Regional Pulmonary Perfusion Assessed with Continuous Intravenous Infusion of Kr-81m: A Comparison with Tc-99m Macroaggregates

G. Ciofetta, T. A. Pratt, and J. M. B. Hughes

Royal Postgraduate Medical School, Hammersmith Hospital, London, England

The radioactive gas krypton-81m ($T_{1/2}$ = 13 sec) can be produced in the gaseous form or in solution by passing air or water over a resin column to which the parent nuclide rubidium-81 ($T_{1/2}$ = 4.6 hr) is bound. Due to the rapid radioactive decay, a continuous administration of Kr-81m into the inflow of an organ yields a functional image of tracer arrival, that is, regional distribution of flow in that organ. Continuous inhalation of Kr-81m gas therefore produces functional images of pulmonary ventilation. We investigated the feasibility of assessing regional pulmonary blood flow by a continuous i.v. infusion of Kr-81m solution. Krypton-81m ventilation and perfusion images, together with a routine Tc-99m macroaggregate (Tc-HAM) perfusion lung scan, were obtained in 20 patients with various chest disorders. There was excellent agreement between Kr-81m and Tc-HAM perfusion images when the ventilation was not disturbed, as in patients with pulmonary embolism. In the presence of macroscopic ventilation abnormalities, however, the correlation between the Kr-81m perfusion and the Tc-HAM scans is less good. This is understandable because Kr-81m that diffuses into the alveoli will be exhaled unevenly. The main advantages of Kr-81m over Tc-HAM for assessment of pulmonary blood flow are: a) absolute safety in children, especially in the presence of right-to-left shunts; b) continuous monitoring during changing clinical and experimental conditions; and c) low radiation dose.

J Nucl Med 19: 1126–1130, 1978

In order to obtain high-quality images of ventilation distribution for clinical use, comparable with the conventional perfusion lung scans, a technique has recently been developed using the very short-lived gas krypton-81m (*1*). An image recorded with a gamma camera during the continuous inhalation of air containing Kr-81m reflects the arrival of the tracer in the alveolar compartment ($\dot{V}$), since the very short half-life (13 sec) does not allow the alveolar radioactivity to reach an equilibrium with the inspired concentration.

The same principle has also been used for assessing coronary (*2*) and cerebral (*3*) blood flow, following arterial infusion of Kr-81m dissolved in physiologic saline solution. Intravenous infusion of Kr-81m in solution should therefore reflect arrival of the tracer in the pulmonary capillary bed, yielding images of pulmonary blood flow. However, this is not entirely true: when an insoluble radioactive gas, like krypton-81m, is continuously infused intravenously during tidal breathing, a steady state is reached that reflects the balance between a) blood flow for the arrival and b) alveolar ventilation plus radioactive decay for the removal (*4*).

Received Feb. 3, 1978; revision accepted Apr. 19, 1978.

For reprints contact: J. M. B. Hughes, Royal Postgraduate Medical School, Hammersmith Hospital, London, England W12 OHS.

The purpose of this investigation was to assess the contribution of uneven regional ventilatory washout towards misinterpretation of Kr-81m perfusion lung scans. A comparison was therefore undertaken, in the same patients, between these scans and those obtained by injection of Tc-99m-labeled macroaggregate (Tc-HAM), the latter procedure being regarded as a reference technique (*5*).

Theory. When Tc-99m-labeled radioactive particles are administered intravenously, they will impact with the pulmonary vascular bed in a distribution proportional to regional blood flow. Their removal takes place over several hours. The signal of radioactivity recorded over the chest is related to perfusion as follows:

$$\text{Tc-99m signal} = \dot{Q} \cdot K_1 \cdot C_1, \qquad (1)$$

where $\dot{Q}_1$ is pulmonary perfusion, as a fraction of cardiac output, K_1 is the geometrical factor, and C_1 is the total activity delivered.

When an insoluble radioactive gas is administered intravenously it will follow pulmonary blood flow and diffuse into the alveolar compartment. During tidal breathing a constant fraction of the labeled gas will be removed by ventilation, and if the gas is infused continuously a steady state will be reached. With Kr-81m the very short physical half-life (the decay constant $\lambda = 3.2\ \text{min}^{-1}$) dominates the removal process. The steady state can be written:

$$\text{Kr-81m signal} = \frac{\dot{Q}_2 \cdot K_2 \cdot C_2}{\dot{V}/\text{VOL} + \lambda}, \qquad (2)$$

where $\dot{Q}_2$ = blood flow as a fraction of cardiac output;
K_2 = geometric factor for Kr-81m;
C_2 = activity of Kr-81m delivered;
$\dot{V}/\text{VOL}$ = ventilation in liters per minute, per liter of lung volume; and
λ = decay constant (min^{-1}) for Kr-81m.

