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Lung Function Studies Using Short-Lived Krypton-81m and the Scintillation Camera

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Introduction

Studies of pulmonary function with radioisotopes usually involve the evaluation of regional pulmonary perfusion with labeled aggregates or the assessment of pulmonary ventilation and exchange capacity with radioactive gases. Most perfusion studies are now being done with aggregated particles of albumin or hydrous ferric oxide labeled with radioisotopes such as iodine-131 (1), technetium-99m (2), or indium-113m (3). Ventilation and exchange studies are being done with the radioactive inert gases xenon-133 (4) and krypton-85. Other studies are being done with the very-short-half-life gases such as ^{15}O, ^{11}CO and $^{11}CO_2$ (5). These short-half-life isotopes must be used near the cyclotron where production occurs.

We have investigated the radioactive gas krypton-81m for both pulmonary perfusion and ventilation studies with the Donner Laboratory scintillation camera, as a further development of generator-produced short-lived radioisotopes for visualizing blood vessels and organs (6).

Krypton-81m, which decays with a half-life of 13 sec, can be milked every few minutes from its 4.7-h parent isotope ^{81}Rb. Krypton-81m has a more favorable gamma-ray energy of 190 keV for use with the scintillation camera than the 81-keV gamma-ray emission of xenon-133.

Figure 1 shows the decay scheme for both the 4.7-h ^{81}Rb parent and the 13-sec ^{81m}Kr, which decays by isomeric transition and emission of 190-keV gamma rays (65% abundant and 35% internally converted) to ^{81}Kr. This isotope then decays by electron capture with a half-life of 2.1×10^5 y to stable ^{81}Br (7).

Methods and Materials

The parent isotope ^{81}Rb is produced by irradiating about 400 mg of reagent grade NaBr with 50-MeV alpha particles in the Lawrence Radiation Laboratory 88-inch cyclotron. The nuclear reaction on the nonenriched, 49.5% abundant ^{81}Br is $^{81}_{35}Br(^{4}_{2}He, 4n)^{81}_{37}Rb$, and it has a threshold energy of 30.8 MeV. The yield of ^{81}Rb averaged from four production runs is 2.9 MCi/μA-h, using an average beam current of 15 μA.

The thickness of the NaBr target is < 0.025 in., to prevent the 50-MeV alpha paaticles from being degraded below 30 MeV in the target, thereby minimizing the $^{81}Br(^{4}_{2}He, 3n)^{82m}Rb$ reaction. Furthermore the ^{82m}Rb that is produced decays to stable ^{82}Kr in the generator and does not interfer with ^{81m}Kr studies. The $^{81}Br(^{4}_{2}He, 2n)^{83}Rb$ reaction produces 10^{-3} part of unwanted ^{83}Rb ($T_{1/2}$ = 1.8 h), which decays to ^{83}Kr ($T_{1/2}$ = 83 d). Natural bromine contains 50.5% ^{79}Br, which produces ^{79}Rb by the reaction $^{79}Br(^{4}_{2}He, 4n)^{79}Rb$. Rubidium-79 decays with a half-life of 24 min to ^{79}Kr ($T_{1/2}$= 1.45 d). The long-half-life ^{79}Kr and ^{83}Kr are washed from the ion-exchange column in a preelution so that subsequent elutions contain only the 13-sec ^{81m}Kr. Because of the large differences in half-life, ^{81m}Kr is rapidly built up to its maximum yield while only negligible amounts of ^{83}Kr and ^{79}Kr are produced in the 5- to 10-minute intervals between elutions.

Rubidium-81 could also be produced by $^{3}_{2}$He particles from a small cyclotron, either by the nuclear reaction $^{81}_{35}Br(^{3}_{2}He, 3n)^{81}_{31}Rb$, Q-value-12.2 MeV, or $^{79}_{35}Br(^{3}_{2}He, n)^{81}_{37}Rb$, Q-value 6.6 MeV.

The radiation level from the NaBr target, after irradiation with 50-MeV alpha particles for 25 μA-h, is > 50 r/h at 6 in. Because of this

high radiation field it is necessary to use at least 2 in. of Pb shielding during the processing of the target material. All the processing of ^{81}Rb is done in a 2-in. Pb cave by tong operation from outside the shielded area.

The NaBr target material is washed from the powder plate holder with a stream of sterile distilled water into a sterile 250-ml flask and diluted to a volume of 125 ml. This dilution is necessary to reduce the concentration of NaBr, because salt solutions > 0.5% displace the ^{81}Rb parent from the ion-exchange column.

