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EVALUATION OF AN INTEGRATED ^{133}Xe REGIONAL PULMONARY-FUNCTION ANALYZER

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An integrated system for diagnostic, quantitative, static and dynamic, regional pulmonary-function analysis—both ventilation and perfusion—using ^{133}Xe has recently been developed by Ohio-Nuclear. This paper considers this equipment in a clinical setting and describes the results obtained from 50 normal subjects. Functionally, the analyzer was found to be satisfactory and its operation simple and easy to learn. Patient discomfort is minimal and the complete ventilation–perfusion analysis can be performed and reported in less than 30 min. The results from normal subjects were comparable with published results.

Most routine pulmonary-function tests measure overall pulmonary function, and regional information about ventilation and perfusion is not obtained. Bronchospirometry, devised in 1932 (*1*), never gained widespread popularity because of its invasive nature and because of the problem of resistance breathing (*2*). Until recently, estimations of regional ventilation and perfusion were made from plain chest radiographs, supported by pulmonary arteriography whenever a more detailed analysis of perfusion was required. Knipping et al (*3*) in 1955 were the first to study pulmonary function with radioactive gases, and since then many techniques have been developed for measuring regional ventilation and perfusion distributions using various gamma-emitters. Such techniques have played a major role in the advancement of pulmonary physiology. However, the only such technique to become widely established in routine clinical practice is the qualitative evaluation of regional perfusion with externally positioned scintillation detectors after intravenous injection of radioactively labeled aggregated albumin. Most other techniques are not widely used because of the need for complex equipment, skilled operators, laborious data processing, and the long interval required before results can be presented in a clinically interpretable form. The usefulness of such detailed regional analyses in routine clinical diagnosis thus remains speculative.

An integrated system for diagnostic, quantitative, static and dynamic, regional pulmonary-function analysis—both ventilation and perfusion—using ^{133}Xe has recently been developed by Ohio-Nuclear (Solon, Ohio). This paper considers this equipment in a clinical setting and presents results from 100 studies, including data from 50 normal subjects.

THE SYSTEM

The Regional Pulmonary Function Analyzer (RPFA) has been so designed that a single technologist may operate it after minimal instruction. Most of its functions are computer-controlled and the operator need only select the sequence. The regional information is processed by a built-in computer and can be read directly from a digital display (analog information is also presented). Demands on the patient are minimized since this noninvasive measurement requires only several sequences of maximal inspirations and 4-sec breath-holdings. The whole procedure, from arrival of the patient to presentation of the analyzed results, can be performed in less than 30 min. The techniques employed are essentially those described by Ball et al in 1962 (*4*), and an early prototype of this equipment was developed and reported by Blum in 1971 (*5*). More recently, abstracts reporting the system have been published (*6,7*).

The RPFA is composed of two units (Fig. 1). A mobile console contains the operating controls and data readout, a ^{133}Xe delivery and rebreath system,

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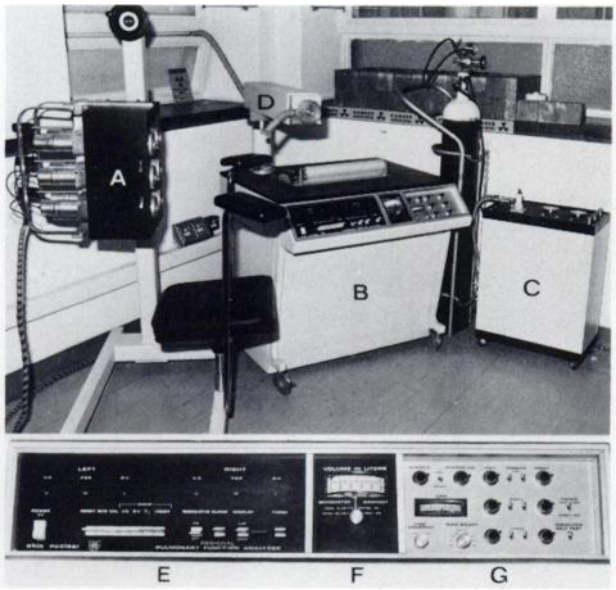

