Limitations of Kr-81m for Quantitation of Ventilation Scans

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Predictions of Kr-81m behavior in the lungs have been based on a single-compartment model of well-mixed gas. To determine the validity of this model, anesthetized, paralyzed dogs were ventilated mechanically over a wide range of ventilations with Kr-81m in the inspirate. Averaged data obtained from 1.5- to 2-min images were compared with the model's predictions. Krypton-81m concentration appeared more linearly related to ventilation than the model predicts. This suggests that the Kr-81m may not be distributed to the entire resident gas volume or that its distribution changes with lung volume. Estimation of end-expiratory volume (FRC)—based on the tidal volume and the maximum-to-minimum count ratio over the lung during gated acquisitions—underestimated the true FRC by about 40%. The magnitude of error depended upon the combination of tidal volume and frequency and the inspiratory time. Thus, Kr-81m does not mix well with resident lung gas, and the well-mixed, single-compartment model is not a good predictor of Kr-81m behavior in the lung.

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Krypton-81m is beginning to be used widely as a ventilation imaging agent. Its short half-life (13 sec) is generally cited as the key advantage over other agents such as xenon-133 (*1–4*). Mathematical models of single-compartment lungs with well-mixed gases predict that if a tracer has a half-life that is short relative to its removal rate by ventilation, its local concentration in the lung during repeated inspiration of the gas should reflect the distribution of ventilation (*5,6*).

It has been assumed that, with respect to Kr-81m inhalation, the one-compartment model can be extended to the lung and that activity monitored over the lung is proportional to local ventilation. This assumption, however, has not been tested experimentally.

The purpose of this study was to examine the relationship between ventilation and Kr-81m activity measured over the lung during continuous Kr-81m inhalation. Variables considered include acquisition mode, acquisition view, tidal volume and frequency changes, end-expiratory lung volume, and the inspiratory to expiratory time ratio.

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METHODS

Sixteen adult mongrel dogs weighing 19.1 ± 1.9 (s.d.) kg were used in this study. The animals were anesthetized with 30 mg/kg pentobarbital sodium and intubated with a cuffed endotracheal tube. Catheters were placed in the jugular vein and carotid artery for administration of supplemental anesthesia and monitoring of systemic arterial blood pressure. All animals were paralyzed with 5 mg/kg succinylcholine chloride administered intramuscularly; they were ventilated in a supine position with a volume-limited ventilator.* Gas to the ventilator was supplied from a reservoir bag in which air was mixed continuously with Kr-81m. The krypton was obtained by passing air through a generator consisting of rubidium-81m fixed to an ion-exchange column. As the Rb-81 decays to Kr-81m, the krypton is eluted by the gas flow.

Four types of experiments were conducted. Effects of ventilation on count rate using two acquisition modes

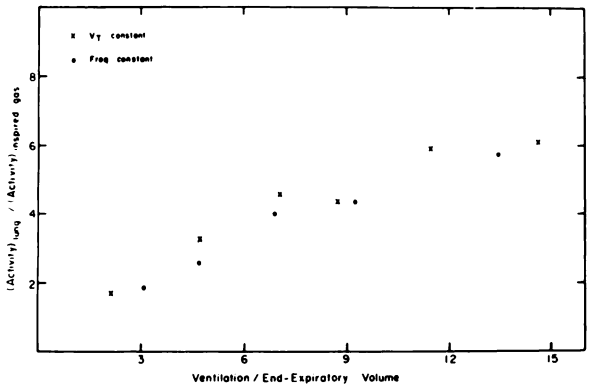

FIG. 1. Krypton-81m activity measured over lung as a function of ventilation/volume. Ventilation was changed by changing frequency at fixed tidal volume (x) or by changing tidal volume at fixed frequency (●). Each point represents the mean of data from three or more trials in two to five animals.

