EVALUATION OF ^{133}Xe TECHNIQUES FOR MEASUREMENT OF REGIONAL VENTILATION

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Despite widespread clinical use of radioactive gases for evaluation of regional ventilation, little evidence is available for evaluating the accuracy of these techniques. Excised dog lung preparations with controlled perfusion and ventilation were used in the present study to compare known ventilation to the rate of alveolar clearance of ^{133}Xe. Xenon-133 was administered by three different methods in separate groups of determinations. Perfusion of the excised lung preparations with blood collected by exsanguination permitted assessment of ventilation by a technique similar to the injection of ^{133}Xe dissolved in saline in patients. The standard error of the distribution of ventilation measured by this approach in 17 determinations was 4.1%. In the second group of experiments, ^{133}Xe in air was administered by a single inhalation and the washout of ^{133}Xe compared with the known distribution of ventilation with a standard error of 5.1%. In a third group of determinations, the lung preparations were ventilated with ^{133}Xe mixed in air until counts reached equilibrium and the rate of ^{133}Xe clearance during subsequent air breathing was determined. The distribution of ventilation measured by this approach demonstrated the greatest accuracy of all techniques examined with a standard error of 2.6%. In addition, the actual minute volume was compared with absolute slope values of ^{133}Xe clearance in this single lung preparation and the correlation coefficient of 0.96 further substantiates the inherent accuracy of ^{133}Xe washout for assessment of regional ventilation.

Following initial application of radioactive gases for assessment of ventilation in 1955, the potential clinical usefulness of this approach was rapidly appreciated. A number of early radionuclide studies of regional pulmonary perfusion and ventilation provided useful physiologic information. However, radioactivity detectors used for these studies were several individual scintillation probes positioned over the chest which provided only limited anatomic detail within the lungs. The development of the gamma camera has more recently renewed interest in the use of radioactive gases for determination of regional ventilation in patients (*1,2*). These instruments provide rapid, simultaneous assessment of radioactivity within small regions over the entire chest, which permits both a pictorial and a quantitative display of changes in distribution of a tracer gas in the lungs. Despite increasing clinical use of these studies, little attention has been devoted to evaluation of the accuracy of radionuclide techniques for measuring regional ventilation using a radioactive gas. The present study examines the accuracy of these techniques by using an excised dog lung preparation to compare indirect radionuclide measurement of ventilation to known, controlled ventilation.

METHODS

Lungs were excised from anesthetized, heparinized dogs after exsanguination through a femoral artery catheter. Cannulas were inserted into the left atrial cuff and into each main stem bronchus and main pulmonary artery. Suspension of the lungs over the detector surface from the hilar structures caused no significant anatomic deformity. An encasing Lucite box supported the lungs and prevented their extension from the detector field during inspiration. Separate, fixed-volume Harvard respirators ventilated each lung at selected rates and volumes. A tubing deadspace volume of 55 cc was interposed between

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each main bronchus and the expiratory valve of the respirator. Allowance was made in the respirator setting for deadspace and the tidal volumes reported represent only lung ventilation. A water seal providing 10 cm H_2O end expiratory pressure counterbalanced the intrinsic lung elasticity and maintained a stable expiratory lung volume throughout the period of study. Studies in the lung preparations were complete within 2 hr after excision and the preparations were repeatedly moistened with warm saline during the study. The preparation provided an organic phantom ideally suited to evaluate radionuclide measurement of regional ventilation.

