INVESTIGATIVE NUCLEAR MEDICINE

Sensitivity of Kr-81m and Xe-127 in Evaluating Nonembolic Pulmonary Disease

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The relative sensitivities of Kr-81m and Xe-127 in detecting lung ventilation defects was evaluated in 80 patients with *nonembolic* pulmonary diseases. Krypton-81m ventilation images (500,000 count) were interdigitated with Tc-99m MAA perfusion images; both were compared with Xe-127 images. The distributions of the two gases were also compared on the basis of point-by-point computer analyses. Xenon-127 was found to be more sensitive than Kr-81m in clinical evaluations of scintiphotos—although they were equivalent by computer analyses—in indicating regions of impaired ventilation in patients with obstructive airways disease.

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Regional lung ventilation in patients with suspected pulmonary emboli or obstructive pulmonary disease is being extensively evaluated with Xe-133 and Xe-127 (*1–6*), as well as with the very short-lived Kr-81m ($T_{1/2}$ = 13 sec) (*7–15*). Two uniquely different approaches are involved. Rebreathing a xenon-air mixture to equilibrium produces regional counts that are proportional to lung volume. During the subsequent washout, the initial slope of Xe clearance—as well as the first inspiration of Xe at the start of the procedure—are measures of regional ventilation. The retention of Xe during washout shows the lung regions with diminished ventilation.

In the case of Kr-81m, however, the short half-life precludes its equilibration in the lungs. Instead, it is continually inspired in a series of tidal breaths in succession without a pause to record the cumulative regional count rate. The images reflect the approximate distribution of regional ventilation. The principle of the technique was described by Jones et al. (*16*). Amis et al. (*17*) have provided a procedure to correct for the contribution of volume by equilibrating the lungs with the long-lived Kr-85m in addition to the inhalation of Kr-81m. In our study, we have used the 36.4-d Xe-127 instead to correct for regional lung volume.

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Functionally and visually, the Kr-81m ventilation image, more than the Xe image, is a companion to the image of regional perfusion produced by Tc-99m MAA. Since the Kr-81m images represent a steady state, multiple views of regional ventilation and perfusion can be obtained in rapid succession, and regional ventilation-perfusion relationships can be compared (*9,13,15,19–22*).

In a formal comparison of Xe-133 and Kr-81m in 41 patients, Schor et al. (*23*) found that in seven of the 14 cases of pulmonary embolic disease, Kr gave more information than Xe. On the other hand, they found that in obstructive airways disease the retention of Xe-133 in abnormal lung regions during washout was more readily detected than the corresponding defects in the Kr-81m scans. This increased sensitivity in the detection of regions of low ventilation with the washout technique should be even greater with Xe-127 because of its more advantageous properties (*4,18*). Accordingly, we carried out a clinical comparison to evaluate the relative sensitivities of Kr-81m and Xe-127 for detecting lung ventilation defects in a group of 80 patients with a variety of nonembolic pulmonary diseases.

MATERIALS AND METHODS

Radiopharmaceuticals. The Rb-81/Kr-81m generator was obtained from the BLIP or the Brookhaven cyclo-

tron by the $^{84}Kr(p,4n)^{81}Rb$ or $^{82}Kr(p,2n)^{81}Rb$ reactions. The generators produced an effective activity of 0.7 to 5 mCi Kr-81m at the patient's mouth.

Xe-127 was prepared on the BLIP by the $^{133}Cs(p,2p5n)^{127}Xe$ reaction.

For perfusion imaging, Tc-99m from a generator system was used to label MAA.

Instrumentation. A gamma camera with a large field of view was used in all studies. In contrast to the work of some investigators, we used a 280-keV medium-resolution collimator to measure the Kr-81m, since our phantom studies had demonstrated a 24% improvement in spatial resolution over the more commonly used low-energy collimator. To minimize the possibility of patient movement between measurements, we also used the same collimator for Tc-99m. A 25% window was centered over the 140-keV Tc-99m and 190-keV Kr-81m peaks, sequentially. A 400-keV high-energy collimator was used for Xe-127, with a 25% window encompassing the 172- and 203-keV photon peaks. The 375-keV photons (18%) prevented the use of the 280-keV collimator (*4*).

A semiautomated recirculating spirometry system* was used for the xenon study. Data were acquired on a dedicated small-computer system.