FIG. 1. Regional pulmonary-function analyzer (Ohio-Nuclear) with close-up view of control panels. (A) detector stand assembly; (B) mobile console; (C) gas-mixing system; (D) gas-delivery arm with mouthpiece assembly; (E) main panel and controls; (F) volume indicator and selector; (G) nuclear electronics subpanel.

a refrigerated gas trap, and the digital computing electronics. A detector stand assembly supports the patient's chair and the six adjustable NaI scintillation detectors, each with a cylindrical collimator 13 cm in length. An optional third unit (the gas-mixing system) permits the ^{133}Xe to be pumped from a supply vial into a storage tank and mixed with either air or oxygen.

The distributions of ventilation and perfusion are determined with the subject sitting upright with his back in contact with the collimators. These are placed, as far as possible, so that the total lung capacity falls within the detector fields at maximal inspiration. The RPFA can be set for each of the following measurements: background, calibration, vital capacity, residual volume, washout half-times, or normalized data. After exhalation to residual volume, the appropriate measurement is selected and the subject is instructed to inhale to total lung capacity and breath-hold for 4 sec while each detector records counts for computation of results. Depression of a "timer switch" signals the onset of a measurement cycle; a lamp above the switch stays lit while the cycle is in progress. All recordings are thus taken during a 4-sec breath-hold at maximum lung capacity following inspiration from residual volume. Another control switches the subject into or out of a closed circuit with the analyzer's wedge spirometer to permit equilibration and washout studies. Table 1 shows the measurements displayed and computed by the RPFA system.

Perfusion measurements are made after an intravenous injection of ^{133}Xe in saline during breath-holding at functional residual capacity. An estimated 95% of the dissolved gas passes into alveolar gas during its first passage through the pulmonary circulation. Since most of the gas is lost before the blood reaches the left ventricle, gas spaces perfused by the bronchial circulation will not contain ^{133}Xe, and thus the resulting concentration in any region is proportional to the pulmonary capillary blood flow per unit of lung volume in that region.

Calibration. In order to convert radiation intensity (counts per unit volume) into liters of gas, the system (including the patient) is calibrated initially by introducing a known volume of the ^{133}Xe gas mixture (0.25 liter), followed by air, into the subject's lungs as he breathes from residual volume (RV) to total lung capacity (TLC). While he then breath-holds at TLC for 4 sec, the sum of the counts from all six detectors is stored. This number is taken as the equivalent to 0.25 liter of gas, and thus the absolute volume (in liters) can be derived from the count rates as various ventilation maneuvers are performed. The distribution of the calibration bolus need not be known.

Radiation dosage. The radiation dose to the patient is acceptably small by comparison with other modern diagnostic techniques, although it will depend on the evenness of ventilation and will increase if the equilibration and washout times are greatly prolonged. Smith and Mozley (*8*) estimated the absorbed dose per millicurie of ^{133}Xe to be 0.05 rad in the lungs and 0.0002 rad to the whole body. These figures are based on the assumption that ^{133}Xe remains totally in the lungs for 9 min. In the present

TABLE 1. CAPABILITIES OF THE RPFA SYSTEM

Vital capacity	Right	Left	Regional	
Normalized vital capacity (Nsb)*			Regional	
Equilibration data (Ne)			Regional	
Forced expiratory ratio	Right	Left		
Residual volume	Right	Left		
Washout half-time after ventilatory equilibration			Regional	
Normalized washout data (Nvw)			Regional	
Washout volume				Total
Tidal volume				
Normalized perfusion data (Nq)			Regional	
Washout half-time after perfusion analysis			Regional	
Normalized washout data (Nqw)			Regional	
Washout volume				Total

* Normalized in relation to total information from both lungs.

series the longest ventilation studies, in patients with obstructive disease of the airways, were in the range of 9 min.

Assuming a maximal ^{133}Xe concentration of 0.8 mCi/liter and a patient vital capacity of 5.0 liter, the maximal dose for a ventilation–perfusion study would be 0.138 rad for the lung and 0.00055 rad for the whole body.