General availability and suitable physical characteristics have made ^{133}Xe the most commonly used radionuclide for ventilation studies and this was the only tracer used to assess ventilation. Xenon-133 as a gas was obtained in glass ampules from Oak Ridge National Laboratories and a portion of the radionuclide was dissolved in saline and the remainder was mixed in air. Three methods of tracer administration were evaluated. In one group of preparations, ^{133}Xe dissolved in saline was injected into blood perfusing the preparation. In a second group of experiments, a single inhalation of ^{133}Xe in gas was followed by air breathing. In a third group of observations, rebreathing of a ^{133}Xe–air mixture for a period sufficient to equilibrate counts within the lungs was followed by a period of air breathing. In each of the three groups, 17 determinations of ventilation were made. Total ventilation to both lungs of a preparation ranged from 2 to 10 liters/min. Tidal volumes to individual lungs varied from 50 to 400 cc, and respiratory rates were maintained between 10 and 40 breaths/min. The ratio of minute volumes between the two lungs of a preparation ranged from even ventilation to a fourfold greater ventilation in one lung.

Intravenously injected ^{133}Xe dissolved in saline distributes in the lungs of patients proportional to regional perfusion. The poor solubility of the gas causes more than 90% of the tracer to evolve into alveoli at the blood–air interface of the pulmonary capillary. The rate of ^{133}Xe removal from alveoli depends primarily upon alveolar ventilation and provides a method for assessment of regional ventilation. Excised lung preparations were perfused with blood collected by exsanguination for evaluation of ^{133}Xe saline measurement of regional ventilation. Blood passed through a common mixing chamber for injection of 15 mCi of ^{133}Xe in saline and was forced into each lung by separate fixed-volume roller pumps. Direct calibration of perfusion rates of each pump before and after perfusion insured even arterial inflow to each lung. Total pulmonary flow rates of 1,000–2,300 cc/min were used and perfusion pressures remained less than 20 mmHg.

A second group of 17 determinations was performed using a single inhalation of ^{133}Xe in air. A volume of air equal to the total tidal volume and the tubing deadspace was mixed with 15 mCi of ^{133}Xe gas. Using large calibrated syringes, an inspiratory breath equal to the selected tidal volume was delivered to each lung and the tubing was clamped. The endobronchial tubes to each lung were simultaneously opened to separate respirators and the decline of counts indicating tracer clearance was recorded during air breathing.

A third group of determinations was performed on a single excised lung preparation using rebreathing of 15 mCi ^{133}Xe in air. Each lung of the preparation was ventilated with a separate respirator which was arranged as a closed system including a reservoir bag. Rebreathing was continued for a period sufficient to permit even distribution of ^{133}Xe throughout the lungs and both respirators were abruptly opened to air intake. The slope of the semilogrithmic disappearance of ^{133}Xe during air breathing was expressed as a percent of the total and compared with the percent of the total minute volume in each lung. The absolute minute volume was also compared with the calculated slope of xenon disappearance for each of the 34 values of these 17 determinations.

The detecting system used was a matrix of 294 NaI crystals each with a 1-cm^2 front surface, arranged in a 14 $\times$ 21 array. A 1.0-cm-thick lead collimator was used with square holes centered over each crystal with 0.65-cm sides on the crystal aspect and 0.55-cm orifices toward the lungs. The Baird-Atomic Digital Autofluoroscope placed counts from each crystal of the detector onto computer tape at 1-sec intervals. An IBM 360/75 computer provided data manipulation and display and all data were corrected for instrument deadtime loss and variation in detector efficiency prior to analysis. Regions of the detector matrix corresponding to the outline of each lung were visually determined at time of experimentation and correlated well with gradations in count intensities observed in the data.

Counts from all detector units corresponding to each lung were totaled for each 1-sec recording interval during study. The slope of a line fitted by least-squares analysis to a semilogarithmic graph of these data indexed the rate of ^{133}Xe clearance. This rate of ^{133}Xe removal was compared with the known minute volume of each lung which was determined by the respiratory rate times the difference in the total inspiratory volume and the tubing deadspace

volume. Calculated slope values for ^{133}Xe clearance from each lung of a preparation were expressed as a percent and the observed ventilation in the lung with least ventilation was compared with the known percent of the total alveolar ventilation in that lung. The standard error of differences of each of these paired observations described the variation characterizing each group of determinations.

