 107 of the 199 regions studied; the reverse was the case in only 7 regions. Fig. 55 shows the magnitude of this tendency and indicates that such discrepancies in regional washout were found both in relatively well ventilated ($\dot{V}_p/V > 1.0$ L/min/L) and in relatively badly ventilated regions. Though the tendency for $\dot{V}_p/V < \dot{V}_i/V$ is clear when the series is considered as a whole, the prevalence of washout discrepancies varied considerably from patient to patient. Most subjects demonstrated some regions in which $\dot{V}_p/V < \dot{V}_i/V$ and

TABLE 19A. RESULTS OF ^{133}Xe STUDIES IN 5 PATIENTS WITH EMPHYSEMA

		LEFT LUNG					RIGHT LUNG				
		APEX				BASE	APEX				BASE
		L_1	L_2	L_3	L_4	L_5	R_1	R_2	R_3	R_4	R_5
1	$\dot{V}_A/\dot{Q}$	.72	.78	.63	.61	.45	.62	.55	.65	.68	.61
	$\dot{Q}_i$	139	152	122	112	73	67	105	79	71	58
	$\dot{V}_p/V$	.88	1.04	.70	.41	.18	.47	.45	.26	.28	.30
	$\dot{V}_i/V$	1.50	1.50	1.20	.60	.37	.53	.44	.49	.32	.28
3	$\dot{V}_A/\dot{Q}$	.33	.29	.26	.30	.12	.41	.33	.37	.34	.30
	$\dot{Q}_i$	54	54	70	78	76	109	129	136	139	131
	$\dot{V}_p/V$	.15	.18	.28	.14	.37	.37	.43	.34	.36	.36
	$\dot{V}_L/V$	.25	.26	.47	.21	.68	.68	.67	.46	.39	.48
6	$\dot{V}_A/\dot{Q}$	.04	.06	.04	.05	.05	.09	.15	.21	.15	.11
	$\dot{Q}_i$	25	33	28	31	36	50	67	89	81	74
	$\dot{V}_p/V$	.21	.20	.28	.28	.29	.38	.29	.50	.41	.38
	$\dot{V}_i/V$	.24	.30	.24	.30	.21	.46	.63	.75	.75	.42
10	$\dot{V}_A/\dot{Q}$	.39	.43	.31	.24	.10	.69	.60	.40	.50	.51
	$\dot{Q}_i$	71	76	83	68	42	75	53	57	54	54
	$\dot{V}_p/V$	.98	1.11	.56	.19	.10	1.42	1.07	.75	.46	.30
	$\dot{V}_i/V$	.69	1.36	.43	.25	.16	1.62	1.13	.77	.47	.52
13	$\dot{V}_A/\dot{Q}$	.56	.45	.45	.46	.37	.55	.43	.61	.60	.63
	$\dot{Q}_i$	108	87	39	26	34	116	113	46	53	38
	$\dot{V}_p/V$	.59	.20	.09	.06	1.39	1.39	1.31	.67	.53	.50
	$\dot{V}_i/V$	1.42	1.11	.35	.19	.11	1.58	1.77	1.47	1.13	.59

TABLE 20. CARDIAC OUTPUT, VENTILATION AND $\dot{V}_{Xe}$ IN PATIENTS WITH EMPHYSEMA

Patient No.	Cardiac Output (L/min)	Ventilation (L/min)	$\dot{V}_{Xe}$/Infusion rate (%)
1	5.50	9.50	91
2	7.15	7.70	88
3	7.73	7.72	70
4	9.83	9.73	97
5	8.13	10.70	72
6	10.86	5.40	77
7	5.45	7.45	64
8	6.18	7.00	75
9	7.20	9.25	
10	4.67	6.75	92
11	7.90	8.40	92
12	5.02	7.70	86
13	4.60	6.50	95
14	6.10	6.97	74
15	8.35	7.30	83
16	4.12	9.15	104
17	3.47	5.72	97
18	3.96	5.68	86
19	6.85	5.50	84
20	6.02	5.60	81

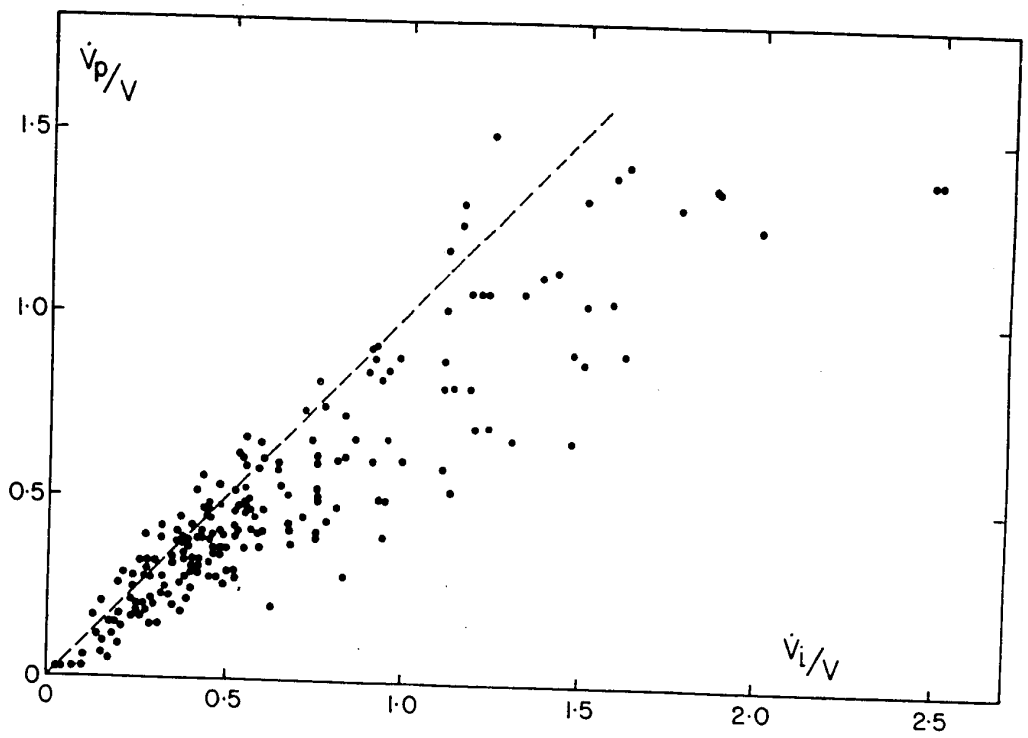


Fig. 55. Comparison of washouts of inspired and infused ^{133}Xe in patients with emphysema. Ordinate: ventilation computed from washout after infusion. Abscissa: ventilation computed from washout after rebreathing. Each point represents a lung region.

others in which $\dot{V}_p/V = \dot{V}_i/V$. In some patients $\dot{V}_p/V < \dot{V}_i/V$ in all lung regions though minute ventilation was constant throughout the experiment, and finally in a few patients $\dot{V}_i/V$ did not significantly exceed $\dot{V}_p/V$ in any lung region.

Two lung regions in the series exhibited $\dot{V}_i/V > 2.00$ L/min/L, and regions with $\dot{V}_i/V$ ranging from 1.00 L/min/L to 2.00 L/min/L were not uncommon. Though such values are ordinarily compatible with normal regional function, it cannot be concluded that these regions were in fact normal. All subjects had regions with grossly prolonged washout and in most instances such regions constituted the majority. When an important fraction of the lung is underventilated, structurally normal regions would be expected to demonstrate an increased as opposed to a normal ventilation. The absence from this series of any lung regions with truly high $\dot{V}_i/V$ or $\dot{V}_p/V$ indicated, then, that all lung regions were diseased or at least had reduced ventilatory capacities.

The failure to demonstrate regions with rapid washout cannot, however, be interpreted as indicating the absence of such units from the emphysematous lung. Indeed, the presence of units with very high ventilation per unit volume has been repeatedly demonstrated in patients with emphysema[38,42]; the present failure to demonstrate such units is analogous to the failure to demonstrate units with high $\dot{V}_A/\dot{Q}$.