Errors. The potential sources of error in evaluating regional pulmonary function using ^{133}Xe are, in the main, common to most published techniques and have been reviewed by Milic-Emili (*9*). Probably the major source of error unique to this system is that relating to the calibration procedure. Following an initial assumption that a given quantity of ^{133}Xe yields a fixed detectable count rate irrespective of differences in either distance from the counters or absorption or scatter, correct analysis will result only if the whole of the calibration bolus and the whole of the total lung capacity, or an identical proportion of each, fall within the detector fields. Because the total number of counts from the calibration bolus is measured, factors affecting its distribution in the lungs [e.g., preinspiratory lung volume (*10*) and inspiratory flow rate (*11*)] need not be controlled.

A further major source of error results from the fact that all measurements are based on the comparison of count rates from the same counters at different points in time. Thus, the geometry and position of the lungs and chest must be the same on each occasion. The RPFA attempts to overcome these two variables, firstly, by placing the subject in a relatively fixed position by means of the collimators, gas-delivery arm, and arm rests and, secondly, by taking all counts during breath-holding at TLC after a maximal inspiration from RV. Problems of measurement are also complicated by the relative detector positions. Clearly, in a subject with a large chest, areas of total lung capacity will not fall within the field of any detector and, conversely, in the subject with a small chest, some detector fields will overlap and be counted twice.

During rebreathing some ^{133}Xe will dissolve in the blood and be distributed throughout body tissues, including areas of chest wall within the detector fields. The contribution of chest wall radiation to the total number of counts may not introduce significant error in a normally ventilated lung, but if a detector field contains a large volume of unventilated lung, so that the equilibrium count is low, then the percentage error due to ^{133}Xe in the chest wall may reach significant proportions (*12,13*). In the RPFA analysis, extrapulmonary ^{133}Xe may also introduce a significant error in the measurement of RV when, after equilibration, the subject exhales maximally and then inhales to TLC with air, thus diluting the concentration of ^{133}Xe in the lung without allowing time for the extrapulmonary concentrations of ^{133}Xe to fall.

RESULTS AND DISCUSSION

Statistical methods. Differences between groups of data were analyzed using either a paired or unpaired t-test as appropriate. When the variance ratio test showed that the use of parametric tests was unjustified, the Wilcoxon matched-pairs signed-ranks test (*14*) was employed. The level of significance has been taken as $p < 0.05$ in either a two-tailed or one-tailed test.

Patient studies. One hundred ventilation studies were performed in 87 subjects. Of these, 52 studies were performed in 45 normal volunteers, the remaining studies being in patients having a wide variety of respiratory diseases.

Vital capacity and residual volume. The RPFA computes the absolute vital capacity and residual volume in liters, but these data are of secondary importance, for the main function of a study is to obtain information concerning the distribution of ventilation both between the two lungs and regionally within each lung. Nevertheless, analysis of vital capacity and residual volume indicates the overall capabilities of the equipment and will indicate any major errors in detector positioning or computation. For this reason, the vital capacity of each subject was estimated by spirometry before the ^{133}Xe RPFA study and, in addition, 58 subjects had their residual volume estimated by the helium-rebreathing technique.

The results are shown in Fig. 2. Both the X–Y regression line and the best-fit line passing through the origin have been plotted. The slopes of these lines for both vital capacity and residual volume are significantly different from unity ($p < 0.001$ in all instances). The correlation coefficient for vital capacity is 0.956 and for residual volume is 0.795. Clearly, even with the best detector positioning the RPFA slightly underestimates the vital capacity and seriously overestimates the residual volume. These results were expected from a consideration of the errors of the calibration procedure already discussed.