were determined by changing ventilation frequency (range: 5–35 breaths/min) at a constant tidal volume (15 ml/kg) in eight animals and by changing tidal volume (range: 8–30 ml/kg) at a constant frequency (approximately 12 and 24 breaths/min) in four animals. In another three animals, ventilation was fixed at a tidal volume of 15 ml/kg with a frequency of 15 breaths/min, and the time of inspiration was varied from 30 to 70% of the respiratory cycle. Data were acquired either as "static" or "gated" images from an anterior view of the supine animal. In the static mode, activity over the lung was recorded for 100–120 sec as one image. In the gated mode, the camera and computer were triggered to begin acquiring counts at a given point during the respiratory cycle (95% of expiration) using an impedance plethysmograph signal. Twenty-eight images were acquired per breath. The scheme was repeated on successive breaths, with the images from one breath added to the accumulated images from the previous breaths. The process was continued until 40,000 counts per frame were acquired. In each experiment, a ventilation level was set, and several minutes were allowed for a steady state to become established. The static image was acquired, and, after several minutes, the gated study was acquired. A new experimental condition was then established, and the process was repeated.

Influence of end-expiratory volume on count rate was determined in four animals. These were ventilated at different rates (range: 2.5–11 l/min) with positive end-expiratory pressures (PEEP) of 0, 5, and 10 cm H_2O imposed. Data were acquired from an anterior view using the gated technique. Functional residual capacity (FRC) was measured using an indicator-dilution technique. The animal was removed from the ventilator and ventilated with a one-liter syringe containing a known quantity of xenon-133. Xenon activity in the syringe was again determined after 20 rebreathing breaths (approximately 400 cc per breath), and FRC was calculated using standard indicator-dilution equations (*7*). To determine the change in volume from FRC at each PEEP level, the animal was disconnected from the ventilator, and its lungs were inflated to the previous peak inspiratory pressure with a one-liter syringe. Volume was then withdrawn until the appropriate PEEP level was attained. The difference between the starting volume (airway pressure = 0) and the PEEP level was assumed to equal the change in lung volume from FRC at end expiration.

The purpose of the fourth set of exeriments was to determine whether acquisition view affects the quantitative nature of the image obtained. In five animals, a series of gated images were obtained at several ventilation rates and PEEP levels using an anterior view of the supine animal. FRC was determined with Xe-133, and the sequence was repeated while gated images were obtained using a posterior view.

RESULTS

Data from the static studies that relate Kr-81m activity over the lung to ventilation are shown in Fig. 1. Activity has been corrected for background and normalized to the activity of the inspired gas. The end-expiratory volume to which ventilation was normalized was estimated on the basis of body weight (*8*) or obtained directly using the Xe-133 technique described earlier. Figure 1 demonstrates that activity is related to ventilation in a nearly linear fashion and that this relationship is independent of the combination of tidal volume and frequency used to achieve a given ventilation.

Experimental data are compared with the theoretical prediction of concentration as a function of ventilation in Fig. 2. Because lung volume varies between FRC and end-inspiratory volume during a static acquisition, it is difficult to determine what volume is most appropriate

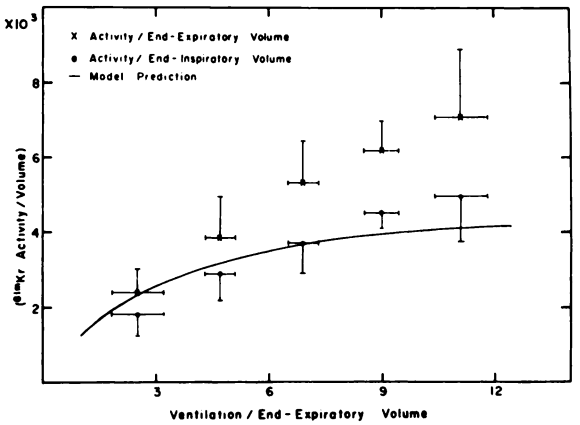

FIG. 2. Krypton-81m concentration measured over lung, as a function of ventilation/volume, in seven animals compared with prediction from a well-mixed, single-compartment model. Concentration was calculated assuming volume remained constant at either end-expiratory (x) or end-inspiratory (●) volume. Actual concentration at any ventilation level should lie between these extremes. Standard errors of the mean are indicated.