In general, the regional perfusion distribution was similar to that of regional ventilation: in a given patient the regions with the highest $\dot{V}_i/V$ had a high $\dot{Q}_i$, and the regions with the lowest $\dot{V}_i/V$ or $\dot{V}_p/V$ tended to have a low $\dot{Q}_i$. Measurements of $\dot{Q}_i$ were available in 18 patients in this series; in 14 of these there was a significant correlation between $\dot{Q}_i$ and both $\dot{V}_p/V$ and $\dot{V}_i/V$. In two other patients these correlations were suggested; in one both

correlations barely missed significance and the other exhibited a significant correlation between $\dot{Q}_i$ and $\dot{V}_i/V$ but not between $\dot{Q}_i$ and $\dot{V}_p/V$. Patients 4 and 19 were quite distinctive in that their regional perfusion distribution appeared to be totally independent of regional ventilation distribution.

Correlation between ^{133}Xe results and the results of other pulmonary function tests was poor. Overall assessment of ^{133}Xe results in each patient was attempted in two ways: 1. regional values were averaged, yielding mean $\dot{V}_p/V$, $\dot{V}_i/V$ and mean $\dot{V}_A/\dot{Q}$ for each patient, and 2. using statistical technique, the standard deviation of the mean regional $\dot{V}_p/V$, $\dot{V}_i/V$ and $\dot{V}_A/\dot{Q}$ was calculated for each patient. The former approach was thought to produce indices of the overall functional level of the patient, the latter to give indices of the amount of interregional variation of function in each patient. Patients with abnormal arterial saturations ($Sa_{O_2} < 94$) had significantly lower mean $\dot{V}_p/V$ ($P < .01$) and lower mean $\dot{V}/\dot{Q}$ ($P < .01$) than did those patients with normal Sa_{O_2}. Similarly, patients with elevated Pa_{CO_2} (> 46 mmHg) had significantly lower mean $\dot{V}_p/V$ ($P < .02$) and lower mean $\dot{V}_A/\dot{Q}$ ($P < .01$) than did patients with normal Pa_{CO_2}. No correlation could be established between other function tests and mean $\dot{V}_i/V$, mean $\dot{V}_p/V$ or mean $\dot{V}_A/\dot{Q}$. When each patient's overall lung function tests were compared to his regional variation of function (standard deviation), only one significant correlation emerged, that between regional variation in $\dot{V}_A/\dot{Q}$ and D_{LCO} expressed as percent of predicted (Fig. 56).

As noted previously[118] several geographic patterns of disease were encountered. The most common of these consisted of a steady decrease in ventilation, $\dot{V}_A/\dot{Q}$ and $\dot{Q}_i$ from apex to base which was often fairly symmetrical from side to side. These patients, in general, tended to have the greatest regional differences in washout and blood flow. The reverse pattern, that of better function

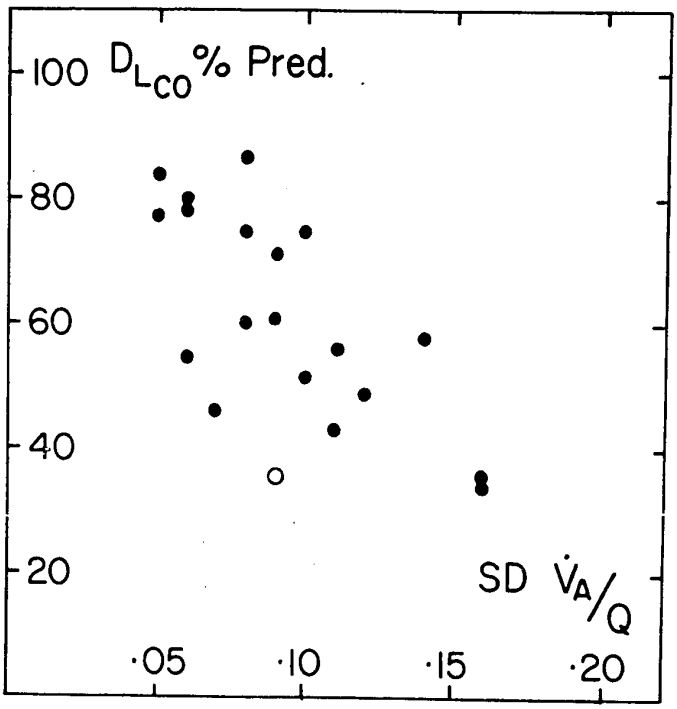


Fig. 56. Correlation between diffusing capacity and inter-regional variation in $\dot{V}_A/\dot{Q}$. Ordinate: diffusing capacity expressed as a per cent of predicted normal. Abscissa: standard deviation of mean regional $\dot{V}_A/\dot{Q}$. Each point represents one patient. The open circle represents patient 13, who had undergone lobectomy before these studies.

at the apices than at the bases, was seen less often, and was usually associated with less dramatic interregional differences in function. Four patients (No: 3, 6, 12, 18) showed distinct lateralization of disease, in that the best ventilated region in one lung washed out no more quickly than the worst ventilated region of the other. There were, of course, a number of patients who showed more than one of the above patterns or who conformed to none of them.

The patients who form the subject of this study were selected so as to ensure the highest probability that their lungs were affected by morphological pulmonary emphysema. The criteria were two: 1. pulmonary function tests which were thought typical of the disease, and 2. a period of clinical observation, either inside or outside the hospital, long enough to convince observers that the patient was clinically stable. It is not surprising then, that pulmonary function as routinely assessed (Table 18) was grossly abnormal in a way typical of emphysema. No attempt was made to specifically include patients with chronic bronchitis, but almost all the patients gave a history of chronic productive cough. If patients with cough and sputum had been excluded, compiling a series of even the present size would have been most difficult. These results, then, must be interpreted as reflecting a combination of the effects of chronic bronchitis and of emphysema.

The above problem is not greatly clarified by comparing these results with those of patients with chronic bronchitis only. Bronchitics demonstrated regions with prolonged washout, low $\dot{V}_A/\dot{Q}$ and reduced perfusion; the washout of inhaled ^{133}Xe was often faster than that of infused isotope. These are the major findings of the present study, but they all are much more striking in these patients with emphysema. The pure bronchitics did not demonstrate

regional variations in ventilation $\dot{V}_A/\dot{Q}$ or perfusion as large as those shown in Table 9. Neither regional ventilation nor $\dot{V}_A/\dot{Q}$ approached the very low values commonly seen in emphysema, and in bronchitis relatively well ventilated regions washed out much more quickly than did the best ventilated regions of patients with emphysema. Washout discrepancies were evident only in relatively poorly ventilated regions in bronchitis, whereas in these patients with emphysema washout discrepancies were noted both in relatively well ventilated and in relatively badly ventilated regions. The differences, then were quantitative not qualitative. Overall pulmonary function differed greatly between the two series with the emphysema patients being much the worst. Thus, though the differences between the two series might be ascribed to the presence of emphysema in one, they are equally explainable on the basis of different degrees of the same disease process.

In view of the severity of the impairment of pulmonary function shown by these patients, it was not surprising that their regional function as assessed by ^{133}Xe was uniformly bad. ^{133}Xe washouts were very prolonged, and regional $\dot{V}_A/\dot{Q}$ often attained extremely low levels. There was also much greater interregional variation of function than has been noted in other disease.

However, no units with either high ventilation per unit volume or high $\dot{V}_A/\dot{Q}$ were demonstrated in these studies though such units must have existed in these patients. The methods used are not intrinsically unable to discern well ventilated high $\dot{V}_A/\dot{Q}$ regions; such regions were demonstrated both in normal subjects and in patients with pulmonary embolism. As discussed above, errors arising from the application of these techniques to patients with bronchitis and emphysema tend to cause overestimation not underestimation of $\dot{V}_i/V$, $\dot{V}_p/V$ and $\dot{V}_A/\dot{Q}$.