Forced expiratory ratio (FER). This measure of airways obstruction is defined as the fraction of total lung capacity expired in 1 sec of a forced expiration. It is determined by integrating the counts 0.5–1.5 sec after the start of a forced expiration and expressing this as a ratio of the total vital capacity (VC) counts. This ratio is asserted to be analogous to the conventional measure of airways obstruction FEV_1/VC, but we have been unable to find any data in the literature supporting this statement. Initially, therefore, 72 spirographic records (Bernstein spirometer)

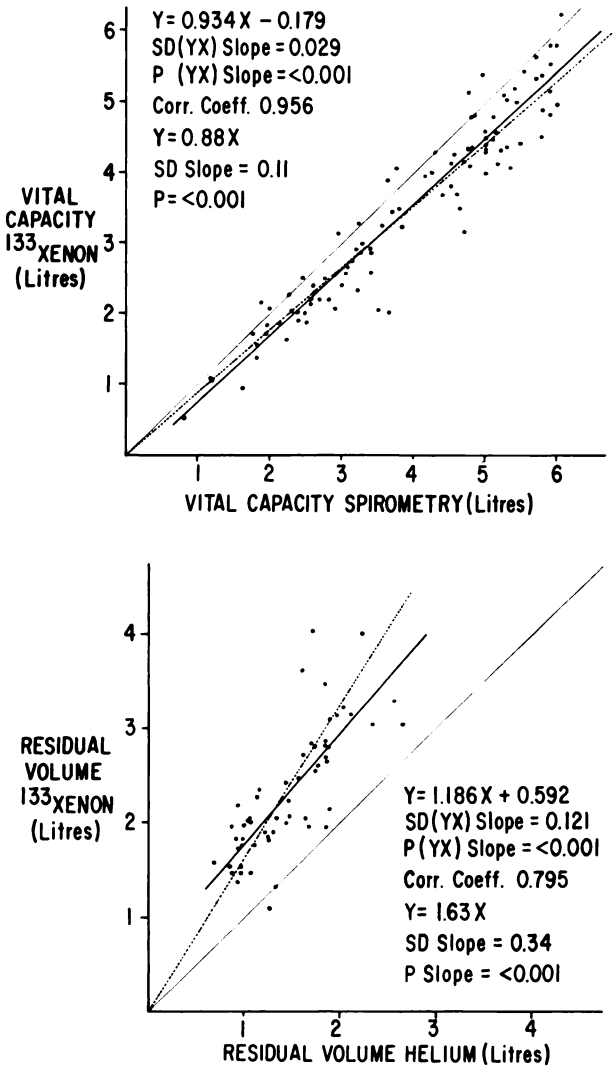

FIG. 2. (Top) Vital capacity determined by spirometry (X axis) versus that determined by RPFA ^{133}Xe (Y axis) in 100 subjects. (Bottom) Residual volume determined by helium dilution (X axis) versus residual volume determined by RPFA ^{133}Xe (Y axis) in 58 subjects. Lines of identity, regression lines (dark solid lines), and lines of best fit through origin (interrupted lines) are shown.

of forced expiration performed by both normal and abnormal subjects were analyzed in terms of FEV_1/VC and the FER derived by planimetry. The results indicate a correlation coefficient of 0.962, not statistically different from a line drawn through the origin with a slope of unity.

Once this relationship was established, the FEV_1/VC (spirometry) was plotted against the mean of the right and left FER computed during the ^{133}Xe study. The result (Fig. 3) indicates a correlation coefficient of 0.773 with slopes significantly different from unity. This loss of correlation may perhaps be explained by the changing geometry of the chest in relation to the detectors during the forced expiratory maneuver. However, an alternative explanation may be that a forced expiration through the high-resistance system of the analyzer (7 cm H_2O at 1 liter/sec) is unphysiologic and could possibly hinder expiratory flow. In order to investigate this further, the changes in the RPFA spirometer volume were recorded using the voltage output at the rear of the console; the voltage produced was shown to be a linear function of the volume in the RPFA wedge spirometer. Comparison between the spirometric traces performed before and during the ^{133}Xe study indicated an excellent correlation for VC, FEV_1, FEV_1/VC, and FER (correlation coefficients 0.91, 0.93, 0.87, and 0.85, respectively). There was also good correlation (0.88) between FEV_1/VC and FER derived from the RPFA spirometer. We thus concluded that the discrepancy between FEV_1/VC (spirometry) and FER (^{133}Xe) is most probably due to changes in lung geometry in relation to the detectors during the forced expiration and not due to the performance of a forced expiratory maneuver through the high-resistance system of the RPFA.