RESULTS

Typical data obtained after ^{133}Xe in saline injection demonstrated an abrupt rise in lung counts and a 2–4 sec plateau followed by a semilogarithmic decline (Fig. 1). The plateau represents a combination of tracer delivery by blood flow and the time of initial movement of radioactive gas from alveoli into the larger airways. The removal of ^{133}Xe from the lungs by ventilation is incremental and the small rise in counts with inspiration represents reintroduction into detector view of ^{133}Xe from tubing outside the counting field during expiration. Similar fluctuations are observed in patient studies due to the volume of air in the upper airway. In 17 ventilation determinations using ^{133}Xe in saline, the percent of total ventilation measured in the lung with least ventilation correlated only moderately (s.e. = 4.1) with the known distribution of ventilation (Fig. 2).

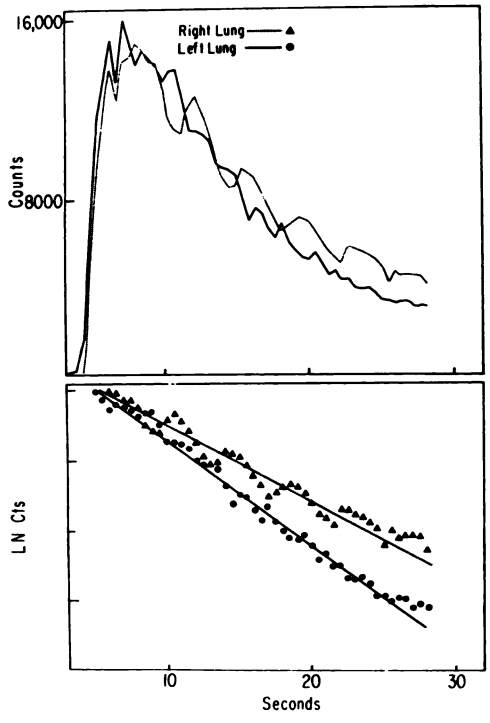

FIG. 1. These data illustrate counts and natural logarithm of counts at 1-sec intervals following injection of 15 mCi of ^{133}Xe-saline into blood perfusing excised dog lung preparation. Following abrupt rise, counts plateau for several seconds and decline semilogarithmically. Incremental fluctuations in counts correspond to respiratory rate. Blood flow in right lung was 715 cc/min, blood flow in left lung was 740 cc/min. Right lung was ventilated with 10 300-cc breaths/min and left lung with 20 200-cc breaths/min.

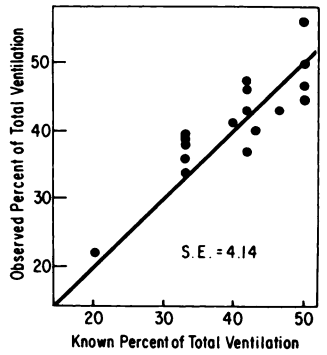

FIG. 2. These data compare known percent of total ventilation in lung with least ventilation with percent of total ventilation calculated from ^{133}Xe clearance following administration of ^{133}Xe in saline.

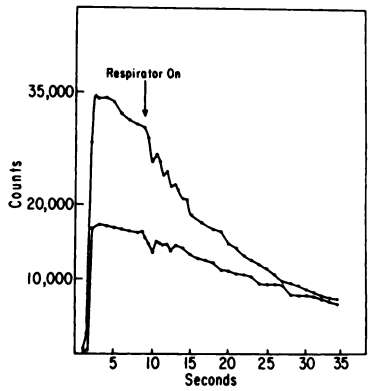

FIG. 3. These data illustrate typical curves following administration of ^{133}Xe in air by single inhalation. Upper curve represents counts over right lung ventilated with 20 350-cc breaths/min. Lower curve represents counts over left lung ventilated with 20 breaths of 150 cc air/min.