In order for the data of Tables 19 and 19-A to be taken literally, it is first necessary to assume that each region is homogeneous or nearly so as regards function. If all units in any region behaved in the same way, then these studies would produce quantitatively accurate information regarding the region. If, however, the region consisted of two or more subregions with differing ventilation, perfusion, and $\dot{V}_A/\dot{Q}$, then regional $\dot{V}_A/\dot{Q}$, $\dot{V}_p/V$ and $\dot{V}_i/V$ were mean values and may not have accurately reflected the function of any single unit within the region and the problem of intraregional inhomogeneity of function will be reviewed again.

The basic measurements made in these studies were those of regional count rate. Since regional count rates represent the amount (concentration x volume) of isotope present, mean values derived from a non-homogeneous region were weighted according to the relative volume of the region's functional components. The problem of intraregional inhomogeneity is somewhat more complex than is implied above in the case of regional $\dot{V}_A/\dot{Q}$, $\dot{V}_p/V$ and $\dot{V}_i/V$. A non-homogeneous region does not produce $\dot{V}_A/\dot{Q}$, $\dot{V}_p/V$, $\dot{V}_i/V$ which are simple volume weighted means of its component parts. This is illustrated by Table 21 in which are shown the $\dot{V}_A/\dot{Q}$, $\dot{V}_p/V$ and $\dot{V}_i/V$ for hypothetical lung regions composed of two subregions with varying ventilation, $\dot{V}_A/\dot{Q}$ and volume. Subregional perfusion per unit volume has been held constant. Regional $\dot{V}_A/\dot{Q}$ are low, considerably lower than the volume-weighted mean of the $\dot{V}_A/\dot{Q}$ present in the two subregions. In the presence of intraregional differences in $\dot{V}_A/\dot{Q}$, regional $\dot{V}_A/\dot{Q}$ is heavily biased in favor of the low $\dot{V}_A/\dot{Q}$ subregions. It is possible for a region with low $\dot{V}_A/\dot{Q}$ to contain a very significant number of units with high $\dot{V}_A/\dot{Q}$ because the measurement of regional $\dot{V}_A/\dot{Q}$ is much more sensitive to subregions with low $\dot{V}_A/\dot{Q}$ than to

TABLE 21 - MEAN REGIONAL FUNCTION OF HYPOTHETICAL REGIONS MADE UP OF TWO SUBREGIONS (X AND Y) WITH VARYING $\dot{V}_A/\dot{Q}$ VENTILATION ($\dot{V}/V$) AND VOLUME

REGION			SUBREGION X			SUBREGION Y		
$\dot{V}_A/\dot{Q}$	$\dot{V}_P/V$	$\dot{V}_I/V$	V_X/V_r*	$\dot{V}_A/\dot{Q}$	$\dot{V}/V$	V_y/V_r*	$\dot{V}_A/\dot{Q}$	$\dot{V}/V$
.38	.45	0.85	0.50	1.00	1.40	0.50	0.20	0.28
.38	.23	1.87	0.50	2.50	3.50	0.50	0.14	0.20
.38	.35	1.07	0.33	2.50	3.50	0.67	0.23	0.32
.38	.48	0.67	0.33	1.00	1.40	0.67	0.27	0.38
.38	.43	0.71	0.20	2.50	3.50	0.80	0.29	0.41

* V_X/V_r and V_y/V_r - Fractional Volume of Region Taken Up By Subregion X or Y

subregions with high $\dot{V}_A/\dot{Q}$. Briefly, this effect is due to the relatively small solubility of ^{133}Xe. Because of the low solubility of ^{133}Xe, units with low $\dot{V}_A/\dot{Q}$ attain very high concentrations during ^{133}Xe infusion and do not attain very low concentrations during rebreathing. If a very soluble gas were used as a tracer regional $\dot{V}_A/\dot{Q}$ would be influenced more by high $\dot{V}_A/\dot{Q}$ units than low ones.

A second characteristic of the regions shown in Table 21 is that $\dot{V}_p/V < \dot{V}_i/V$. Under the circumstances shown, i.e., regions containing units with high ventilation and $\dot{V}_A/\dot{Q}$ and other units with low ventilation and $\dot{V}_A/\dot{Q}$, such washout discrepancies must always develop, as discussed in the previous section. Regions in which $\dot{V}_p/V < \dot{V}_i/V$ were commonly observed in these patients, giving direct evidence for the type of intraregional inhomogeneity of function illustrated in Table 21.

Another approach to the problem of intraregional inhomogeneity is afforded by the measurements we made of arterial ^{133}Xe during the rebreathing and infusion procedures. Arterial ^{133}Xe concentrations can be computed, or predicted, on the basis of regional $\dot{V}_A/\dot{Q}$ values. Arterial ^{133}Xe concentrations during both rebreathing and infusion were predicted by calculating the regional blood concentrations according to regional $\dot{V}_A/\dot{Q}$ and by weighting the concentrations according to the regional $\dot{Q}_i$. Regional volumes were thus considered equal in each patient. Some of the results of these computations are presented in Table 22, along with measured arterial ^{133}Xe values. Similar figures derived from three subjects with normal ^{133}Xe studies are included for comparison. These show good agreement between predicted and measured values.

Predicted Ca_p was consistantly higher than measured in the patients with emphysema. Therefore, the arterial blood of these patients contained contributions

TABLE 22 - COMPARISON OF MEASURED AND PREDICTED
^{133}Xe Arterial Concentrations

PATIENT	MEASURED C_{a_p}*	MEASURED C_{a_i}+	PREDICTED C_{a_p}	PREDICTED C_{a_i}	HIGH $\dot{V}_A/\dot{Q}$ $\dot{V}_A/\dot{Q}$	COMPARTMENT % $\dot{Q}_T$°
1	.035	.038	.046	.043		
3	.046	.033	.056	.029	2.27	24
6	.084	.082	.106	.074	4.07	22
N	.031	.042	.032	.041		
N	.054	.057	.055	.060		
N	.049	.071	.047	.071		

* C_{a_p} - arterial ^{133}Xe concentration during infusion (mc/L)

\+ C_{a_i} - arterial ^{133}Xe concentration during rebreathing (mc/L)

° $\%\dot{Q}_T$ - % of cardiac output received by this compartment

from units which did not have regional representation; these units must have had low ^{133}Xe concentrations, and, therefore, high $\dot{V}_A/\dot{Q}$. Differences between predicted and measured arterial ^{133}Xe concentrations during rebreathing were in general small and did not show a consistent pattern. Measured Ca_i was higher than that predicted in 6 patients, lower than that predicted in 3 patients and the two values were equal in one patient. If high $\dot{V}_A/\dot{Q}$ units without regional representation influenced arterial ^{133}Xe levels during rebreathing, predicted Ca_i should have been consistently lower than measured. In other words, the relationship of measured and predicted Ca_i was not always consistent with the relationship between measured and predicted Ca_p. This is probably because F_{A_i} is less sensitive to $\dot{V}_A/\dot{Q}$ than is F_{A_p}, so high $\dot{V}_A/\dot{Q}$ units would have a smaller effect on Ca_i than Ca_p, and errors of measurement of arterial ^{133}Xe concentrations would have greater significance in terms of $\dot{V}_A/\dot{Q}$ in the case of Ca_i than in the case of Ca_p.

Assuming that the discrepancies between predicted and measured arterial ^{133}Xe levels were due to unappreciated or "missed" units with high $\dot{V}_A/\dot{Q}$, a model was constructed to characterize these units further. The lung was divided into two hypothetical compartments. The first compartment was represented by the regional data of Table 19; the blood draining this compartment had ^{133}Xe concentrations equal to those predicted in Table 22. The other, "high $\dot{V}_A/\dot{Q}$" compartment supplied blood which, when mixed with that from the first compartment in the proper proportions, produced the measured arterial ^{133}Xe levels. When data from both rebreathing and infusion were used, it became theoretically possible to calculate both the amount of blood flow through the high $\dot{V}_A/\dot{Q}$ compartment and its ^{133}Xe concentration. From the latter, the $\dot{V}_A/\dot{Q}$

of this compartment was computed. In four of the ten patients in whom arterial ^{133}Xe concentrations were available, rational solutions were possible. These four demonstrated "missed" compartments with $\dot{V}_A/\dot{Q}$ ranging from 1.65 to 4.07, which received 13 to 32 per cent of the cardiac output. Characteristics of this "high $\dot{V}_A/\dot{Q}$ compartment" of patients 3 and 6 are shown in Table 22.