The derived FER appears to provide only an approximate guide as to the presence or absence of airways obstruction in the clinical setting, and if an FEV_1/VC below 75% may be considered abnormal (*15*), an FER below 49% may also be considered abnormal (Fig. 3).

Regional studies in normal subjects. Forty-five normal subjects, 40 men and 5 women, ranging in age from 19 to 53 years, were studied on the RPFA. Fifty-two ventilation studies were performed on 45 subjects and 20 perfusion studies on 19 subjects. In the analysis of these results, no distinction has been made between subjects according to age, sex, or smoking habit. None of these subjects had any his-

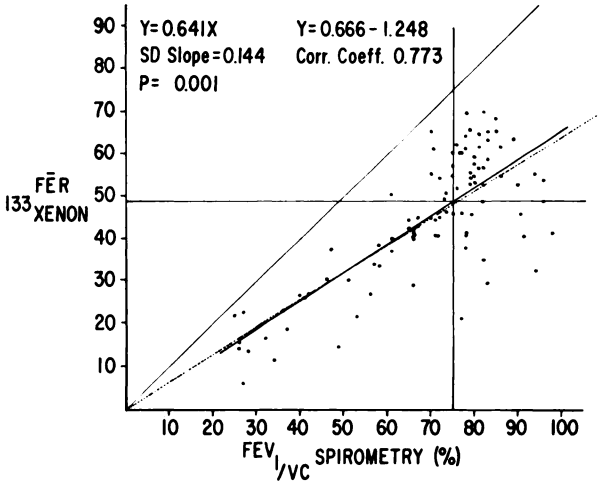

FIG. 3. Forced expiratory ratio (FER) derived by RPFA ^{133}Xe (Y axis) versus FEV_1/VC determined by spirometry (X axis). Lower limits of normality are represented by vertical line drawn at FEV_1/VC ratio of 75% and horizontal line drawn at FER ratio of 49%.

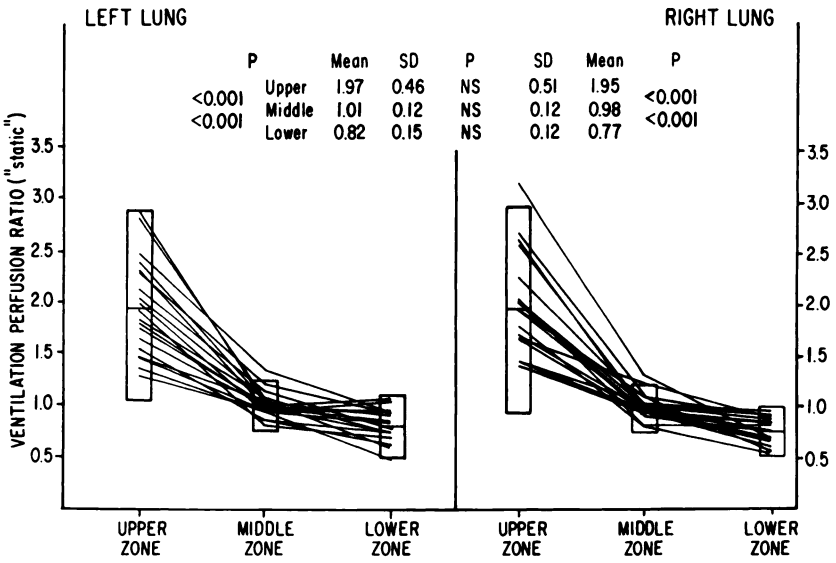

FIG. 4. Distribution of ventilation index for left and right lungs in 45 normal subjects. Open boxes indicate mean ± 2 s.d. for each region.

tory of respiratory disease and all had vital capacity and FEV_1 within their predicted range.