In the group of ventilation studies performed using a single inhalation of ^{133}Xe in air, the maximum counting rate over each lung of the preparation demonstrated a general relationship to the fraction of the tidal volume in that lung (Fig. 3). However, the separation of the upper airway in the preparation used prohibits meaningful comparison of counting rates after a single-breath inhalation with known inspiratory volumes. After ^{133}Xe in air inhalation, counts during subsequent air breathing declined semilogarithmically. Regional ventilation was assessed by the rate of ^{133}Xe washout after a single inhalation of tracer in 17 determinations (Fig. 4). The distribution of ventilation measured by this approach demonstrated the least correlation with known ventilation of the three techniques studied (s.e. = 5.1).

Counts over each lung during a period of ^{133}Xe in air rebreathing reach equilibrium within 60 sec in all determinations (Fig. 5). After ^{133}Xe equilibra-

tion in the lungs, air breathing produces a semilogarithmic decline in counts (Fig. 6). Regular count fluctuations observed about the semilogarithmic decline correlated with the respiratory rate in all preparations. In the preparation illustrated (Fig. 6), the left lung ventilated with 20 200-cc breaths/min demonstrates a slope of —0.0734 and the right lung ventilated with 10 300-cc breaths/min demonstrates a slope of —0.0496. Using the slope of ^{133}Xe clearance from each lung, the percent of the total ventilation in each lung was compared with the known distribution of ventilation in 17 determinations (Fig. 7). The rate of ^{133}Xe disappearance correlated closely with the known distribution of ventilation (s.e. = 2.6). These data suggested that after ^{133}Xe air rebreathing, the regional rates of ^{133}Xe disappearance from the lungs during subsequent air breathing provided an accurate index of the distribution of alveolar ventilation. The absolute slope and half-time of ^{133}Xe clearance calculated from each lung were compared with known minute volumes for each of

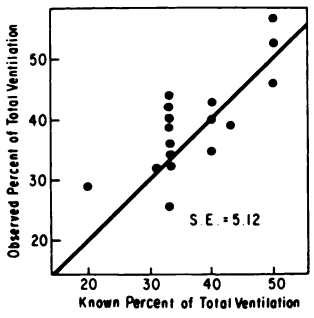

FIG. 4. These data compare known percent of total ventilation in lung with least ventilation with distribution of ventilation calculated from ^{133}Xe clearance following administration by single breath of tracer.

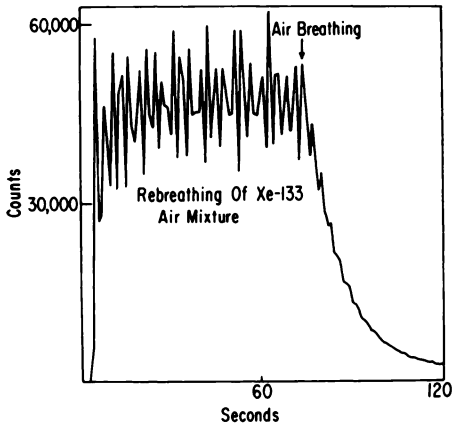

FIG. 5. These counts were obtained from single lung during period of rebreathing of ^{133}Xe in air followed by air breathing. Equilibrium of counts was achieved within 60 sec in all preparations studied.

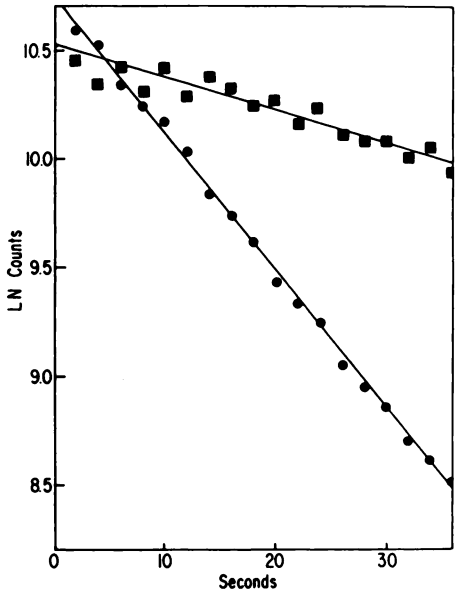

FIG. 6. These data represent natural logarithm of counts over two lungs of preparation during ^{133}Xe clearance after administration by rebreathing. Right lung (squares) was ventilated with 10 300-cc breaths/min and demonstrates slope of —0.496. Left lung (circles) was ventilated with twenty 200-cc breaths/min and demonstrates slope of —0.0734.