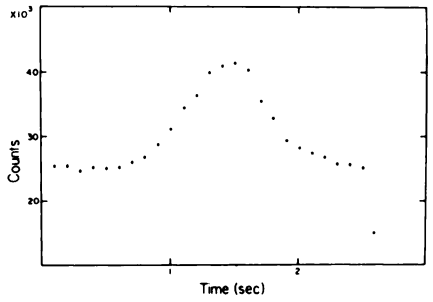

FIG. 3. Krypton-81m activity measured over lung during respiratory cycle; data obtained from gated study (see text). Last point "drops out" indicating completion of respiratory cycle within 25 frames.

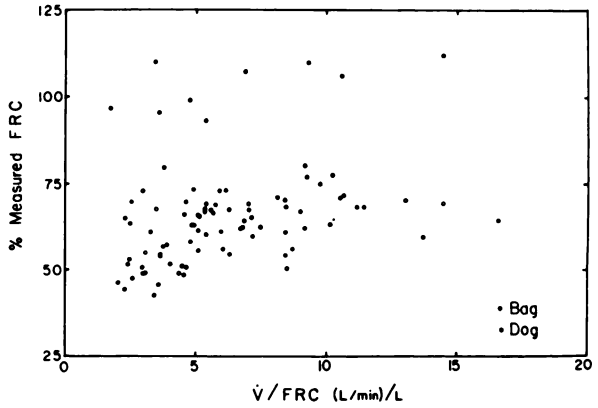

FIG. 4. End-expiratory volume calculated from gated studies as a function of ventilation/volume. Calculated values are expressed as per cent of measured end-expiratory volume. Data from ventilated bag study (●) and studies in nine dogs (O) are shown.

when calculating Kr-81m concentration within the lung. Hence, concentration was calculated at FRC (yielding an overestimate) and at end-inspiratory volume (yielding an underestimate). The actual concentration at any level of ventilation should lie between these extremes. The theoretical curve shown in Fig. 2 was determined using the single-compartment equation presented by Fazio and Jones (*5*) and forcing the curve through the experimental point yielding the best fit by eye to the range of possible concentrations in the "linear" range defined by Fazio and Jones (*5*) and Goris et al. (*6*). Statistical fitting of this curve to the experimental data was not feasible since the correct volume with which to calculate Kr-81m concentration at each ventilation was not known. The single-compartment model appears to fit the data at very low levels of ventilation, but Fig. 2 suggests that the Kr-81m concentration is more linearly related to the normalized ventilation than theory predicts. Data analyzed in a similar manner from the gated studies yielded similar results. This relationship was not altered by varying the time allowed for inspiration from 30 to 70% of the respiratory cycle.

We postulated that the apparent discrepancy between theory and the experimental data could be explained if the effective volume being ventilated with tracer changed with ventilation. To test this hypothesis, we analyzed data from images acquired using the gated acquisition mode.

A typical plot of activity over the lung as a function of time during the respiratory cycle obtained from a gated study in one animal experiment is shown in Fig. 3. We reasoned that, in a well-mixed system, the peak activity seen during the cycle should be proportional to the total lung volume in which the Kr-81m is distributed at end inspiration (V_I). Similarly, the minimum activity, corrected for Kr-81m decay, should be proportional to the Kr-81m distribution volume at end expiration (V_0). If these relationships are true and if tidal volume is known, the end-expiratory volume can be calculated from the gated-study activity curve as follows:

$$A_{peak}/A_{min} = V_I/V_0 = (V_0 + V_t)/V_0,$$

where A_{peak} is the peak activity, A_{min} the minimum activity corrected for Kr-81m decay, and V_t the tidal volume.