Vital capacity and residual volume. The distribution of vital capacity between the left and right lungs was studied, each as a percentage of the total. The mean for the left lung was 47.8% (s.d. 3.16%), and the difference between the right and left lungs is highly significant ($p < 0.001$). These results are in agreement with other studies (*16–18*). The distribution of vital capacity can be studied further by comparison of the left and right lungs in the upper, middle, and lower regions. There was no significant difference between the upper zones ($p > 0.05$), but there were significant differences for the middle and lower zones, the right side being greater than the left ($p < 0.01$). This pattern of differential regional vital capacities, with a significantly lower volume in the left middle and lower zones, is that expected from a consideration of gross anatomy, with the heart and associated mediastinal structures lying in the lower left chest. This was further supported by a study in a patient with dextrocardia (total situs inversus) without evidence of pulmonary disease, in whom 53.5% of the total vital capacity was found on the left side together with a mirror image of the normal regional vital capacity distribution.

The distribution of residual volume between the left and right lungs was comparable with the differential distribution of vital capacity: 46.8% (s.d. 3.02%) of the total was on the left side. This represents a highly significant difference between the two sides ($p < 0.0001$) and these results are also in agreement with other studies (*16*).

Forced expiratory ratio. In the 45 normal subjects, the mean FER for the left lung was 52.25% (s.d. 9.7%) and for the right lung 54.60% (s.d. 10.3%). This highly significant difference ($p < 0.01$) between the two groups suggests that the left bronchial tree has a slightly greater resistance than the right. This may be a function of the greater curvature of the left main bronchus.

Ventilation index (Nsb/Ne). In clinical practice it is of value to derive a ventilation (distribution) index comparable to that first described by Ball et al (*4*); it is calculated by dividing the normalized regional vital capacities (Nsb) by normalized equilibration data (Ne). The ventilation index is independent of lung volume and will be proportional to the regional ventilation "per alveolus" (*9*); it depends on static mechanical factors of pulmonary and chest wall compliance rather than dynamic factors of airway resistance.

The distributions of the ventilation index for the two lungs are shown in Fig. 4. No significant difference was found between the upper zones on each side or between the lower zones on each side. A significant difference was found between the two middle zones, but the biologic significance of this is uncertain. On the average, within each lung the ventilation index increased steadily from upper to middle to lower zones, with a significant difference between adjacent zones in each lung. However, there was considerable individual variation. In those seven subjects in whom duplicate ventilation studies were performed, the results of the ventilation index indicated up to 5% error from the mean of that subject's results, in any given lung region. These results differ somewhat from those of other published studies (*4,19*), probably because of differences in technique.

Washout index (Nvw/Ne). The washout of a non-

radioactive gas (nitrogen or helium) from the lungs provides an established method of studying pulmonary ventilation (*20*). Using a radioactive gas (^{133}Xe) and external scintillation detectors, regional washout curves may be obtained; these will depend upon dynamic factors and thus, in part, reflect regional airways resistance. The major sources of error in the determination of the washout curves will depend on the solubility of ^{133}Xe in blood, accumulation of the emitter in the chest wall, removal of ^{133}Xe by the blood during rebreathing, and the addition to the lungs of ^{133}Xe removed from elsewhere by venous blood (*12*). Nevertheless, none of these invalidates the method as an approximate test for clinical purposes.

Washout curves, washout half-times, washout volumes, and respiratory frequency can be determined from the digital displays and analog output of the RPFA. From these data, given the FRC and dead space derived independently, one should be able to determine the degree of nonuniformity of ventilation within each lung region, but in practice this is a complex analysis and it is difficult to define the washout data adequately by a single number.

Immediately following the display of all six washout half-times by the RPFA, the subject is instructed to inhale maximally to TLC to ensure constant lung geometry, and a 4-sec count is recorded. This count is normalized and presented on the digital display for each region. A washout index (ventilation) may then be derived by dividing these normalized indices by the previously obtained equilibration data (Ne). As in the derivation of the ventilation index, this procedure will negate differences due to volume. Theoretically, the washout index should vary inversely with the washout half-times: a high index will represent underventilation of that particular lung region, and a low index, overventilation. Tests on normal subjects confirmed this, except in the lower zones where the washout indices indicated a disproportionate underventilation. This discrepancy can be accounted for by the high count rates in the chest wall, relative to those remaining in the well-ventilated lower zones of the lungs, after washout for a time determined by the region with the longest half-time. The derived washout index cannot therefore be considered as good an index of dynamic regional ventilation as the regional washout half-times.