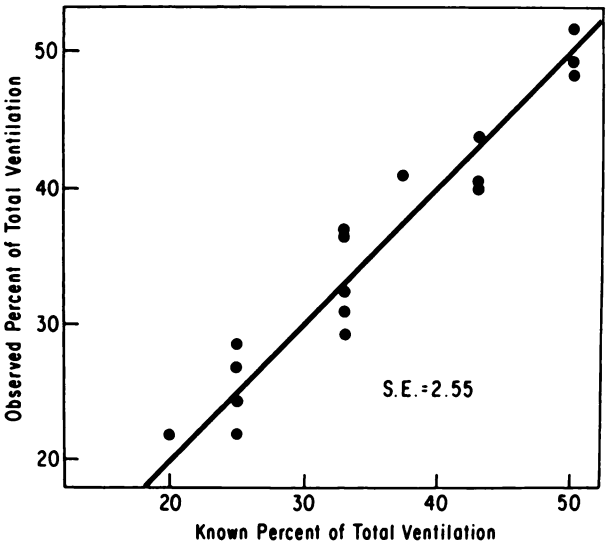

FIG. 7. Known distribution of ventilation to lung with least ventilation is compared with distribution of ventilation calculated from ^{133}Xe clearance after administration by rebreathing.

the 17 determinations (Fig. 8). Individual variations in aerated lung volumes would cause an inconsistent relationship between the absolute slope of ^{133}Xe removal and the actual minute volume in different subjects. However, because of the constant aerated lung volume in this single preparation, the rate of ^{133}Xe clearance correlated well with the minute volume (r = 0.96). This close correlation between slope values of ^{133}Xe removal and actual minute volumes in this single preparation provides further

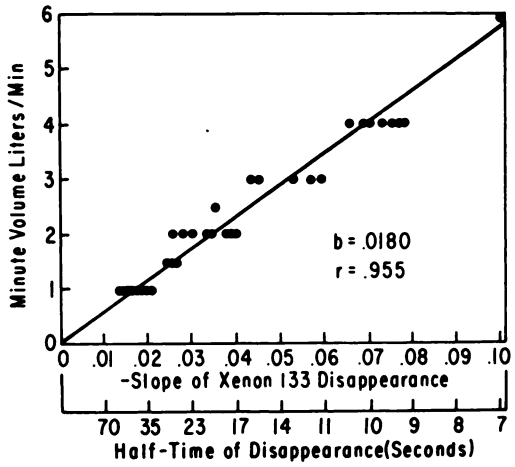

FIG. 8. These data compare minute volume in each lung of single preparation with absolute value of ^{133}Xe clearance following administration by rebreathing.

evidence of the inherent accuracy of the ^{133}Xe washout for regional ventilation measurement.

DISCUSSION

Experimental and clinical studies of regional ventilation using radioactive gases have described several methods of tracer administration and various approaches for relating observed counts to ventilation (*3,4*). Ball, et al (*5*) first suggested that after rebreathing of radioactive gas to a point of equilibrium, counts over the chest indexed the relative volume of aerated lung tissue within different detector fields. Using equilibrium counts as a relative index of aerated lung volumes, separate determinations of dynamic function could be normalized to provide regional measurements of perfusion and ventilation which were independent of differences in lung geometry. Definition of function per unit of aerated lung tissue has proven particularly valuable in physiologic studies of differences in regional lung function (*6*). The present study was not designed to evaluate the reasonable assumption that equilibrium counts after rebreathing of a radioactive gas defines the regional aerated lung volume.