It is most unlikely, however, that as assumed above, high $\dot{V}_A/\dot{Q}$ units were actually "missed". The counter system employed in these studies covered virtually the entire lung field of each patient. As discussed earlier, the regional $\dot{V}_A/\dot{Q}$ measured in these patients were compatible with the existance of sizable subregions with high $\dot{V}_A/\dot{Q}$. These subregions were not then missed. However, if lung regions conformed to the models shown in Table 21, there would be no difference between predicted and measured arterial ^{133}Xe levels. This is because the subregions of Table 21 were assumed to have uniform perfusion per unit volume. Under these circumstances, volume weighted mean alveolar concentrations must be the same as perfusion weighted mean arterial concentrations. The fact that measured arterial concentrations differed from those predicted on a regional basis, therefore, indicated that perfusion per unit volume must have differed within single lung regions, and the fact that the measured arterial ^{133}Xe consistently reflected high $\dot{V}_A/\dot{Q}$ units showed that these subregions were over-perfused in relation to low $\dot{V}_A/\dot{Q}$ subregions.

In summary, these data revealed evidence for variation of $\dot{V}_A/\dot{Q}$, ventilation per unit volume, and perfusion per unit volume within single lung regions. In a lung in which there are functional differences within single regions, measured functional differences between regions necessarily represent the minimum differences which could exist throughout the lung. Some of the examples shown in

Table 21 have regional $\dot{V}_A/\dot{Q}$, $\dot{V}_p/V$ and $\dot{V}_i/V$ similar to those of Tables 19 and 19-A; the component subregions of Table 21 have strikingly different ventilation and $\dot{V}_A/\dot{Q}$. Thus, it was very likely that in the majority of patients functional differences within single regions were much greater than region-to-region variation of function.

In light of the above, variations of ventilation and $\dot{V}_A/\dot{Q}$ within regions were probably the most important determinants of such overall tests of function as the arterial blood gases, the $D_{L_{CO}}$, and the mixing efficiency. It was of interest that the interregional variation of $\dot{V}_A/\dot{Q}$ (expressed as the standard deviation of the mean $\dot{V}_A/\dot{Q}$) in each patient correlated with that patient's steady state $D_{L_{CO}}$. Though this might be interpreted as indicating that the $D_{L_{CO}}$ was determined by $\dot{V}_A/\dot{Q}$ discrepancies of a regional nature, it is more probable that the amount of regional variation in $\dot{V}_A/\dot{Q}$ was indicative of the amount of intraregional $\dot{V}_A/\dot{Q}$ dispersion. It would seem likely that subjects with relatively large variations of $\dot{V}_A/\dot{Q}$ from region to region would have relatively large intraregional variation of $\dot{V}_A/\dot{Q}$, which would depress the steady state $D_{L_{CO}}$. Variations in ^{133}Xe washout from region to region did not correlate with inert gas washin, as detected by the mixing index. In an attempt to assess intraregional variations of ventilation, advantage was taken of differences between $\dot{V}_p/V$ and $\dot{V}_i/V$ which, in part, reflect intraregional ventilatory differences. The ratio of $\dot{V}_p/V$ to $\dot{V}_i/V$ was taken in each lung region and, in the case of each patient, the variance of this ratio from an ideal ratio of unity was calculated. The resulting standard deviation might be an approximate index of the degree of intraregional inhomogeneity present in each patient. Somewhat to our surprise, this index correlated significantly with

the mixing efficiency (Fig. 57), supporting the argument that the speed of inert gas washin was dependent on the dispersion of ventilatory function single regions.

Regional perfusion has been shown to exhibit an approximate correlation with regional ventilation both in other lung diseases and in a previous study of emphysema[118]. This tendency was obvious in the present series. Regional alveolar hypoxia has been proposed as a mechanism causing hypoperfusion in poorly ventilated lung regions. This might be important in determining regional perfusion distribution in emphysema, since regions with prolonged washout generally exhibited relatively low $\dot{V}_A/\dot{Q}$, and, therefore, had relatively low mean oxygen tensions. On the other hand, emphysema destroys the lung parenchyma, including the pulmonary microcirculation; the regional distributions of both ventilation and perfusion might simply reflect the distribution and extent of parenchymal destruction. In regard to these hypotheses, patients 4 and 19, who demonstrated no relationship between perfusion distribution and ventilation distribution, are of particular interest. If regional alveolar hypoxia were an important determinant of pulmonary blood flow distribution in most patients with emphysema, it would appear that this adaptive mechanism did not exist in these patients. It has been postulated that some normal subjects do not respond to alveolar hypoxia with pulmonary vasoconstriction[21]. Alternatively, if flow distribution in emphysema were usually determined by the amount of vascular destruction present in various lung regions, dissociation of the distributions of ventilation and perfusion might indicate that the severity of vascular disease was independent of the severity of lesions involving the remainder of the lung parenchyma. Before applying either of the above hypotheses to patients

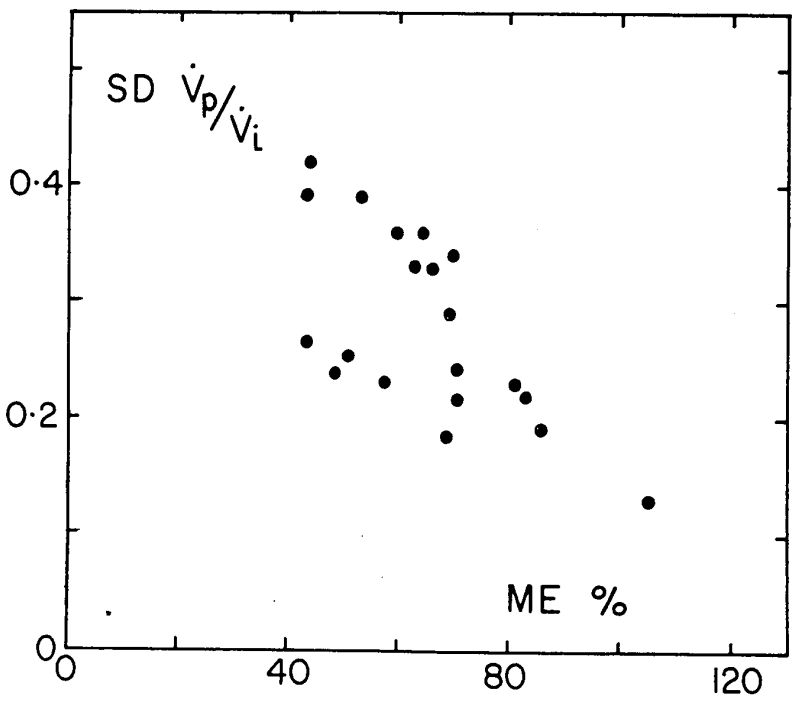


Fig. 57. Relationship of mixing efficiency with an index of intraregional variation of ventilation in patients with emphysema. Ordinate: intra-regional variation of ventilation. This was derived by taking the variance of the ratio of $\dot{V}_p/V$ to $\dot{V}_i/V$ from an ideal value of unity. Ascissa: mixing efficiency expressed as a per cent of the predicted normal value. Each point represents a patient.

4 and 19, however, it should be noted that these patients exhibited less inter-regional variation in ventilation than did most (but not all) of the subjects in whom this correlation was significant.