Perfusion. A regional perfusion count, following the intravenous injection of a bolus of ^{133}Xe, is normalized and displayed by the RPFA (Nq). From these data the distribution of perfusion between the left and right lungs was studied, each as a percentage of the total. The mean for the left lung is 45.7% (s.d. 4.1%) and the difference between the left and right lungs is highly significant ($p < 0.001$). These results are in agreement with the study of Miorner (*17*).

Perfusion index (Nq/Ne). A perfusion index is derived by dividing the normalized perfusion count (Nq) by the normalized equilibration data (Ne) derived from the ventilation study. The resulting regional perfusion indices will, by analogy with the ventilation indices, be proportional to the regional perfusion "per alveolus." The distribution of perfusion indices for the two lungs is shown in Fig. 5. No significant differences were found between the upper, middle, or lower pairs. Within each lung there is an increase in perfusion index from the upper to middle to lower zones, with a significant difference between adjacent zones in each lung.

The method of determining the distribution of perfusion in this study is comparable to other published series, and the only differences will be due to the number, positioning, and collimation of the scintillation detectors.

Ventilation–perfusion ratios (Nsb/Nq). Ventilation–perfusion ratios for each lung region are derived by dividing the ventilation index by the perfusion index. The results obtained were expected to differ from other published V/Q ratios because the ventilation and perfusion indices derived in the present study are not strictly comparable: the present ventilation index relates to a maximal inspiration from RV, and the perfusion index to FRC (Fig. 6). There are no significant differences between the upper, middle, or lower zones on each side. Within each lung there is a decreasing ratio from upper to middle to lower zones, with a significant difference between adjacent zones in each lung. The mean ventilation–perfusion ratio is 1.96 in the upper zone, 0.995 in the middle zone, and 0.795 in the lower zone. Corresponding ratios derived from the data of Ball (*4*) were 1.78, 1.21, and 0.75, respectively, and from the data of Newhouse (*19*), 1.85, 1.09, and 0.90. In the study of Bryan (*22*), who employed a tidal breath inspiration to derive the ventilation index, the reported ventilation–perfusion ratios were 1.37 in the upper zone, 0.95 in the middle zone, and 0.67 in the lower zone.

Comparison of ventilation and perfusion washouts. Following the intravenous injection of ^{133}Xe and analysis of perfusion distribution, the washout of ^{133}Xe from the six lung regions is recorded during tidal breathing. Immediately following the display of all six washout half-times, a regional count is recorded and the data are normalized and displayed by the RPFA (Nqw). A washout index (perfusion), corresponding to the washout index (ventilation), may then be calculated (Nqw/Ne). The washout

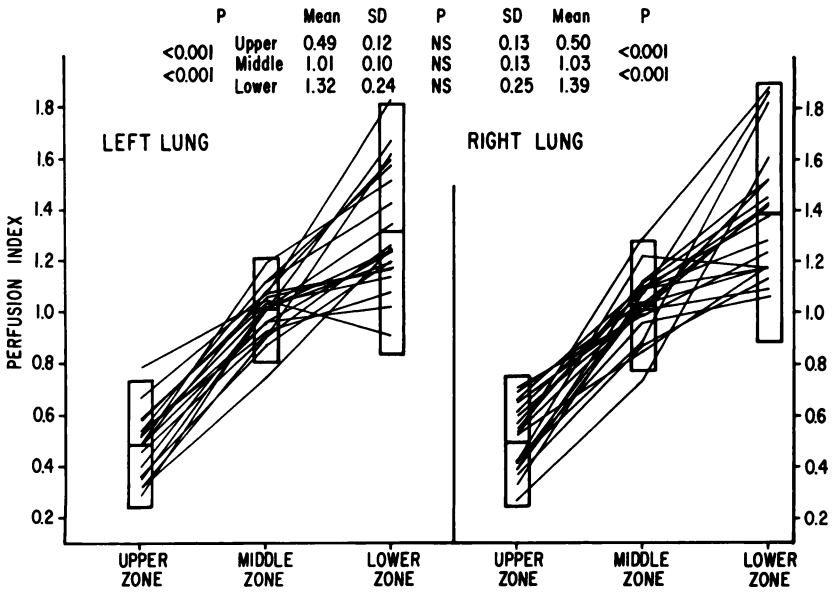

FIG. 5. Distribution of perfusion index for left and right lungs in 19 normal subjects.