The numerator of Eq. 2 represents the arrival of activity in the counting field: $\dot{Q}_1$ and $\dot{Q}_2$ are assumed to be the same for Kr-81m and Tc-99m. The denominator reflects the removal processes. From Eqs. 1 and 2, it follows that if C_1 and C_2 are known, the difference between the two blood-flow measurements is related to the factor $\dot{V}/\text{VOL} + \lambda$, which may alter the Kr-81m signal even if regional perfusion ($\dot{Q}$) remains unchanged. Obviously the decay constant is not interfering with regional signals, since it is common to all areas. According to this criterion, a Kr-81m perfusion lung scan should underestimate perfusion when compared with a Tc-HAM lung scan in regions of high ventilation. This is represented in Fig. 2A, where the ratio between Kr-81m and Tc-99m signals is plotted against different values of $\dot{V}/\text{VOL}$. For this theoretical comparison, $K_1/K_2 \times C_1/C_2$ is taken as unity and the ratio of signals equals one when $\dot{V}/\text{VOL}$ is zero—which situation can be achieved only when the subject holds his breath. In the present study the subject was allowed to breathe normally, under physiologic conditions.

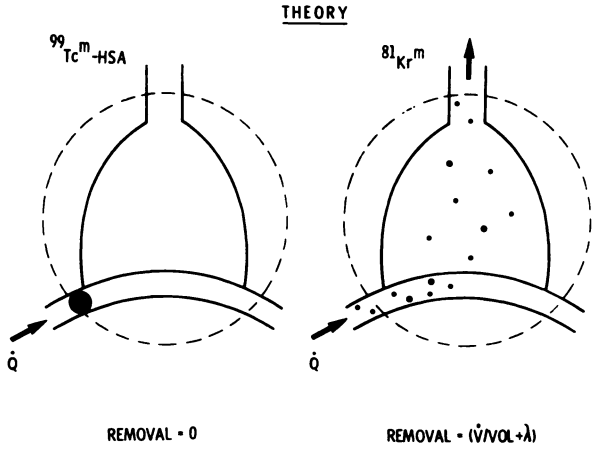

FIG. 1. Single-compartment lung model to illustrate difference between blood-flow measurements with Tc-99m macroaggregates (Tc-HAM) and a radioactive gas such as Kr-81m. Interrupted circle represents counting field. Kr-81m arrival by perfusion is balanced by removal by ventilatory washout (V̇/VOL) and radioactive decay (λ).

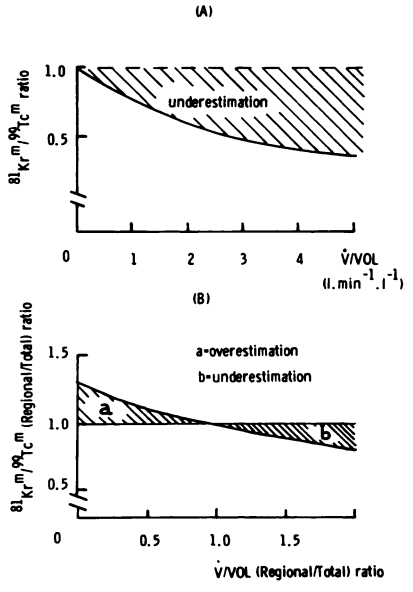

FIG. 2. (A) Theoretical relationship between krypton-81m and technetium-99m perfusion counts for different levels of ventilation per unit volume (V̇/VOL) in liters per min per liter, assuming a ratio of 1 between Kr-81m and Tc-99m count rates when there is no ventilation. (B) Ratio of regional Kr-81m and Tc-99m perfusion signals, each as percentage of total activity in lung fields (see Eq. 3), at different levels of regional ventilation per unit volume (V̇/VOL) and normalized to a total V/VOL of 1.0.