Finally, the dominant result of these studies was the finding that, though regional ventilation and $\dot{V}_A/\dot{Q}$ were very low, well-ventilated, well-perfused high $\dot{V}_A/\dot{Q}$ subregions existed in the lungs of these patients. The volume of these units within any region could not be accurately assessed, but it may be argued that such units very seldom accounted for as much as half a lung region. Had this been the case, such regions would probably have demonstrated rather high $\dot{V}_I/V$ since this regional washout is importantly influenced by such units (Table 21). Since intra-regional inhomogeneities were widespread and since high $\dot{V}_A/\dot{Q}$ units did not dominate any lung region, they were probably scattered throughout the lung.

This is consistent with the hypothesis that high $\dot{V}_A/\dot{Q}$ units are normal lung lobules arranged in parallel with diseased lung. On the other hand, it is perhaps more attractive to postulate that many high $\dot{V}_A/\dot{Q}$ units are arranged in series with their low $\dot{V}_A/\dot{Q}$ counterparts. The proximal or central portions of diseased lung lobules might constitute the high $\dot{V}_A/\dot{Q}$ compartment; only the proximal portion of the lobule would be ventilated by a mass flow of inspired gas[120,121]. The distal portion of the lobule would be "ventilated" by gaseous diffusion or by collateral ventilation from other lobules. Because of the large size of the emphysematous lobule, these processes could well be inefficient with the result that the larger distal portions of the lobule would be under-ventilated and have low $\dot{V}_A/\dot{Q}$.

In any event, when studied with ^{133}Xe, these patients appeared to have diffuse pulmonary dysfunction. These results do not indicate that surgical

obliteration or extirpation of lung regions would greatly help the patient with emphysema and chronic bronchitis. It would be difficult to select on the basis of the data of Table 19 lung regions which, if excised, would result in marked improvement of pulmonary gas exchange. Our experience with the surgical therapy of emphysema has supported this in that there has been little objective evidence for improvement after regional surgery. It should be noted, however, that ^{133}Xe may not be the best isotope to use in pre-operative evaluation. If an important aspect of this evaluation is the identification and location of high $\dot{V}_A/\dot{Q}$ units, then a more soluble isotope should be used.

In summary, study of 20 patients with severe emphysema and bronchitis revealed striking ventilatory abnormalities in almost all lung regions, coupled with low regional $\dot{V}_A/\dot{Q}$; no lung regions were seen which could be called normal. Though no regions with high ventilation and ventilation-perfusion ratios were demonstrated, analysis of regional washout curves revealed that units with these characteristics must have been scattered throughout the lung. Analysis of arterial ^{133}Xe concentrations showed that there also must have been differences in perfusion within single lung regions with over-ventilated high ventilation-perfusion ratio subregions being over-perfused. The low solubility of ^{133}Xe makes detection of units with high ventilation-perfusion ratios difficult when this isotope is used. Regional perfusion distribution was usually but not always similar to regional ventilation distribution. Some gross correlations were evident between regional and overall function tests; these, however, were not very impressive.

APPENDIX. RADIATION DOSE CALCULATIONS

The author is not a physicist, a radiation biologist, or even a very good mathematician. Because of this our approach to the computation of radiation dosage has been governed by two principles: first, dose calculations must be simple, and second, they must tend to overestimate the dose given. The present treatment is derived from that of Hine and Brownell,[122] and though simple, is probably not as rigorous as the schemata of Lassen[123] or Matthews et al.[124]

Radiation dosage obviously depends on the isotope used, the amount of it administered, and its distribution in the body. We consider ^{133}Xe to be distributed to two compartments, the lung and the rest of the body, and doses are calculated for these compartments, each of which are assumed to be homogenous. This is justifiable in the lungs of normals, since procedures such as rebreathing contribute most of the dose; in abnormals a quantitative treatment of intrapulmonary inhomogeneities for dose purposes is prone to gross and incalculable error. The assumption that the body is homogenous results in overestimation of the dose to most tissues, but underestimation of the dose to fat, where ^{133}Xe accumulates. Such an approach also ignores the dose contributed to the body by gamma radiation from isotope in the lung, but this contribution is not large, particularly when one considers organs some distance from the lungs such as gonads.[124] It is assumed that ^{133}Xe is distributed between the gas and blood phases in the lung according to its solubility (α = 0.18 ml Xe/ml blood/atmosphere at 38° C[58]). We have also assumed that while ^{133}Xe is being administered, there is only accumulation of isotope in the body, i.e. no isotope leaves peripheral tissue and recirculates until ^{133}Xe administration ceases. This, of course, results in overestimation of body dose. Further, we have assumed that ^{133}Xe build up to final con-

centration is virtually instantaneous in both body and lung. While this assumption does not influence body dose significantly, it does result in overestimation of lung dose. In normal subjects, the average ^{133}Xe molecule in the body compartment takes 43 minutes to leave the body; this (125) is the effective half life (Teff) of the isotope in the body, and probably this figure is not influenced by the presence of lung disease. The effective half life of isotope in the normal lung approximates one minute, in abnormals Teff is longer, perhaps 5 minutes.

Constants used in ^{133}Xe dose calculations are listed below. These have not been defined, other than in terms of their dimensions; their derivation may be found in any standard text.(122)

$\bar{E}_\beta$ = Average energy in Mev of β particles

$\bar{E}_\beta$ = 0.128 Mev(124)

Γ = Gamma ray dose constant in cm^2- rad/mc- r

Γ = 0.556

g = Geometrical factor for lung and body which calculates gamma dose to center of sphere of radius 10cm.

g = 100(124)

Equations used in dose calculations are presented below:[122]

Beta dose (D_β)

$D_\beta = 35.5\ \bar{E}_\beta\ C\ t$ mrad

where $\bar{E}_\beta$ is the mean β particle energy, C is isotope concentration in μc/gm of tissue, and t is time in minutes. This equation is used when C is not changing.

$D_\beta = 51.2\ \bar{E}_\beta\ Co\ Teff$

where Teff is the effective half life of the isotope in the tissue considered. This is used after ^{133}Xe administration has stopped and concentration is falling from peak level Co.

Gamma dose (D_γ)

$D_\gamma = 1.67 \times 10^{-2}\ p\ \Gamma\ g\ C\ t$ mrad

where p is density, Γ is the gamma dose rate constant, g is the geometry factor, and t is time in minutes. This equation is used when concentration, C, is unchanging.

$D_\gamma = 1.67 \times 10^{-2}\ p\ \Gamma\ g\ Co\ Teff$

where symbols are as above; this equation is used during washout from peak concentration Co.

Using these equations we have calculated the radiation dose to a normal man who received a 2mc slug injection of ^{133}Xe, a 5 minute infusion at a rate of 2 mc/min and a 5 minute rebreathing period with a final pulmonary ^{133}Xe concentration of 0.35 mc/liter. The subject was assumed to weigh 70 kg and to have an FRC of 3.5 liters, a cardiac output of 7 L/min, a lung weight of 1000gm and a lung density of 0.3 gm/cc. The overall (mean) $\dot{V}_A/\dot{Q}$ was 0.8, and 2% of the right heart output was assumed to be shunted through the lungs to the body. The Teff for the lung was 1 min, and for the body was 43 min.

	Lung dose (millirads)	Body dose (millirads)
i.v. slug	18.6	1.6
rebreathing	54.3	10.1
infusion	56.6	12.4

Similar calculations were carried out in a hypothetical abnormal. Conditions were the same except that 10 min periods of infusion and rebreathing were used and the infusion rate was lower - 1.5 mc/min. In addition, overall $\dot{V}_A/\dot{Q}$ was 0.4 and the Teff of ^{133}Xe in the lung was 5 min.

	Lung dose (millirads)	Body dose (millirads)
i.v. slug	70.8	1.6
rebreathing	103.8	16.5
infusion.	109.4	18.8

It can be seen that the lung dose has been considerably increased. Though it is conceivable that some patients with very bad function received even higher doses, it is most unlikely that the total dose to the lung exceeded 500 mrad, or that total dose to the body exceeded 60 mrad.