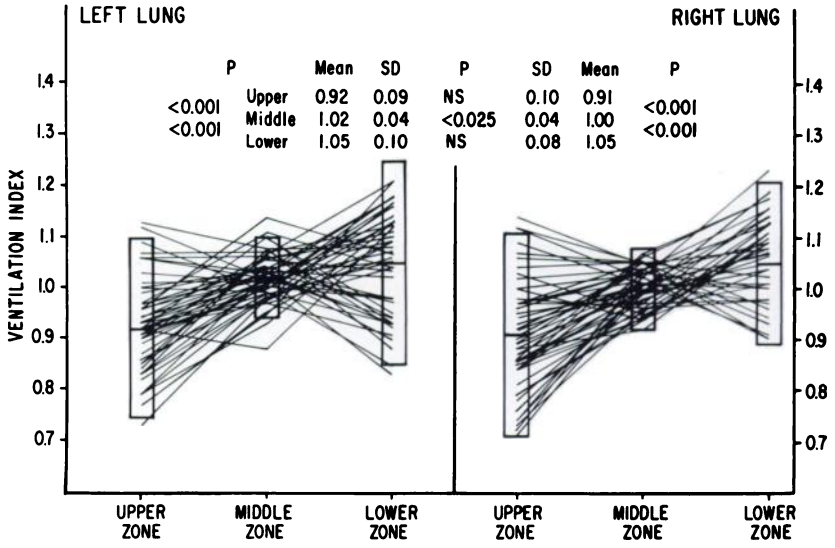

FIG. 6. Distribution of static ventilation–perfusion ratios (Nsb/Nq) for left and right lungs in 19 normal subjects.

curve from this study will be proportional to the ventilation of perfused alveoli. The washout half-times and washout index (perfusion), however, will depend not only on the ventilation of perfused alveoli, but also on the perfusion of ventilated and nonventilated alveoli. A ventilation–perfusion ratio, representing dynamic relationships, may thus be obtained by dividing the washout index (ventilation) by the washout index (perfusion):

$$\frac{\text{Ventilation of both perfused and nonperfused alveoli}}{\text{Ventilation of perfused alveoli} + \text{perfusion of nonventilated gas-containing alveoli}} = \frac{Nvw}{Nqw}.$$

This index will be influenced predominantly by dead space (ventilation of nonperfused alveoli), which will cause the ratio to fall from unity, and by the presence of "trapped gas" (perfusion of nonventilated gas-containing alveoli), which will cause the ratio to rise from unity.

CONCLUSION

The Ohio-Nuclear regional pulmonary-function analyzer is a self-contained unit with built-in computer analysis designed for clinical use. Functionally it was found to be satisfactory and its operation simple and easy to learn. Patient discomfort is minimal and the complete ventilation–perfusion analysis can be performed and reported in less than 30 min.

In the present series, subjects have been studied only in the sitting position with the scintillation detectors placed posteriorly; regional analysis can, however, also be performed with the subject supine

or with the detectors placed anteriorly. The limitation of the equipment is in the inflexibility of its built-in programs. It is possible, however, by using the perfusion program and modifying the mouthpiece with addition of an external spirometer, to study the distribution of inspired boluses of ^{133}Xe with control of preinspiratory lung volume and inspiratory flow rates. This procedure has been considered to indicate further any differences in regional airways resistance or in regional lung compliance. The limitation of these techniques for routine pulmonary-function analysis is that breath-holding and vital capacity maneuvers are unphysiologic and do not describe the regional function that exists during resting tidal breathing. Methods by which this may be evaluated have been reported using ^{133}Xe (*23*), and more recently using ^{81m}Kr (*24*).

The results from the present series of 50 normal subjects have been analyzed in terms of ventilation and perfusion indices and found to be comparable with other published series.

ACKNOWLEDGMENTS

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