Methods. Eighty patients were referred to our hospital for evaluation of regional ventilation and perfusion related to obstructive or parenchymal lung disease by their personal physicians; some were from the Veterans Administration Hospital at Northport, N.Y.; others were employees presenting at the BNL chest clinic. No patient was referred for suspected pulmonary embolism, and none was found on the basis of the $\dot{V}$ and $\dot{Q}$ scans. All patients had chest radiographs and spirometry to measure lung volumes, 1-sec forced expiratory volume (FEV_1), closing volume, flow-volume loops, and maximum midexpiratory flow rate. The order of the procedures was: spirometry, a Kr-81m ventilation study interdigitated with a perfusion study with Tc-99m MAA, and a Xe-127 ventilation study. Approximately 4 mCi of Tc-99m MAA was injected i.v. with the patient sitting upright so that the distribution of pulmonary blood flow matched that of ventilation.

The patients breathed through a face mask or mouthpiece attached to a three-way nonrebreathing valve. A steady flow of ~25 ml/min of air flowing through the Rb/Kr generator to elute the Kr-81m was mixed with room air inspired through the inlet valve port. The expired air left through the outlet-valve port and was vented through a disposable plastic hose.

Scintiphotos of the Kr-81m ventilation images were obtained in the posterior, anterior, and right and left posterior oblique positions, and were interdigitated with Tc-99m MAA perfusion images. Scintiphotos containing 500,000 counts were acquired for optimum information density (*24*) and the data were stored on magnetic tape for each ventilation and perfusion image.

The Xe-127 ventilation studies were carried out with the patient rebreathing through a rubber mouthpiece attached to the inlet of the recirculating spirometry system. Carbon dioxide was removed with soda lime and O_2 automatically introduced as required to maintain a constant volume during the equilibration phase. The patient was seated in front of the scintillation camera, with the back of the chest against the collimator face. After a suitable time for patient adjustment, and background counts for 1 min, the radioxenon was injected as an ~5-mCi bolus directly into the mouthpiece at functional residual capacity (FRC) as the patient was inhaling slowly to total lung capacity (TLC). The first inhalation was held for 20–30 sec, after which the patient resumed normal breathing for 6–8 min to equilibrate the concentrations of radioactive xenon in the lungs and spirometer. A second 20–30 sec breath hold at TLC was obtained just before washout, which was then carried out for 5–10 min. The gas was vented through a charcoal trap.

Scintiphotos were obtained at TLC during the first inhalation and again after equilibration. Then continuous 1-min scintiphotos were obtained during tidal breathing; first at equilibrium and then during the washout of radioxenon. Computer acquisition at 5-sec intervals was carried out during the entire study. Care was taken to position the patients in front of the camera for the Tc-99m/Kr-81m and then the Xe-127 studies.

The scintiphotos were evaluated jointly by three investigators on the basis of two criteria: image clarity and definition, and detectability of defects. The size and number of discrete lesions (1, 2, 3, or several) versus diffuse disease were recorded for the four Kr-81m and Tc-99m views, and compared with the posterior Xe-127 views showing the initial bolus inspiration and the retention after 2 and 5 min of washout. In addition, the Xe-127 equilibrium view was evaluated to determine

TABLE 1. PATIENTS STUDIED IN COMPARING Kr-81m AND Xe-127

Diagnosis	No. of patients
Emphysema	13
Chronic bronchitis	9
Asthma	7
Mass lesion	7
Small-airway disease	6
Sarcoidosis	3
Pulmonary fibrosis	3
Lung infiltrate	2
Interstitial pneumonitis	2
Kyphoscoliosis	2
Combined emphysema and chronic bronchitis	26
Total	80

TABLE 2. COMPARISON OF Kr-81m AND Xe-127 IMAGES

Superior image	No. of studies
Xe-127	20 (25%)
Kr-81m	15 (19%)
Xe-127 and Kr-81m equivalent	45 (56%)
Total	80
Essential to diagnosis	
Xe-127	10 (13%)
Kr-81m	1 (1.3%)

whether all lung regions—even those distal to obstructed airways—were patent. All images were of good quality and the lung fields were well defined. The respective Kr and Tc images were well matched. Since it was obvious to the investigators which images were obtained with Kr-81m and which with Xe-127, the study was evaluated as a unit for each patient, rather than blind.

