both total and tidal ^{81m}Kr activity are closely related to regional ventilation, although tidally exchanged ^{81m}Kr activity is a more accurate guide.

In one child, in whom there was a gross disparity between volume and ventilation, tidal ^{81m}Kr activity may give a more accurate guide to regional ventilation.

The contribution of resident ^{81m}Kr to total activity is similar in all age groups. Steady-state ^{81m}Kr images can therefore be used throughout childhood to monitor the progress of pediatric respiratory disease as long as there is no gross disparity of lung volumes on chest radiography.

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EDITORIAL

Go with the Flow—But How Far?

There is well-established logic behind the use of ^{81m}Kr in evaluating lung disease (*1–7*). Its energy allows ^{81m}Kr ventilation studies to follow ^{99m}Tc-MAA perfusion scans. Its short 13.4-sec half-life allows it to be administered intermittently, so that ventilation images can be alternated with perfusion images. Krypton-81m studies can be easily performed on infants, children and on patients being mechanically ventilated. The gas does not require expensive delivery systems, room monitors, ventilation ducts, fans or charcoal traps. Its low dosimetry and absence of radioactive waste disposal problems make it a very attractive alternative to ^{133}Xe or ^{127}Xe. Perhaps most important, the static distribution of ^{81m}Kr reflects the pattern of lung ventilation ($\dot{V}$). It is therefore directly comparable to ^{99m}Tc-MAA perfusion ($\dot{Q}$) studies obtained to screen for pulmonary emboli. The tidally ventilated gas volume ($\dot{V}$) is also an important element of the ventilation-perfusion ratio ($\dot{V}/\dot{Q}$), a parameter describing the lung's primary function of gas exchange (*5,8,9*).

Static ^{81m}Kr images reflect ventilation because of the nature of bulk air flow in the lung. When ^{81m}Kr enters the oropharynx, it is swept along the inhaled air, moving down the branching labyrinth of narrowing bronchi, past 19 to 21 divisions of airways. At about the 20th generation of bronchiole, the transporting motion of the tidal air has diminished to the extent that any farther progress toward the alveolar membrane is by diffusion alone. Although the remaining journey is but a small fraction of the total distance, the last few millimeters are the longest in the trip, consuming minutes of time. This paradox of travel is due to the ever increasing arborization of the airway. The pyramid of volume comprising the lung airspace is arranged such that of the 3.5 liters of resting lung gas only 220 ml occupy the space in the first 17 generations of conducting airway. The cross-sectional area expands from 2.5 cm^2 in the trachea to over 180 cm^2 by the beginning of the pulmonary respiratory zone. It continues to expand to a surface area of over 70 square meters at the pyramid's base, the alveolar membrane. The resting tidal volume of 550 cc is partially expended in the conducting airway such that about 300 cc enters the respiratory zone of the lung. Thus, about 10% of the alveolar air is exchanged with each resting tidal breath. This respiratory tidal flow acts to maintain a diffusion gradient of gas tensions in the alveolus such that transfer of CO_2 and O_2 takes place efficiently. Beyond the gases in the dead space, a significant fraction of the molecules inhaled into the alveoli with each breath are also exhaled. What importance does this have? It means that the radioactive species of a short-lived isotope is primarily concentrated in the dead space, in the terminal conducting airways and in the proximal respiratory zone. The molecules that occupy the more distal alveolar regions (90% of lung volume) have had a much longer residence and a correspondingly lower specific activity. This consequence of the short ^{81m}Kr half-life means that the remaining radioactive gas resides primarily in the tidal space of the lung. Hence, count rates from the chest increase dramatically with inspiration. The faster the tidal volume is refreshed, the higher its mean activity,

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and the higher the lung image intensity. In several early papers, Jones, Fazio and Amis described the theoretical and clinical use of ^{81m}Kr (*2,10*). They used a well-mixed model of the lung to relate tidal ventilation to ^{81m}Kr activity in lung images. Subsequently, many authors have confirmed the usefulness of ^{81m}Kr in clinical evaluations of lung dysfunction and pulmonary embolism screening (*3,11–13*). But do images of ^{81m}Kr always depict $\dot{V}$? Are there situations where these images are also strongly influenced by regional lung volume? In their "classic" description of ^{81m}Kr, Fazio and Jones (*2*) suggested that lung activity was theoretically proportional to

$$\frac{\dot{V}}{(\dot{V}/\dot{V} + \lambda)}. \qquad \text{Eq. 1}$$

They argued that where ventilation rates are normal or reduced by disease, ^{81m}Kr lung activity is proportional to $\dot{V}$, since the denominator of Equation 1 is dominated by the ^{81m}Kr decay constant λ. However, as the value of $\dot{V}/\dot{V}$ approaches and exceeds λ (3.2 min^{-1}), ^{81m}Kr activity in the residual lung volume should contribute a greater fraction of the total lung count (*2,14*). Given that high flow rates are common in infants, children and where tachypnea is present, there may be clinical situations where ^{81m}Kr images depict a complex combination of ventilation and regional lung volume.