When regional counts (R) for both perfusion scans are expressed as percentage of total counts (T) in the lung field, the total underestimation illustrated in Fig. 2A is replaced by an overestimation of Kr-81m relative to Tc-99m in areas of low ventilation, and by an underestimation in units with high ventilation (Fig. 2B). Under these circumstances, the following equation is obtained:

$$\frac{\text{Kr-81m (R/T) signal}}{\text{Tc-99m (R/T) signal}} = \frac{(\dot{V}/VOL + \lambda)\ T}{(\dot{V}/VOL + \lambda)\ R'} \quad (3)$$

Therefore the Kr-81m signal in any given region may underestimate or overestimate the fractional distribution of perfusion when compared with the Tc-99m signal, because of regional variations of ventilation.

MATERIALS AND METHODS

Perfusion lung scans with Kr-81m and Tc-99m were performed on 20 patients with various lung diseases, including asthma, pulmonary embolism, chronic bronchitis, and pulmonary emphysema. Krypton-81m is separated from its Rb-81 parent in a generator where Rb-81 is bound on an ion-exchange column. The Kr-81m daughter is recovered in solution by the elution of the column with water (*6*); it is then administered in physiologic saline by continuous infusion into an antecubital vein at a rate of 10 ml/min. Technetium-99m was injected through the same needle, soon after the Kr-81m perfusion scan. Ventilation lung scans with Kr-81m were also performed: the gas was added to a face mask at a flow of 1 l/min, and posterior views of radioactivity distribution were recorded in the erect posture with a gamma camera equipped with a medium-energy collimator and linked with a computer. The images were stored on magnetic discs. Care was taken to avoid any change in the patient's position between the lung scans. The main photon energies of Tc-99m (140 keV) and Kr-81m (190 keV) are sufficiently similar for a direct comparison to be made.

The high-resolution low-energy collimator (up to 150 keV), normally used for Tc-99m studies, was replaced by a medium-energy collimator (up to 250 keV) in order to minimize septal penetration by the 190-keV photons of Kr-81m. For each image 250 kilocounts were accumulated within the lung fields, excluding counts present in the large veins during Kr-81m infusion. The accumulation time ranged from 0.5 to 2 min. The whole procedure required approximately 15 min for each patient. The radiation dose due to the two krypton scans was about 3.5 mrad to the lungs, whereas that due to the injection of 1.5 mCi of Tc-99m was about 250 mrad. A computerized regional analysis program was used to divide each lung field in 12 horizontal slices and to operate the ratio of regional (R) to total (T) counts for each pair of perfusion scans.

RESULTS

Figure 3 shows two examples of blood-flow measurements with Tc-HAM and Kr-81m infusion in the presence of a uniform distribution of activity in the krypton-81m ventilation scan. In a case of pulmonary embolism (Fig. 3, top), the defect of blood flow is shown equally well by the two methods. For the normal subject (Fig. 3, bottom), the low apical blood flow in the seated position can be seen with both tracers relative to the more uniform distribution of ventilation. In Fig. 4, by contrast, two patients are shown with macroscopic defects of ventilation in the Kr-81m inhalation scan. The posterior perfusion scans are different in the two cases. For the patient with chronic bronchitis (Fig. 4, top), two defects of perfusion in the left lung (arrows), which correspond to areas of reduced counts in the inhalation scan, are not seen in the Kr-81m perfusion scan, for reasons outlined in the Theory section, above. In the case of emphysema (Fig. 4, bottom) the relatively poor ventilation on the right side is associated with a larger krypton image on the perfusion scan than on the technetium scan. A possible explanation is that the krypton evolving into perfused alveoli is cleared extremely slowly by ventilatory washout; thus there is time for the radioactivity in the gas phase to diffuse through collateral channels to poorly perfused parts of the lung.

The data in Fig. 5 have been collected from several patients, each point representing a single lung region from the horizontal slices. There is very good agreement when ventilation is homogeneously

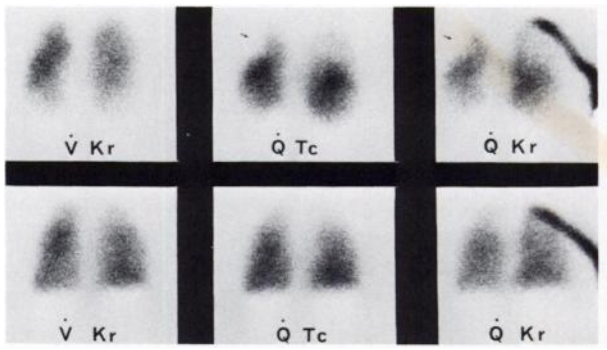

FIG. 3. Kr-81m ventilation (V̇ Kr), Tc-99m perfusion (Q̇ Tc), and Kr-81m perfusion (Q̇ Kr) posterior scans in two subjects with homogenous ventilation distribution. Above: perfusion defect (pulmonary embolus), in left upper zone is shown equally well by both tracers. Below: a normal subject: Note activity in axillary and subclavian veins under Kr-81m infusion.