The Kr-81m and Xe-127 distributions for each patient were subsequently analyzed with a CDC 7600 computer and displayed on a 64 × 64 matrix with a gray scale for comparison with the scintiphotos. Each patient's posterior Kr-81m and Tc-99m images were normalized to 500,000 counts, as was the 1-min Xe-127 image obtained during tidal breathing at equilibrium. However, the 1-min washout images were compared with the 1-min Xe-127 equilibration image as the basis. The 1-min background counts were subtracted from each Xe-127 image before computer analysis. The outer edges of the regions of interest of the lung field were determined by automatically eliminating all pixels whose Kr-81m, Tc-99m, and Xe-127 activities were less than 20% of the maximum counts in a single pixel in that image, but all areas within these regions were included. The distribution of regional ventilation was then corrected for the distribution of regional alveolar volume by dividing the Kr-81m activities by the Xe-127 activities at equilibrium. The results for each pixel were thus approximately proportional to ventilation per unit alveolar volume ($\dot{V}/V_A$). In addition, the regional $\dot{V}/V_A$ was also evaluated by displaying it graphically as a function of lung height. The mean $\dot{V}/V_A$ was determined for each horizontal slice between apex and base, and expressed as a percentage of the value for the maximum pixel.

RESULTS

The breakdown by patient's disease is shown in Table 1. Diagnosis was on the basis of a physical examination, personal history, chest radiographs and pulmonary function measurements.

In 20 of the 80 studies (25%), the Xe-127 scintiphotos were judged to be clearly superior to those of Kr-81m (Table 2); in 10 of these, Xe-127 was essential to the diagnosis, since the Kr-81m images were normal. The

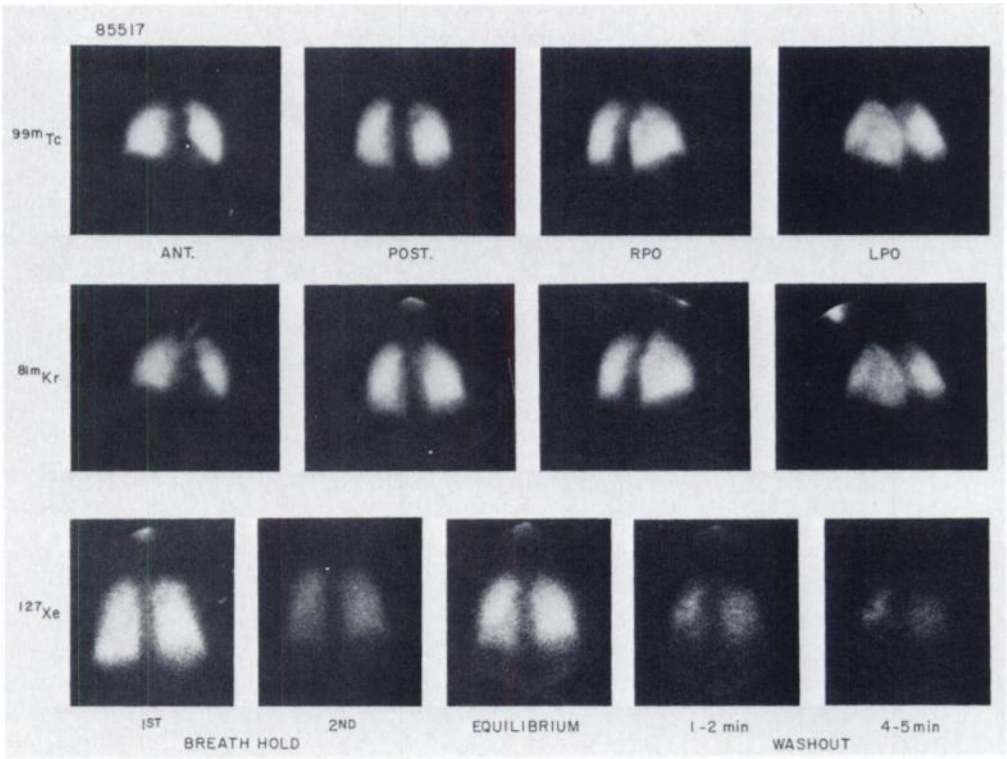

FIG. 1. Scintiphotos obtained with Tc-99m, Kr-81m, and Xe-127 from a 64-year-old asthmatic patient. Xe-127 images were obtained in posterior position. Regions of Xe-127 retention in both lungs after 2 and 5 min of washout are clearly shown, whereas Kr-81m and Tc-99m images appear normal.