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TABLE 18. RESULTS OF PULMONARY FUNCTION TESTS IN PATIENTS WITH EMPHYSEMA AND BRONCHITIS

(Predicted normal values in parentheses)

Patient	Age	Sex	VC (L)	FRC (L)	RV (L)	ME (%)	MMFR (L/sec)	$FEV_{.75}$ (L)	$D_{L_{CO}}$ (ml/min/mm Hg)	$P_{a_{CO_2}}$ (mm Hg)	Sa_{O_2} (%)
1	53	M	3.08 (4.81)	5.44 (4.21)	4.50 (2.54)	37 (53)	0.69 (3.53)	0.70 (2.92)	1o.2 (16.7)	41	94
2	55	M	4.51 (4.01)	5.38 (3.63)	3.72 (2.23)	35 (52)	0.64 (3.22)	1.15 (2.58)	12.3 (15.3)	45	98
3	67	M	2.06 (3.76)	4.01 (3.74)	3.51 (2.47)	24 (45)	0.22 (2.66)	0.45 (1.98)	9.9 (11.3)	47	88
4	56	M	1.33 (3.72)	4.22 (3.23)	4.11 (1.87)	25 (55)	0.68 (3.28)	0.78 (2.50)	12.4 (16.1)	46	92
5	63	M	2.43 (4.38)	5.53 (3.99)	4.86 (2.47)	43 (50)	0.69 (3.17)	0.90 (2.48)	11.2 (14.2)	46	99
6	36	F	1.30 (3.15)	4.28 (2.43)	3.86 (1.28)	39 (65)	0.30 (3.43)	0.35 (2.20)	10.4 (18.9)	70	79
7	65	M	2.21 (3.74)	3.15 (3.48)	2.73 (2.17)	35 (50)	0.40 (2.98)	0.52 (2.25)	9.8 (13.7)	40	90
8	34	M	2.46 (4.46)	4.29 (3.57)	3.60 (1.62)	26 (60)	0.95 (4.18)	1.02 (3.05)	11.1 (21.8)	58	77
9	66	M	1.41 (3.12)	3.01 (3.23)	2.71 (2.17)	35 (50)	0.30 (2.46)	0.38 (1.78)	8.0 (10.6)	51	89
10	48	F	2.23 (3.23)	3.14 (2.78)	2.71 (1.74)	40 (56)	0.30 (2.65)	0.52 (2.00)	5.2 (14.7)	38	93
11	66	M	1.97 (3.74)	3.80 (3.48)	3.01 (2.17)	24 (47)	0041 (2.98)	0.42 (2.25)	7.0 (12.1)	55	89
12	55	M	1.43 (4.06)	3.11 (3.74)	2.71 (2.32)	32 (50)	0.50 (3.07)	0.48 (2.35)	5.7 (16.5)	51	90
13	45	M	1.41 (4.57)	2.68 (3.82)	2.08 (2.18)	25 (57)	0.25 (3.70)	0.42 (3.05)	5.9 (16.2)	44	89
14	51	M	2.35 (3.72)	3.57 (3.23)	2.62 (1.87)	38 (55)	0.40 (3.28)	0.62 (2.50)	11.4 (16.0)	51	92
15	60	M	2.42 (3.86)	4.61 (3.63)	3.89 (2.31)	42 (50)	0.26 (3.01)	0.48 (2.38)	10.5 (12.2)	49	91
16	58	M	1.64 (3.90)	4.92 (3.61)	4.49 (2.25)	29 (50)	0.34 (3.05)	0.38 (2.30)	6.8 (13.9)	46	94
17	60	M	3.24 (3.48)	6.o8 (3.30)	4.70 (2.10)	41 (50)	0.29 (2.93)	0.38 (2.25)	7.0 (12.1)	45	91
18	51	F	1.41 (2.78)	3.63 (2.42)	3.19 (1.56)	57 (54)	0.24 (2.41)	0.30 (1.80)	6.2 (13.4)	45	96
19	57	F	2.17 (2.87)	3.82 (2.67)	3.40 (1.65)	32 (50)	0.43 (2.40)	0.58 (1.68)	6.6 (11.8)	42	99
20	41	F	2.28 (3.76)	3.70 (3.14)	2.90 (1.75)	38 (60)	0.30 (3.30)	1.05 (2.25)	7.4 (11.5)	36	86

LTS OF PULMONARY FUNCTION TESTS IN PATIENTS WITH

EMPHYSEMA AND BRONCHITIS

ted normal values in parentheses)

FRC (L)	RV (L)	ME (%)	MMFR (L/sec)	$FEV_{.75}$ (L)	$D_{L_{CO}}$ (ml/min/mm Hg)	$P_{a_{CO_2}}$ (mm Hg)	Sa_{O2} (%)	C_{st} (L/cm H_2O)	R_L (cm H_2O/L/s
5.44 (4.21)	4.50 (2.54)	37 (53)	0.69 (3.53)	0.70 (2.92)	1o.2 (16.7)	41	94	0.25 (0.20)	7.0 (< 2.0)
5.38 (3.63)	3.72 (2.23)	35 (52)	0.64 (3.22)	1.15 (2.58)	12.3 (15.3)	45	98		
4.01 (3.74)	3.51 (2.47)	24 (45)	0.22 (2.66)	0.45 (1.98)	9.9 (11.3)	47	88		
4.22 (3.23)	4.11 (1.87)	25 (55)	0.68 (3.28)	0.78 (2.50)	12.4 (16.1)	46	92		
5.53 (3.99)	4.86 (2.47)	43 (50)	0.69 (3.17)	0.90 (2.48)	11.2 (14.2)	46	99		
4.28 (2.43)	3.86 (1.28)	39 (65)	0.30 (3.43)	0.35 (2.20)	10.4 (18.9)	70	79	0.12 (0.14)	33.0 (< 2.0)
3.15 (3.48)	2.73 (2.17)	35 (50)	0.40 (2.98)	0.52 (2.25)	9.8 (13.7)	40	90		
4.29 (4.57)	3.60 (1.62)	26 (60)	0.95 (4.18)	1.02 (3.05)	11.1 (21.8)	58	77	0.19 (0.15)	12.0 (< 2.0)
3.01 (3.23)	2.71 (2.17)	35 (50)	0.30 (2.46)	0.38 (1.78)	8.0 (10.6)	51	89		
3.14 (2.78)	2.71 (1.74)	40 (56)	0.30 (2.65)	0.52 (2.00)	5.2 (14.7)	38	93	0.36 (0.13)	6.5 (< 2.0)
3.80 (3.48)	3.01 (2.17)	24 (47)	0041 (2.98)	0.42 (2.25)	7.0 (12.1)	55	89		
3.11 (3.74)	2.71 (2.32)	32 (50)	0.50 (3.07)	0.48 (2.35)	5.7 (16.5)	51	90	0.34 (0.20)	10.1 (< 2.0)
2.68 (3.82)	2.08 (2.18)	25 (57)	0.25 (3.70)	0.42 (3.05)	5.9 (16.2)	44	89	o.44 (0.17)	7.3 (< 2.0)
3.57 (3.23)	2.62 (1.87)	38 (55)	0.40 (3.28)	0.62 (2.50)	11.4 (16.0)	51	92	0.14 (0.14)	8.5 (< 2.0)
4.61 (3.63)	3.89 (2.31)	42 (50)	0.26 (3.01)	0.48 (2.38)	10.5 (12.2)	49	91		
4.92 (3.61)	4.49 (2.25)	29 (50)	0.34 (3.05)	0.38 (2.30)	6.8 (13.9)	46	94	0.17 (0.17)	9.0 (< 2.0)
6.o8 (3.30)	4.70 (2.10)	41 (50)	0.29 (2.93)	0.38 (2.25)	7.0 (12.1)	45	91	0.55 (0.20)	3.0 (< 2.0)
3.63 (2.42)	3.19 (1.56)	57 (54)	0.24 (2.41)	0.30 (1.80)	6.2 (13.4)	45	96		
3.82 (2.67)	3.40 (1.65)	32 (50)	0.43 (2.40)	0.58 (1.68)	6.6 (11.8)	42	99		
3.70 (3.14)	2.90 (1.75)	38 (60)	0.30 (3.30)	1.05 (2.25)	7.4 (11.5)	36	86	0.45 (0.20)	5.0 (< 2.0)