Certain clinical studies have used counts over the lungs following a single inhalation of radioactive gas to describe regional ventilation (*7*). The artificial configuration of the upper airway used in the excised lung preparation of this study prevented evaluation of this approach for comparison of the distribution of a single breath containing tracer to dynamic alveolar ventilation. However, the observation of Dollfus, et al (*8*) that the distribution of a single bolus of inhaled ^{133}Xe is greatly influenced by the lung volume at which inspiration of tracer gas begins identifies one potential error of this approach. In addition, counts over the lungs following a single inhalation of ^{133}Xe include tracer within large conducting airways as well as within alveoli. Both of these potential sources of error could be accentuated by certain pulmonary diseases and ventilation might be more accurately described by assessing dynamic exchange of the tracer gas.

The regional appearance and clearance rates of ^{133}Xe provides an alternate approach for assessment of regional ventilation. Techniques describing ventilation by the accumulation rate of a radioactive gas require administration of a constant concentration of tracer. Because of this limitation, the clearance rate of the tracer gas during air breathing can be obtained in patients more easily than the accumulation rate. The washout of ^{133}Xe from the lungs is semilogarithmic and the function can be described by a single slope or half-time. The radioactive gas may be introduced into alveoli by a period of rebreathing, by a single inhalation, or by diffusion of the poorly soluble inert gas across the pulmonary capillary after intravenous administration. The present study was designed to determine the inherent accuracy of ^{133}Xe washout for evaluation of regional ventilation and to examine the three methods of tracer administration which have been used clinically.

The excised dog lung preparation used permitted control of both perfusion and ventilation for comparison with radionuclide measurements. Previous experiments using this preparation for assessing radionuclide perfusion techniques have been reported (*9*). The configuration of the excised lung preparation was arranged to insure optimal positioning for radiation detection. Measurement of the volume of the major component of deadspace ventilation permitted a close approximation of alveolar ventilation. Although excision may inflict some degree of abnormal function upon these preparations, the distribution gradients of ^{133}Xe at equilibrium in excised dog lungs was similar to that observed in other intact animals, which indicated that ventilation patterns were not greatly altered. In addition, other workers have observed stable function in excised dog lung preparations for periods greater than 12 hr (*10*).

The detecting system used provides no unique advantage or increased accuracy over other gamma cameras interfaced with digital data retrieval systems. However, the Digital Autoflouroscope is well suited for rapid simultaneous measurements of radioactivity in small regions over the detector field and is adaptable for dynamic ventilation measurements in patients (*11*). The instrument permits digital counts at rapid time intervals from 294 individual crystals to be interfaced with a computer to facilitate data use. Previous work has demonstrated that data

distortion caused by the 24-μsec deadtime of the instrument can be eliminated by computer correction of observed counts (*12*).

A potential clinical advantage for use of ^{133}Xe in saline is that both perfusion and ventilation might be determined from a single administration of tracer. Blood solubility characteristics cause more than 90% of ^{133}Xe present in pulmonary capillaries to evolve into alveoli. The ^{133}Xe which remains dissolved in blood and which passes through pulmonary vessels that do not permit diffusion is removed from the lungs by perfusion. However, the removal of blood containing ^{133}Xe from the detector field is rapid because of the pulmonary capillary-to-left atrium mean transit time of about 3 sec. The rapid removal from the lungs of ^{133}Xe remaining in blood and the small quantity removed by perfusion compared with that removed by ventilation minimizes the influence of pulmonary perfusion on measurements of ventilation. In the present study, the rate of decline of counts over the lungs after perfusion with ^{133}Xe saline was described by a single exponential function. The correlation observed between the known ventilation and the disappearance rate of ^{133}Xe indicates that alveolar ventilation is the primary determinate of this slope. The 17 determinations using ^{133}Xe saline reported in this study had even perfusion to both lungs. In addition to these, a second group of determinations using ^{133}Xe in saline were performed with uneven perfusion and no significant difference was observed between these two groups. These observations indicate that in lungs with normal gas diffusion, differences in regional perfusion cause little influence on ventilation measurements obtained with ^{133}Xe in saline. However, in lungs with a large amount of arterial-venous shunting and in lungs with regions of absent or greatly diminished perfusion, the accuracy of ^{133}Xe saline determination of regional ventilation might be greatly decreased.