Rearranging terms, we obtain

$$V_0 = (V_t A_{min})/(A_{peak} - A_{min}). \quad (1)$$

To test this method of analysis, we repeated a typical experiment using a 3-l weather balloon instead of the dog. The bag was arranged so that it had a constant "end-expiratory" volume of 900 ml. Ventilation was changed by changing frequency at a constant tidal volume and by changing tidal volume at a constant frequency. Krypton-81m activity over the bag was accessed using the gated mode for data acquisition.

End-expiratory volume was calculated in this manner for the bag studies and for the dog studies in which end-expiratory volume was measured independently. The calculated values were then compared with the measured values. Results are shown in Fig. 4. In the bag study, the

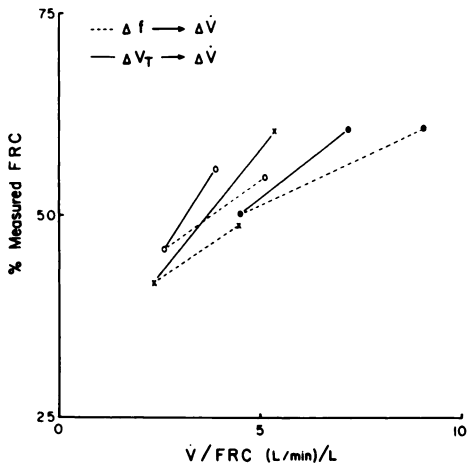

FIG. 5. End-expiratory volume calculated from gated studies as a function of ventilation/volume in three dogs. Calculated values are expressed as per cent of measured end-expiratory volume. Ventilation was increased by increasing frequency at constant tidal volume (dashed lines) or by increasing tidal volume at constant frequency (solid lines).

calculated end-expiratory volume provided a good estimate of the measured value. In the dog studies, however, the calculated value consistently underestimated the measured end-expiratory volume. The degree to which the calculated value underestimated the measured was independent of acquisition view but depended upon ventilation. Furthermore, the extent to which ventilation affected the FRC estimate depended upon how the ventilation change was achieved. This is illustrated in Fig. 5, where data from three animals are presented. The FRC estimates obtained from ventilation increases resulting from tidal-volume increases were significantly higher ($P < 0.025$, unpaired t-test) than those obtained at comparable ventilations achieved by increasing respiratory frequency. These data suggest that the distribution volume of Kr-81m in the lung is substantially less than the end-expiratory volume and is dependent upon a number of variables.

DISCUSSION

The discrepancy between volume calculated from Kr-81m data and that measured with Xe-133 could reflect either the degree to which the Kr-81m mixes with resident gas or experimental error in the Xe-133 dilution technique used to measure end-expiratory volume. The latter is unlikely since "end-expiratory" volume measured repeatedly with Xe-133 in the bag study was consistently within 5% of that measured with a 1-l syringe. If, in the dog, the Xe-133 had not reached equilibrium with the resident lung gas after rebreathing, the volume determined from the indicator-dilution calculation would have underestimated the animal's actual FRC. Hence, the discrepancy between the FRC estimated with Kr-81m and the animal's actual FRC would be larger than our data indicate.

The more likely explanation is that the underlying assumption upon which our analysis is based—that is, that Kr-81m is well mixed with the resident lung gas during inspiration—is not valid. Failure of Kr-81m to mix well during inspiration would result in gas relatively rich in tracer leaving the system during expiration. The gas remaining would contain correspondingly less tracer, and an underestimate of the true volume would be obtained from the analysis.

On the basis of this hypothesis, a larger resident volume would be calculated if conditions were altered to favor gas mixing. In the three animals in which inspiration time was varied with fixed tidal volume and frequency, the end-expiratory volume calculated from the gated acquisitions increased from a mean of 549 ml when inspiration time was 30% of the cycle to a mean of 605 ml when an inspiration time of 70% of the cycle provided more time for gas mixing to occur.