ONARY FUNCTION TESTS IN PATIENTS WITH

AND BRONCHITIS

values in parentheses)

RV (L)	ME (%)	MMFR (L/sec)	$FEV_{.75}$ (L)	$D_{L_{CO}}$ (ml/min/mm Hg)	$P_{a_{CO_2}}$ (mm Hg)	Sa_{O_2} (%)	C_{st} (L/cm H_2O)	R_L (cm H_2O/L/sec)	max Pel (cm H_2O)
.50 .54)	37 (53)	0.69 (3.53)	0.70 (2.92)	1o.2 (16.7)	41	94	0.25 (0.20)	7.0 (< 2.0)	- 9.0 (< - 20.0)
.72 .23)	35 (52)	0.64 (3.22)	1.15 (2.58)	12.3 (15.3)	45	98			
.51 .47)	24 (45)	0.22 (2.66)	0.45 (1.98)	9.9 (11.3)	47	88			
.11 .87)	25 (55)	0.68 (3.28)	0.78 (2.50)	12.4 (16.1)	46	92			
.86 .47)	43 (50)	0.69 (3.17)	0.90 (2.48)	11.2 (14.2)	46	99			
.86 .28)	39 (65)	0.30 (3.43)	0.35 (2.20)	10.4 (18.9)	70	79	0.12 (0.14)	33.0 (< 2.0)	- 14.0 (< - 20.0)
.73 .17)	35 (50)	0.40 (2.98)	0.52 (2.25)	9.8 (13.7)	40	90			
.60 .62)	26 (60)	0.95 (4.18)	1.02 (3.05)	11.1 (21.8)	58	77	0.19 (0.15)	12.0 (< 2.0)	- 17.0 (< - 20.0)
.71 .17)	35 (50)	0.30 (2.46)	0.38 (1.78)	8.0 (10.6)	51	89			
.71 .74)	40 (56)	0.30 (2.65)	0.52 (2.00)	5.2 (14.7)	38	93	0.36 (0.13)	6.5 (< 2.0)	- 12.5 (< - 20.0)
.01 .17)	24 (47)	0041 (2.98)	0.42 (2.25)	7.0 (12.1)	55	89			
.71 .32)	32 (50)	0.50 (3.07)	0.48 (2.35)	5.7 (16.5)	51	90	0.34 (0.20)	10.1 (< 2.0)	- 18.0 (< - 20.0)
.08 .18)	25 (57)	0.25 (3.70)	0.42 (3.05)	5.9 (16.2)	44	89	o.44 (0.17)	7.3 (< 2.0)	- 7.5 (< - 20.0)
.62 .87)	38 (55)	0.40 (3.28)	0.62 (2.50)	11.4 (16.0)	51	92	0.14 (0.14)	8.5 (< 2.0)	- 17.0 (< - 20.0)
.89 .31)	42 (50)	0.26 (3.01)	0.48 (2.38)	10.5 (12.2)	49	91			
.49 .25)	29 (50)	0.34 (3.05)	0.38 (2.30)	6.8 (13.9)	46	94	0.17 (0.17)	9.0 (< 2.0)	- 15.0 (< - 20.0)
.70 .10)	41 (50)	0.29 (2.93)	0.38 (2.25)	7.0 (12.1)	45	91	0.55 (0.20)	3.0 (< 2.0)	- 10.0 (< - 20.0)
.19 .56)	57 (54)	0.24 (2.41)	0.30 (1.80)	6.2 (13.4)	45	96			
.40 .65)	32 (50)	0.43 (2.40)	0.58 (1.68)	6.6 (11.8)	42	99			
.90 .75)	38 (60)	0.30 (3.30)	1.05 (2.25)	7.4 (11.5)	36	86	0.45 (0.20)	5.0 (< 2.0)	- 14.0 (< - 20.0)

TABLE 19. RESULTS OF ^{133}Xe STUDIES IN PATIENTS WITH EMPHYSEMA AND BRONCHITIS

Patient		Right Lung					Left Lung				
		R_1	R_2	R_3	R_4	R_5	L_1	L_2	L_3	L_4	L_5
1	$\dot{V}_A/\dot{Q}$	0.62	0.55	0.65	0.68	0.61	0.72	0.78	0.63	0.61	0.45
	$\dot{Q}_i$	67	105	79	71	58	139	152	122	112	73
	$\dot{V}_p/V$	0.47	0.45	0.26	0.28	0.30	0.88	1.04	0.70	0.41	0.18
	$\dot{V}_i/V$	0.53	0.44	0.49	0.32	0.28	1.50	1.50	1.20	0.60	0.37
2	$\dot{V}_A/\dot{Q}$	0.48	0.49	0.54	0.62	0.54	0.41	0.47	0.55	0.55	0.55
	$\dot{Q}_i$	31	29	53	98	85	43	33	77	112	91
	$\dot{V}_p/V$	0.31	0.39	0.60	1.25	1.02	0.38	0.39	0.88	1.39	1.39
	$\dot{V}_i/V$	0.40 0.41	0.49	0.91	2.00	1.67	0.43	0.46	1.11	2.50	2.50
3	$\dot{V}_A/\dot{Q}$	0.41	0.33	0.37	0.34	0.30	0.33	0.29	0.26	0.30	0.12
	$\dot{Q}_i$	109	129	136	139	131	54	54	70	78	76
	$\dot{V}_p/V$	0.37	0.43	0.34	0.36	0.36	0.15	0.18	0.18	0.28	0.14
	$\dot{V}_i/V$	0.68	0.67	0.46	0.59	0.48	0.31	0.25	0.26	0.47	0.21
4	$\dot{V}_A/\dot{Q}$	0.28	0.25	0.19	0.21	0.23	0.20	0.18	0.18	0.11	0.21
	$\dot{Q}_i$	67	75	81	69	87	69	68	57	56	67
	$\dot{V}_p/V$	0.40	0.45	0.28	0.25	0.51	0.46	0.42	0.30	0.40	0.60
	$\dot{V}_i/V$	0.53	0.71	0.45	0.33	0.75	0.43	0.40	0.40	0.36	0.75
5	$\dot{V}_A/\dot{Q}$	0.52	0.52	0.43	0.44	0.46	0.62	0.56	0.52	0.52	0.59
	$\dot{Q}_i$	113	99	66	99	58	136	112	77	86	89
	$\dot{V}_p/V$	0.73	0.52	0.32	0.61	0.52	1.50	0.90	0.38	0.30	0.32
	$\dot{V}_i/V$	0.83	0.42	0.26	0.60	0.55	1.13	0.91	0.39	0.28	0.45
6	$\dot{V}_A/\dot{Q}$	0.09	0.15	0.21	0.15	0.11	0.04	0.06	0.04	0.05	0.05
	$\dot{Q}_i$	50	67	89	81	74	25	33	28	31	36
	$\dot{V}_p/V$	0.36	0.29	0.50	0.41	0.38	0.21	0.20	0.28	0.28	0.29
	$\dot{V}_i/V$	0.46	0.83	0.75	0.75	0.42	0.24	0.30	0.24	0.38	0.21
7	$\dot{V}_A/\dot{Q}$	0.53	0.61	0.57	0.46	0.39	0.30	0.34	0.39	0.41	0.42
	$\dot{Q}_i$	57	66	57	50	23	28	25	32	44	23
	$\dot{V}_p/V$	0.70	1.02	0.61	0.46	0.20	0.12	0.15	0.23	0.22	0.23
	$\dot{V}_i/V$	1.25	1.11	0.81	0.52	0.25	0.18	0.20	0.34	0.29	0.32