In recognizing this potential problem, Lythgoe et al. ask the question "Can dynamic ^{81m}Kr imaging separate regional ventilation and volume?" and describe a technique that may address the need (*15*). To assess regional ventilation, the authors rapidly collect a series of images during tidal respiration of ^{81m}Kr gas from which they extract the dynamically changing component of the lung activity. This fraction is shown to correlate with the quantity of tidally exchanged gas in a series of validation studies using a simple model of the lung.

In assessing the utility of this technique, it is appropriate to further examine the notion that ^{81m}Kr breaks down as an estimator of regional ventilation at high flow rates. Surprisingly, the best available evidence suggests that ^{81m}Kr does a good job in reflecting $\dot{V}$ at the ventilatory turn over rates found in infants and children (*16*). This discrepancy is probably due to nonphysiologic assumptions in the model that underlies Equation 1. For example, it is assumed that all lung regions are ventilated independently with no interregional gas transfer; that tracer transit through the airways dead space does not affect the tracer concentration in the lung; and that tracer is distributed uniformly in a constant volume, well-mixed compartment of alveolar gas (*17*). The alveolus, however, is not a well-mixed compartment physiologically. Bulk transport, through the conducting bronchioles, assures mixing in only a fraction of the lung volume. The remainder is in a diffusional equilibrium and demonstrates stratified gradients of gas concentrations that are not well mixed. Based on gated lung studies over a range of respiratory frequencies, tidal volumes and alveolar turnover rates, Modell and Graham found that the single compartment "well-mixed" model did a poor job of predicting pulmonary ^{81m}Kr activity. They showed that both end-expiration and end-inspiration activities were linearly related to $\dot{V}$ for ventilatory turnover rates up to and exceeding 10 per minute (*16*).

The perspex lung model that Lythgoe et al. use to evaluate their method is probably neither well mixed nor stratified. The authors do not report any assessment of the uniformity of tracer activity in the bags of the lung model, but given the description of the apparatus, it is unlikely that complete mixing occurs. Limited details are provided as to the procedure for defining the resident and tidal activity compartments, but the authors do show a good correlation between fractional tidal activity and fractional tidal volume as delivered to one of the bag "lungs." The analysis procedure takes advantage of the ability of the gamma camera to record the distribution of counts in an inhaled stream of gas. If the concentration of ^{81m}Kr in the inhaled gas is constant, the procedure should have good reproducibility and should accurately describe the right-to-left lung partitioning of tidal volume.

In the conclusion of the manuscript, the authors suggest that the dynamic steady-state ventilation image can be analyzed to separate tidally exchanged and resident ^{81m}Kr. They also suggest that the procedure may allow "regional ventilation" to be distinguished from "regional volume." It is important to exercise caution in interpreting the meaning of regional ventilation and volume in this context. Regional ventilation refers to the regional fraction (left versus right lung) of total ventilation and does not imply that this fraction measures regional gas delivery. The term regional volume must be taken with even greater care. The authors certainly do not imply that residual ^{81m}Kr reflects regional volume. Indeed, they have found that there is a poor relationship between resident ^{81m}Kr activity and resident volume as respective fractions of total activity and volume. Thus, the authors have shown that they can measure fractional ventilation distribution, but this is not, in the literal sense, a mechanism to quantify regional ventilation or regional volume. So the answer to the question, "can dynamic ^{81m}Kr imaging separate regional ventilation and volume," is a resounding yes and no! But, does it matter? Is dynamic analysis necessary if static ^{81m}Kr imaging is adequate for usual adult respiratory flow rates and the higher rates found in infants and children?

The authors present the case of a child in whom there was a significant disparity between their dynamic and routine static assessments of fractional ventilation, but certainly this was not caused by high ventilatory turnover rates. The lung region that apparently caused this discrepancy was one with a low flow rate and an increased relative volume. It is likely that intermittent air trapping caused prolonged re-

tention of ^{81m}Kr in the hyperexpanded lung region. Intermittent trapping and release would increase the activity in the static ^{81m}Kr image out of proportion to that expected from ventilation. Although the true value of ventilation in this zone is unknown, the authors' dynamic procedure is less affected by such trapping and is probably more accurate in estimating fractional ventilation.