FIG. 2. Pixel-by-pixel distribution of Kr-81m activity, determined by computer analysis for patient described in Fig. 1. Relative intensity (counts) is shown on scale at the right.

Kr-81m scintiphotos were judged to be superior to those of Xe-127 in 15 studies; in one of these Kr-81m was essential to the diagnosis, since the Xe-127 image was normal. However, Kr-81m and Xe-127 were judged to be equally useful in evaluating the remaining 45 studies (56%). Krypton-81m was therefore essential to the diagnosis in only one study (1.2%) and superior to Xe-127 in only 15 studies (19%).

A typical study of an asthmatic patient (No. 44), in which the Xe-127 scintiphotos of the posterior images are clearly superior to those of the multiple Kr-81m images, is shown in Fig. 1. Regions of Xe-127 retention are shown in the upper half of the left lung and in the mid portion of the right lung of the 2- and 5-min washout images, while the Kr-81m distribution, and also that of Tc-99m, appear to be normal. The pixel-by-pixel distribution of ventilation, in counts of Kr-81m, from the computer analysis, is shown in Fig. 2. We can see that there is an increasing intensity of Kr-81m activity for about three quarters of the distance down the lung, followed by a decrease towards the base. The distributions in the right and left lungs are dissimilar. There is also some nonuniformity at the various horizontal levels. Similar printouts were obtained for the distributions of Xe-127 (V_A) and Kr-81m/Xe-127 ($\dot{V}/V_A$) activities. The mean $\dot{V}/V_A$ in each horizontal slice was then plotted as a function of its vertical position in the lung (Fig. 3). Instead of increasing from apex to lower lobes, as would be expected for normal lungs, the $\dot{V}/V_A$ remained constant over the upper 40% of the right lung and then increased in a very irregular fashion for the remaining distance. The distribution of $\dot{V}/V_A$ in the left lung is closer to that in a normal lung, but still quite irregular.

DISCUSSION

The Xe clearance technique gives absolute values of ventilation, but the spatial resolution is poor because large lung areas must be chosen to overcome statistical problems. On the other hand, the multibreath Kr-81m technique gives only relative values, but with a more detailed pulmonary topography. Nevertheless, Kr-81m provides functional images of ventilation in multiple views that can be obtained quickly during tidal breathing without the patient's cooperation. These images can then be directly compared with images of regional lung perfusion obtained with Tc-99m MAA because of the similar energies of the two respective gamma photons.

Unlike Xe-133, the high 172- and 203-keV photon peaks of Xe-127 are similar to the 190-keV photon peak of Kr-81m, so that their intrinsic spatial resolutions and tissue penetrations are equivalent. In addition, the FWHM of Kr-81m and Xe-127 were essentially the same when used with a 280-keV medium-energy collimator. As expected, therefore, our study verified the resulting correspondence between Kr-81m and Xe-127 for the detection of ventilation abnormalities—but only on the basis of a computer analysis.

However, when evaluating scintiphotos of pulmonary studies in patients with nonembolic pulmonary disease, we found that the use of Xe-127 was preferred since it facilitated patient evaluation. The Xe-127 washout