A similar result was obtained when ventilation was increased. Robertson and his colleagues (*9*) and Bake and co-workers (*10*) have demonstrated that a more even distribution of ventilation results when inspiratory flow rate is increased. Thus, with increased frequency, better gas mixing and hence a larger calculated FRC would be predicted. In the lower ventilation/volume range (below 10 $ml/min \cdot ml^{-1}$), this was the case (Fig. 5).

Increased ventilation resulting from larger tidal volumes enhances gas mixing more than a similar ventilation increase resulting from frequency changes (*11*). The better mixing could be due in part to the influence of decreased mean airway resistance accompanying a larger mean lung volume on convective and diffusive mixing and to the larger volume of fresh gas that enters the resident gas volume. The result of better gas mixing would be a correspondingly larger calculated end-expiratory volume, as shown in Fig. 5.

Data obtained when PEEP was imposed on the animal provide a way of assessing the influence of mean lung volume on Kr-81m mixing with resident lung gas. By imposing 10 cm H_2O PEEP, we increased the end-expiratory volume by 51% from 943 ml to 1425 ml. Although ventilation was held constant, the end-expiratory volume calculated on the basis of the gated analysis increased by the same proportion from 518 ml to 772 ml. The increase could reflect better gas mixing at the higher end-expiratory volume. Analysis of a two-compartment model representing the tidal and resident volumes, however, indicates that enhanced mixing would yield a better estimate of the true resident volume. The same degree of mixing before and after a resident-volume increase would yield a calculated volume representing the same fraction of the true end-expiratory volume. Our experimental results best fit the latter condition. Hence, we conclude that increasing resident volume did not alter Kr-81m mixing significantly

Extension of this model to the case where an increased tidal volume occurs indicates that the estimate of FRC would actually be less than that obtained with the smaller tidal volume unless better gas mixing accompanied the tidal-volume change.

Data presented in Fig. 4 suggest that a gas-mixing limit may be reached beyond which further increases in ventilation do not enhance mixing. However, because the higher ventilation rates in this study were achieved by increases in frequency, this trend may reflect only a limit associated with increased flow rate.

Data from the static acquisitions shown in Fig. 1 do not indicate a dependence of Kr-81m activity on ventilation mode. This does not contradict the gated analysis. The static acquisition represents a time-averaged indication of activity over the lung. When expressed as activity, the data reflect the quantity of Kr-81m reaching the lung rather than distribution of that tracer. The quantity of tracer reaching the lung is determined by volume per unit time delivered, and the Kr-81m quantity by volume delivered. Hence, for a given ventilation, the

same activity level relative to inspired gas activity would be reached regardless of the combination of tidal volume and frequency.

The inhomogeneity of Kr-81m distribution and its dependence on factors such as combinations of tidal volume and frequency and inspiratory time could explain the differences between the experimental data and theoretical curves generated from a single-compartment, well-mixed model (Fig. 2). In such a model, the distribution volume of the tracer used to calculate concentration is the compartment volume. In the lung, however, this is not the case. The effective distribution volume of the Kr-81m depends upon a number of variables, and it changes during the course of a breath. Hence, the single-compartment, well-mixed model is not a good predictor of Kr-81m behavior in the lung.

Use of Kr-81m in lung imaging may, in fact, provide more information than the single-compartment model suggests. When used in conjunction with Xe-133 or other tracers allowing a determination of regional lung-volume distribution, quantitative information may be obtained regarding distribution of ventilation and the extent of further mixing of inspired and resident lung gas. Use of the gated imaging technique with Kr-81m and a longer-lived tracer may provide a means of quantitating gas mixing during the respiratory cycle.

FOOTNOTE

* Harvard Apparatus Model 613.

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