The disappearance rate of a single inhalation of ^{133}Xe provided the least accurate description of regional ventilation. Lack of uniform mixing of a single breath within the aerated lung volume probably represents the greatest source of error by this approach. The residual lung volume dilutes the concentration of ^{133}Xe in inspired air leaving a lower concentration of gas in alveoli than in the conducting airways. Therefore, the initial washout rate appears more rapid than the rate of alveolar clearance of tracer gas. Error resulting from removal of tracer from conducting airways is minimized following rebreathing of tracer gas which produces a more even distribution of ^{133}Xe within the conducting airways and alveoli.

In the present study, the disappearance rate of ^{133}Xe demonstrated the closest correlation to known ventilation following administration of the tracer by rebreathing. This observation suggests that the rate of ^{133}Xe disappearance from any lung region may be linearly compared with another to establish a ratio which describes regional air exchange. The validity of ^{133}Xe washout rates as an index of regional ventilation is further substantiated by the finding in the single-lung preparation of close correlation ($r = 0.96$) of the slope of ^{133}Xe disappearance with the actual minute volume in each lung.

Although results of the present study confirm the inherent accuracy of regional ventilation measurement by ^{133}Xe washout, certain aspects of study design differ from conditions of patient studies. The excised lung preparations were obtained from normal dogs, and anatomic deformity associated with pulmonary disorders in patients might alter the accuracy of ^{133}Xe washout for assessment of regional ventilation. The difficulty of two-dimensional description of function within a three-dimensional object is well recognized as an inherent limitation of tracer techniques. Regions evaluated in the excised lung preparations were the right and left lungs which were totally isolated. Count fluctuations observed by any radiation detector describe changes throughout the entire volume of lung tissue within the detector view. Superimposition of lung regions with different ventilation rates or inclusion of counts arising from the chest wall might cause a biphasic washout curve which the present study was not designed to evaluate. A third difference between the excised lung data and patient studies is that recirculation of tracer was prevented in the lung preparation. In patients, a small amount of ^{133}Xe may remain in pulmonary venous blood after administration by inhalation or by perfusion. This tracer may recirculate in the field of view by chest wall perfusion or by systemic venous return. However, the influence of tracer recirculation on the accuracy of ^{133}Xe ventilation studies appears quite small.

Despite common clinical use of ^{133}Xe ventilation studies, scant data are available to document the accuracy of these measurements. In one study, a group of dogs was ventilated with Carlens tubes to isolate ventilation to each lung (*13*). The total minute volume correlated with the rate of ^{133}Xe removal from the lungs. However, the Carlens tube did not permit total separation of ventilation to each lung necessary for assessment of regional ventilation. In nine patients studied by Wagner, et al (*14*), a correlation coefficient of 0.87 was observed between the half-time of xenon equilibrium and the known percent of ventilation in each lung. Results of the present study indicate that the rate of ^{133}Xe removal

from the lungs is determined primarily by the alveolar ventilation and is independent of respiratory rate and tidal volume. The data further substantiate the accuracy of relating slope in different lung regions to the regional air exchange. Limitations of the experimental design prevent extension of the accuracy determined in excised lung preparation to patient studies which include other variables. Confirmation, however, of the inherent accuracy of ^{133}Xe washout for determination of regional ventilation provides useful information for evaluation of ^{133}Xe ventilation studies in patients.

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