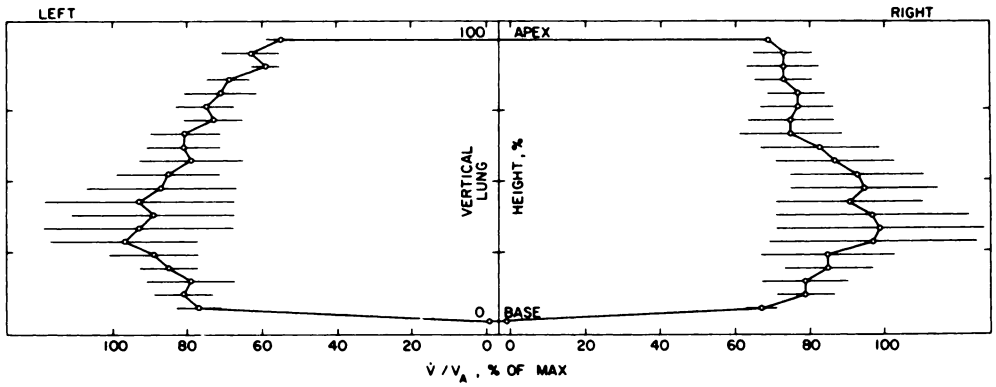

FIG. 3. Topographical distribution of Kr-81m/Xe-127 activity ratio ($\dot{V}/V_A$) for right and left lungs of patient described in Fig. 1. Mean value of $\dot{V}/V_A$ for each horizontal layer of pixels, expressed as percentage of value for maximum pixel, is shown as a function of its vertical position in lungs. Also shown is horizontal dispersion at each position, expressed as standard deviation from mean. $\dot{V}/V_A$ was constant for upper 40% of right lung, then increased in very irregular pattern approaching base. Its distribution in left lung is also very irregular. Horizontal dispersion of $\dot{V}/V_A$ in both lungs is nonuniform.

images were considerably more sensitive than Kr-81m in detecting regional ventilatory abnormalities, because it is easier to discern regions of high radioactivity in a low-activity field than to detect areas of diminished uptake in regions of high Kr-81m count density, also possibly because delayed washout of Xe-127 may be a more sensitive indicator of regional ventilatory dysfunction than inflow-tract kinetics. In any case, no clear advantages were apparent favoring the use of Kr-81m over Xe-127 to measure regional ventilation defects in patients without pulmonary emboli. Only one diagnosis (1.2%) would have been missed if only Xe-127 were used, while 10 diagnoses (12.5%) would have been missed if only Kr-81m were used. The rest of the results were the same with the two tracers. These results are in qualitative agreement with those of Schor et al. (*23*), who compared Kr-81m with Xe-133 in 20 patients with nonembolic disease.

The presentation of the Kr-81m data suffers from an inherent limitation that severely restricts the ability to detect *small* regional impairment in ventilation in patients with obstructive or parenchymal disease: the distribution of ventilation is not uniform even in the normal lung (*25*), but instead increases from apex to base. There is also a dispersion of Kr-81m activity at a given lung height (Fig. 3). The patient's individual distribution of ventilation, or $\dot{V}/V_A$ if corrected for regional volume, must therefore be correlated with that of the normal lung gradient. Clearly this cannot be done by eye, but instead requires computer analysis. On the other hand, pulmonary emboli usually produce perfusion defects over relatively large lung regions, such as a whole lung segment, in which the corresponding ventilation is relatively preserved. Under these conditions, the use of Kr-81m interdigitated with Tc-99m MAA is probably preferred for the evaluation. This is especially the case because it facilitates the ability to obtain multiple lung views. However, even this advantage might be reduced by the modified xenon washout procedure used by Alderson and his co-workers (*1*). They rotate the patient to obtain at least one 6-sec image in the right and left posterior oblique positions, in addition to the usual posterior image during the early part of the washout. Ventilation studies with Kr-81m are also desirable when used in conjunction with Tc-99m MAA. They can be used to evaluate the patient's regional ventilation and perfusion matching and detect subtle regional changes, which may serve as early indicators of disease (*26*). Krypton-81m may also have advantages in the preoperative evaluation of patients with bullous emphysema or lung carcinoma (*27*). A computer analysis with Kr-81m should predict more accurately which patient would benefit from surgery, and improve the assessment of postoperative lung function, because of its better statistics and the ability to provide multiple views, as compared with Xe-127. Since Kr images can readily be repeated, minute-by-minute or longer time changes in regional ventilation can also be studied during acute asthmatic crises and remissions (*11*), and can evaluate changes in patients induced by treatment, such as radiotherapy (*10*).

In conclusion, Xe-127 was found to be more sensitive in clinical practice—as compared with Kr-81m and a computer analysis—in detecting regions of impaired ventilation in patients with obstructive airways disease. On the other hand, Kr-81m is inherently more useful for the clinical diagnosis of pulmonary emboli and in other studies requiring a detailed comparison of regional ventilation and perfusion, for the preoperative evaluation of patients, and the assessment of regional ventilatory changes during acute asthmatic crises and those resulting from treatment.

FOOTNOTE

* RADX Corp., Houston, Texas.

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