The role of a lung imaging study is defined by its potential in screening, staging or serial follow-up applications. Furthermore, realistic assessments must be cast against the background of currently established procedures. It is clear that lung scanning is well established in pulmonary embolism screening. For other forms of lung disease, however, there is little clinical enthusiasm for routine scanning, despite evidence to suggest that regional ventilation studies can be more sensitive to the presence of lung disease than pulmonary function studies or radiographic assessments (*18*). In part, this is due to the nonspecific nature of abnormal findings in a ventilation study. The scan is not a satisfactory means to define the disease etiology or the local cause for ventilation abnormalities, i.e., airway secretions, atelectasis, bronchial obstruction, invasion or collapse, parenchymal destruction, inflammation or edema. Abnormal study findings are also often nonspecific as to pathophysiologic importance (*19*). For example, diffuse ventilation abnormalities were found in 41% of middle-age smokers with either mild or no respiratory symptoms. However, there was only a weak relation between an abnormal ventilation scan and overall lung function (reduced FEV_1 and VC, increased single breath N_2 slope and closing volume) and there was no relation between the presence of chronic expectoration and an abnormal scan (*20*). Although ventilatory dysfunction may be an early sign of disease, the extent of scintigraphic findings due to age-related "normal" dysfunction is unknown. Other reasons for the lack of a routine application of the ventilation scan are logistic and economic, but perhaps the most important is the general utility of standard pulmonary function studies and the chest radiograph. Nonetheless, ventilation studies do have an important role in certain patient populations, i.e., the small child or infant, where lack of cooperation is an issue and where accurate pulmonary function tests are difficult to obtain (*21–23*).

What about staging and the follow-up of lung disease? With the exception of studies performed before lung resection to predict postoperative lung reserve (*24*), ventilation scans are rarely used in staging pulmonary disease (*25*). This is due to reliance on pulmonary function tests and to the relative (nonabsolute) nature of pulmonary scintigraphy. Unlike gallium lung scans or aerosol clearance studies that can detect the acute disease process (*26*), ventilation studies are unable to separate active treatable disease from resulting "static" parenchymal dysfunction. Similar arguments hold for serial assessments of pulmonary disease. As an indicator of overall change, there are too many circumstances where relative measures of regional function are too nonspecific to be useful in following disease progression or response to therapy. The standard chest radiograph and pulmonary functions are not likely to be displaced by routine scintigraphy in such assessments.

Lythgoe et al. have developed a procedure that may improve the utility of ^{81m}Kr scintigraphy, but they are not specific as to its intended use. It is not clear that this procedure will significantly affect the value of ^{81m}Kr scans in screening studies. Beyond identifying patients who deviate from the normal right-to-left partitioning of lung ventilation, it is unlikely to contribute substantially to what is known from the chest x-ray and pulmonary function tests. In staging and follow-up studies, it may also be of limited use. An increase in the relative ventilation of a lung may be due to a number of widely varying etiologies, such as improvement in disease in that lung, deterioration in the opposite lung or less severe deterioration relative to the opposite lung.

Clearly, pulmonary embolism screening is the major indication for ventilation imaging (*27*), and ^{81m}Kr, as it flows from the generator, is very adequate for this purpose (*2,3,12,13*). Yet, in the broadest practical context, ^{81m}Kr is a sleeping genie. Despite all that has been written about the advantages of ^{81m}Kr, fewer than 40 generators are used in the U.S. on a daily basis. The total current capacity for generator production is only a small number of times this amount. It seems that the issues of relative cost, availability and the urgency of the unpredictable embolic event have doomed the routine use of ^{81m}Kr in all but a few sites. It is unlikely that current ^{81m}Kr utilization would change significantly, even with an extremely accurate procedure for estimating regional ventilation. Fortunately, the ^{99m}Tc aerosol study is a satisfactory alternative to ^{81m}Kr in the setting of pulmonary embolism screening (*28–30*). Technetium-99m aerosols are not as accurate as ^{81m}Kr in defining regional ventilation (*11*), but they satisfy the need in most circumstances by identifying regions of normal versus grossly deficient air flow. Given the other uncertainties in $\dot{V}/\dot{Q}$ imaging, aerosol studies are likely to be the preferred scintigraphic method for detecting pulmonary emboli until there is a viable alternative to $\dot{V}/\dot{Q}$ scanning.

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