The parent ^{81}Rb is retained on strongly acidic cation-exchange resin composed of nuclear sulfonic acid exchange groups attached to a styrene-divinylbenzene polymer lattice (Bio Rad AG 50×4, 200–400 mesh). This resin in the hydrogen form is held in a specially constructed Pyrex column, 11 mm i. d. and 60 mm high, fitted with Luer-lock connections at the top and bottom. The operation and construction of the generator system have previously been described (8). The dilute solution of NaBr-^{81}Rb is slowly passed through the ion-exchange column, and it is washed with 100 ml of sterile distilled water. This procedure is done without removing the ion-exchange column from the generator system. The complete generator unit, which is mounted on a reinforced lab cart, is rolled to the side of the Pb cave. Connections are made between the generator and the radioactive ^{81}Rb solution within the Pb cave with sterile polyethylene tubing. This allows the ^{81}Rb solution to be pumped through the resin column and the radioactive eluate to be returned to the Pb cave by a similar tubing connection. The loading of the ion-exchange column is regulated by an electrical motor drive which is controlled from a distance 5 to 6 feet away. This is necessary to reduce radiation exposure while loading the resin column with ^{81}Rb and while washing away the

unwanted ^{79}Kr and ^{83}Kr. The radioisotope generator is then moved from the "hot" lab to the scintillation camera room.

The generator, with external shielding removed, is shown in Fig. 2. Visible are the automatic two-way valves, polyethylene tubing, sterile H_2O for elution, and 2% NaCl solution for mixing with the eluate below the resin column to give an isotonic saline solution for administering ^{81m}Kr by intravenous infusion for lung perfusion studies.

Sterile and pyrogen-free reagents and equipment are used for the procedure. The solution flows through an in-line Millipore filter (0.45 μ) just before intravenous infusion. Sample elutions from each production generator have been checked by an independent laboratory and found to be sterile and pyrogen free.

In actual operation the generator is shielded with 3-3/4 in. of Pb consisting of 1-3/4 in. of interior shield plus 2 in. of outer shielding which is built up from 1/4-in.-thick half-circle layers. This shielding is necessary because of the high radiation level of > 10 r/h at the surface of the resin column. The radiation level from the shielded generator does not interfere with the operation of the scintillation camera, even when the generator is located within 2 feet of the camera head.

With 50 mCi of ^{81}Rb on the resin column, elution with 5 ml of H_2O will yield about 5 mCi of ^{81m}Kr. The leakage of ^{81}Rb for each elution is $< 10^{-5}$ parts of the total ^{81}Rb on the column. The usual injected dose for perfusion studies is 5 mCi of ^{81}Kr with less than 0.5 μCi of contaminating ^{81}Rb.

The radiation dose in human subjects is calculated to be 7.5×10^{-4} rad/mCi to the lungs from ^{81m}Kr and 7.8×10^{-3} rad/μCi to the heart and

kidneys from ^{81}Rb. These calculations assume the biological half-time to be equal to the physical half-life of the isotope.

Krypton-81 can also be eluted by rapidly forcing 50 ml of air through the dry resin column. The ^{81m}Kr in air is inhaled directly by the subject through the polyethylene tubing. The yield of ^{81}Kr for each elution is about 5 to 6 mCi from a 50-mCi generator. It is possible to change back and forth from H_2O elution for perfusion studies to air elution for ventilation studies by attaching a sterile three-way valve control and a sterile 50-ml syringe to the "saftiset" tubing that connects the eluant H_2O reservoir to the automatic two-way valve leading into the ion-exchange column. With the syringe plunger of the central column syringe in the lowered position to reduce the air space above the column, filtered air is taken into the 50-ml syringe and forced through the resin column until all the liquid is pushed through the column and its connecting polyethylene tubing. This usually requires about 100 ml of air. Thereafter 50 ml of air can be forced through the resin column to provide ^{81m}Kr in gaseous form. By reconnecting the H_2O reservoir in place of the 50-ml air syringe, perfusion studies can again be done without altering the characteristic of the ion-exchange resin to strongly retain ^{81}Rb.

Results and Discussion

To determine the antomical, physiological, and diagnostic information that can be obtained by using ^{81m}Kr, preliminary studies have been done on a number of normal volunteers and patients with known respiratory problems. The subjects have been asked to breathe at specified intervals and to control the rate and depth of respiration in

certain instances. There has been no spirometric control for the studies reported here.

For perfusion studies, ^{81m}Kr in 10 ml of isotonic saline was infused for 3 to 5 sec into the right antecubital vein. The patient was lying either supine or prone. Serial scintiphotos were taken, using exposure times of 2 to 5 seconds while the patient held his breath. The depth of inspiration varied from normal to maximum. The tracer usually leaves the right heart within 15 seconds after starting the infusion. In dynamic cardiac studies a 10- to 20-sec exposure was taken at the end of the study to show the distribution within the lungs. Further pictures were then taken as the patients breathed at their usual rate and depth, exposures being terminated when sufficient dots were recorded. Within 2 minutes, activity falls to a level which no longer permits pictures to be taken.