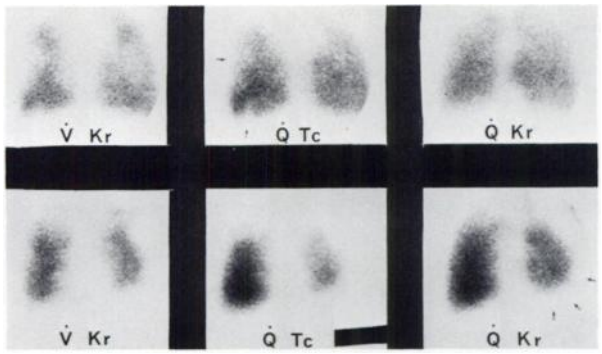

FIG. 4. Scans similar to those of Fig. 3 but in two patients with uneven ventilation distribution. Note differences (arrows) between the two perfusion scans. Above: chronic bronchitis. Below: emphysema. Note larger image of right lung in krypton perfusion scan (Q̇ Kr) than on technetium scan. (See text for explanation).

distributed as judged by the Kr-81m ventilation image, with all points lying close to the identity line in Fig. 5A ($r = 0.97$); on the other hand, gross ventilation abnormalities (Fig. 5B) lead to a dispersion of values from the identity line, so that the correlation is less good ($r = 0.83$).

We conclude that small perfusion defects may be missed during Kr-81m infusion if gross ventilation defects are superimposed on them. Nevertheless, the agreement is excellent if the ventilation scan is uniform.

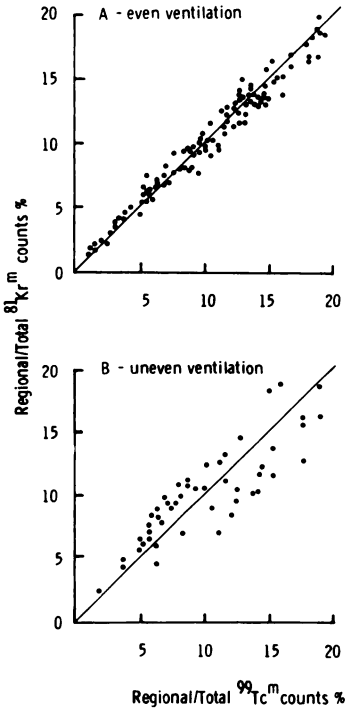

FIG. 5. (A) Regional Kr-81m perfusion counts (as percentage of counts for whole lung) plotted against percent Tc-99m counts in 100 zones in 12 patients with normal ventilation scans. Line of identity is shown. (B) The same relationship as in A in 50 zones in five patients with uneven ventilation scans.

DISCUSSION

Two methods are generally available for assessment of regional pulmonary blood flow: either an i.v. injection of radioactive particles or an injected bolus of a radioactive gas, such as Xe-133, dissolved in saline. Radioactive gases are not used extensively to study perfusion distribution because they involve breath-holding immediately after injection (*7*) in order to minimize redistribution of radioactivity within the lung during the measurement. Cooperation from the patient is required, and this precludes studies in very dyspneic patients, as well as in newborn and other young children. Moreover, the Xe-133 photon energy (81 keV) is rather low, particularly for the Anger camera, and many photons are scattered by the chest wall. Even making allowance for these limitations, it is difficult, using radioactive gases, to get multiple views of regional pulmonary blood flow. With an injection of radioactive particles, however, anterior, posterior, and lateral views can be taken without increasing the radiation dose by repeating the procedure each time.