	$\dot{Q}_i$	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	$\dot{V}_p/V$	0.36	0.29	0.50	0.41	0.38	0.21	0.20	0.28	0.28	0.29
	$\dot{V}_i/V$	0.46	0.83	0.75	0.75	0.42	0.24	0.30	0.24	0.38	0.21
7	$\dot{V}_A/\dot{Q}$	0.53	0.61	0.57	0.46	0.39	0.30	0.34	0.39	0.41	0.42
	$\dot{Q}_i$	57	66	57	50	23	28	25	32	44	23
	$\dot{V}_p/V$	0.70	1.02	0.61	0.46	0.20	0.12	0.15	0.23	0.22	0.23
	$\dot{V}_i/V$	1.25	1.11	0.81	0.52	0.25	0.18	0.20	0.34	0.29	0.32
8	$\dot{V}_A/\dot{Q}$	0.55	0.55	0.42	0.42	0.30	0.59	0.43	0.45	0.38	0.32
	$\dot{Q}_i$	71	64	46	46	53	50	51	59	37	22
	$\dot{V}_p/V$	0.91	1.07	0.46	0.29	0.15	0.52	0.58	0.28	0.11	0.05
	$\dot{V}_i/V$	1.47	1.21	0.55	0.42	0.31	0.75	0.59	0.52	0.14	0.18
9	$\dot{V}_A/\dot{Q}$	0.50	0.46	0.40	0.29	0.32	0.48	0.35	0.32	0.32	0.27
	$\dot{Q}_i$	83	52	27	23	26	98	87	62	25	39
	$\dot{V}_p/V$	1.36	1.31	0.66	0.26	0.33	1.25	0.52	0.18	0.21	0.17
	$\dot{V}_i/V$	1.87	1.15	0.73	0.20	0.35	1.15	0.41	0.20	0.15	0.13
10	$\dot{V}_A/\dot{Q}$	0.69	0.60	0.40	0.50	0.51	0.39	0.43	0.31	0.24	0.18
	$\dot{Q}_i$	75	73	57	54	54	71	76	83	66	42
	$\dot{V}_p/V$	1.42	1.07	0.75	0.46	0.30	0.98	1.11	0.56	0.19	0.10
	$\dot{V}_i/V$	1.62	1.18	0.77	0.47	0.52	0.89	1.38	0.43	0.25	0.16
11	$\dot{V}_A/\dot{Q}$	0.28		0.26	0.29	0.22	0.32	0.31	0.27	0.28	0.48
	$\dot{Q}_i$	30		34	21	21	45	39	22	42	48
	$\dot{V}_p/V$	0.37		0.36	0.22	0.15	0.48	0.40	0.34	0.65	0.74
	$\dot{V}_i/V$	0.36		0.55	0.39	0.17	0.81	0.43	0.38	0.59	0.71
12	$\dot{V}_A/\dot{Q}$	0.37	0.41	0.39	0.32	0.28	0.13	0.11	0.05	0.01	0.01
	$\dot{Q}_i$	121	104	86	67	51	37	12	9	10	8
	$\dot{V}_p/V$	0.91	0.81	0.50	0.20	0.19	0.07	0.03	0.03	0.02	0.02
	$\dot{V}_i/V$	1.47	1.13	0.93	0.62	0.25	0.15	0.09	0.07	0.04	0.04
13	$\dot{V}_A/\dot{Q}$	0.56	0.48	0.61	0.60	0.63	0.56	0.45	0.45	0.46	0.37
	$\dot{Q}_i$	116	113	46	58	38	108	87	39	26	34
	$\dot{V}_p/V$	1.39	1.31	0.67	0.53	0.50	1.13	0.59	0.20	0.09	0.06
	$\dot{V}_i/V$	1.58	1.77	1.47	1.14	0.59	1.42	1.11	0.35	0.19	0.11

	$\dot{V}_p/V$	0.91	0.81	0.50	0.20	0.19	0.07	0.03	0.03	0.02	0.02
	$\dot{V}_i/V$	1.47	1.13	0.93	0.62	0.25	0.15	0.09	0.07	0.04	0.04
13	$\dot{V}_A/\dot{Q}$	0.56	0.48	0.61	0.60	0.63	0.56	0.45	0.45	0.46	0.37
	$\dot{Q}_i$	116	113	46	58	38	108	87	39	26	34
	$\dot{V}_p/V$	1.39	1.31	0.67	0.53	0.50	1.13	0.59	0.20	0.09	0.06
	$\dot{V}_i/V$	1.58	1.77	1.47	1.14	0.59	1.42	1.11	0.35	0.19	0.11
14	$\dot{V}_A/\dot{Q}$	0.45	0.49	0.37	0.37	0.37	0.45	0.67	0.54	0.41	0.43
	$\dot{Q}_i$										
	$\dot{V}_p/V$	0.85	0.85	0.48	0.31	0.54	0.67	0.83	0.48	0.38	0.32
	$\dot{V}_i/V$	0.95	0.89	0.53	0.42	0.48	0.56	0.93	0.48	0.38	0.40
15	$\dot{V}_A/\dot{Q}$	0.33	0.32	0.32	0.32	0.27	0.38	0.30	0.30	0.19	0.25
	$\dot{Q}_i$	38	56	77	98	81	59	83	105	83	61
	$\dot{V}_p/V$	0.27	0.32	0.42	0.67	0.67	0.48	0.54	0.42	0.37	0.29
	$\dot{V}_i/V$	0.28	0.30	0.32	0.55	0.51	0.48	0.54	0.67	0.37	0.28
16	$\dot{V}_A/\dot{Q}$	0.87	0.90	0.81	0.95	0.83	0.78	0.82	0.73	0.58	0.60
	$\dot{Q}_i$	73	86	63	44	33	97	96	74	44	53
	$\dot{V}_p/V$	1.33	1.07	0.62	0.61	0.48	1.25	0.91	0.67	0.37	0.31
	$\dot{V}_i/V$	1.50	1.22	0.83	0.75	0.45	1.58	1.62	0.86	0.39	0.41
17	$\dot{V}_A/\dot{Q}$	0.66	0.72	0.60	0.92	0.83	0.51	0.72	0.58	0.70	0.60
	$\dot{Q}_i$	43	65	82	44	32	68	86	94	68	38
	$\dot{V}_p/V$	0.25	0.38	0.33	0.36	0.25	0.39	0.58	0.40	0.38	0.19
	$\dot{V}i/V$	0.24	0.32	0.30	0.49	0.40	0.29	0.64	0.48	0.45	0.26
18	$\dot{V}_A/\dot{Q}$	0.70	0.70	0.58	0.56	0.64	0.71	0.65	0.66	0.59	0.57
	$\dot{Q}_i$	47	57	61	51	40	70	89	83	78	53
	$\dot{V}_p/V$	0.59	0.58	0.45	0.45	0.44	0.92	1.18	0.89	0.61	0.62
	$\dot{V}_i/V$	0.55	0.64	0.58	0.45	0.37	0.91	1.11	0.91	0.54	0.53
19	$\dot{V}_A/\dot{Q}$	0.31	0.38	0.43	0.54	0.56	0.20	0.36	0.38	0.39	0.47
	$\dot{Q}_i$	69	63	52	70	40	73	90	63	63	75
	$\dot{V}_p/V$	0.39	0.50	0.40	0.81	0.67	0.48	0.44	0.41	0.54	0.81
	$\dot{V}_i/V$	0.52	0.94	0.94	1.18	0.95	0.55	0.78	0.57	0.65	1.11
20	$\dot{V}_A/\dot{Q}$	0.41	0.34	0.44	0.65	0.61	0.47	0.38	0.37	0.57	0.48
	$\dot{Q}_i$										
	$\dot{V}_p/V$	0.47	0.30	0.50	1.07	0.68	0.39	0.26	0.33	0.82	0.61
	$\dot{V}_i/V$	0.60	0.50	0.56	1.33	1.30	0.75	0.37	0.38	0.75	0.99