The injection of particles for perfusion scanning has no detectable effect on pulmonary mechanics or gas exchange (*8*) and the procedure appears to be acceptably safe. Nevertheless, three deaths have been reported following i.v. administration of human macroaggregated albumin (HAM) to patients with severe restriction of the pulmonary vascular bed (*9–11*). Moreover, in children with right-to-left shunt, the radioactive particles can lodge in the brain. Microembolization of the brain is theoretically possible, since the diameter of the brain microcapillaries is about 6 μ, whereas the Tc-99m-labeled particles range between 10 and 50 μ. Up to now there have been no reports of damage to the brain, but more experimental work is needed before radioactive particles can be used safely in children suspected of right-to-left shunt. The use of Kr-81m avoids the problems of possible brain embolization. Under continuous i.v. infusion, the very short half-life of Kr-81m results in an equilibrium distribution of radioactivity that indicates the arrival of blood-flow in each lung region. The method does not require the patient's cooperation, and the results of the study are readily available as functional images of pulmonary perfusion.

The use of Kr-81m for assessing regional pulmonary blood flow is therefore justified in children in situations where ventilation is not severely compromised. The diagnosis of pulmonary embolism can be established with Kr-81m ventilation and perfusion

imaging in multiple views, since ventilation remains relatively unaffected, as shown by other studies (*12–14*). Another, and important, potential advantage of the continuous i.v. infusion of Kr-81m is the possibility of continuously monitoring perfusion during changes induced by different clinical or experimental conditions.

ACKNOWLEDGMENTS

We are grateful to Dr. J. P. Lavender for the use of the gamma camera, to Dr. F. Fazio, Mr. T. Jones, and Mr. T. Amis for helpful discussions, and to the staff of the M.R.C. Cyclotron Unit for the supply of Kr-81m generators. The work has been supported by the Wellcome Trust.

REFERENCES

1. FAZIO F, JONES T: Assessment of regional ventilation by continuous inhalation of radioactive Krypton-81m. *Brit Med J* 3: 673–676, 1975

2. TURNER JH, SELWYN AP, JONES T, et al: Continuous imaging of regional myocardial blood flow in dogs using krypton-81m. *Cardiovasc Res* 10: 398–404, 1976

3. FAZIO F, NARDINI M, FIESCHI C, et al: Assessment of regional cerebral blood flow by continuous carotid infusion of Krypton-81m. *J Nucl Med* 18: 962–966, 1977

4. HARF A, PRATT T, HUGHES JMB: Regional distribution of $\dot{V}A/\dot{Q}$ in man at rest and with exercise measured with Krypton-81m. *J Appl Physiol* 44: 115–123, 1978

5. WAGNER HN, SABISTON DC, MCAFEE JG, et al: Diagnosis of massive pulmonary embolism in man by radioactive scanning. *N Engl J Med* 271: 377–384, 1964

6. JONES T, CLARK JC, HUGHES JMB, et al: ^{81m}Kr generator and its uses in cardiopulmonary studies with the scintillation camera. *J Nucl Med* 11: 118–124, 1970

7. BALL WC, STEWART PB, NEWSHAM LGS, et al: Regional pulmonary function studied with xenon^{133}. *J Clin Invest* 41: 519–531, 1962

8. GOLD WM, MCCORMACK KR: Pulmonary-function response to radioisotope scanning of the lungs. *JAMA* 197: 146–148, 1966

9. DWORKIN HJ, SMITH JR, BULL FE: A reaction following administration of macroaggregated albumin (MAA) for a lung scan. *Amer J Roentgenol* 98: 427–433, 1966

10. VINCENT WR, GOLDBERG SJ, DESILETS D: Fatality immediately following rapid infusion of macroaggregates of ^{99m}Tc albumin (MAA) for lung scan. *Radiology* 91: 1180–1184, 1968

11. WILLIAMS JO: Death following injection of lung scanning agent in a case of pulmonary hypertension. *Brit J Radiol* 47: 61–63, 1974

12. DENARDO GL, GOODWIN DA, BRADLEY BR: Regional ventilation in pulmonary embolism. *J Nucl Med* 10: 331, 1969 (Abst)

13. WAGNER HN, LOPEZ-MAJANO V, LANGAN JK, et al: Radioactive xenon in the differential diagnosis of pulmonary embolism. *Radiology* 91: 1168–1174, 1968

14. BASS H, HECKSCHER T, ANTHONISEN NR: Regional pulmonary gas exchange in patients with pulmonary embolism. *Clin Sci* 33: 355–364, 1967