For ventilation studies, 50 ml of air was forced through the dry generator with a 50-ml syringe. In some instances the patients were asked to inhale through a short length of tubing 1 cm in diameter over a period of 5 to 15 seconds, from forced expiration to maximum inspiration, as the 50 ml of air carrying the ^{81m}Kr was directed into the tubing. A nose clip was used and the studies were performed with the patients in supine and prone positions. Because of the short half-life, it is not possible to achieve an equilibrated state when breathing ^{81m}Kr, and only single-breath respiratory studies have been performed. The exhaled radioactivity was removed via an exhaust system. The exhaled gas should not be allowed to collect immediately adjacent to the camera. If it is not swept away it drifts along the table and produces odd patterns on the scintiphotos.

The position of the lungs and heart in the camera field was determined by a transmission picture taken with a collimated disc source of ^{99m}Tc

placed below the patient, as suggested by Anger and McRae (9). The area of normal lung transmission was compared with the distribution of radioactivity in both the perfusion and ventilation studies.

Figure 3 shows ventilation studies on two normal subjects. Inhalation of gaseous ^{81m}Kr began from maximum expiration. In the case of J. M., a 40-year old male, ^{81m}Kr was administered during normal inspiration, whereas in D.V.D., a 46-year-old male, ^{81m}Kr was given continuously during steady inspiration lasting 10 seconds. The trachea and major bronchi can be recognized, and in the slower inspiration the outward spread of radioactivity is apparent.

Figure 4 (A.H. 3-11-69), left, shows a normal distribution of ^{81m}Kr infused in saline solution as seen in an anterior view. At the top is the transmission picture, which defines the field of view and shows the position of aerated lung. Below and to the left are 4-second exposures of the dynamic study and at the bottom is a picture taken from 30 to 60 seconds postinfusion. In the 8- to 12-second scintiphoto the left ventricle can be seen as an area of diminished radioactivity lying between the right ventricle and the left lung. At the right is the ventilation study of the same patient. The ^{81m}Kr was administered as rapidly as possible as the patient took a deep breath. The tracheo-bronchial tree was not demonstrated. The distribution of activity is similar for both perfusion and ventilation studies, and it corresponds to the transmission picture of the lungs.

Figure 5 (W.A. 3-11-69) shows a patient studied 2 weeks after the onset of right-sided pneumonia. Abnormalities, as demonstrated by x ray, were still present at the right apex. At the top left is a transmission

picture, anterior view. A series of 3-second exposures was taken during inhalation of ^{81m}Kr. The final picture was taken from 11 to 26 seconds during breath-holding. There is a delay in apperance of radioactivity at the right apex. There is also a discrepancy between the ventilated lung, as shown by uptake of ^{81m}Kr and the extent of the right lung base as defined by the transmission picture. On the right at the top of Fig. 5 are posterior ventilation studies taken from 9 to 17 and 17 to 31 seconds after inhalation of ^{81m}Kr. They also show reduced ventilation at the right apex and base. At the bottom right are perfusion studies taken from 9 to 30 and 31 to 61 sec, respectively, with the patient in the same position as the ventilation study. During inflow, the left apex is obscured by radioactivity in the subclavian vein, but the bottom picture shows asymmetry between the two apices, with reduced perfusion at the right apex. The lung bases are symmetrical, and it would appear that perfusion and ventilation do not correspond in the right lung base.

Figure 6 (M. F. 5-14-69) is a study of a female patient with severe obstructive disease associated with considerable sputum at the time of study. The single picture at the top is an anterior transmission picture defining aerated lung, with the patient positioned for the anterior perfusion and ventilation study. The perfusion study shows the right heart and the right and left pulmonary arteries. It shows uniform perfusion throughout the lung field defined in the transmission picture. The anterior ventilation study shows more apical filling on both the right and left, and there are multiple areas throughout both lungs where ventilation is absent or reduced. The posterior ventilation study (patient lying prone) again showed early apical filling and multiple areas of reduced ventilation in both lungs.

Note one particularly large area in the left lower zone.

Figure 7 (C. S. 5-14-69) shows perfusion and ventilation studies of a patient with mild emphysema. The chest x ray did not show any local abnormality in the right lung. There is a localized region which shows reduced activity in both the ventilation and perfusion studies.

Conclusion

Krypton-81m has favorable characteristics for imaging with the scintillation camera. It has an ideal gamma-ray energy with high photon yield, low radiation exposure, and a short physical half-life for repeat studies. The 4.7-hour half-life of the parent makes studies possible throughout one day. A method has been presented for obtaining millicurie amounts of ^{81m}Kr from a ^{81}Rb parent.

Preliminary perfusion and ventilation studies have been done on normal volunteers and a number of patients to explore the type of physiological and clinical information which can be obtained by using the dynamic and static imaging capabilities of the scintillation camera. Excellent resolution of the right heart, left and right pulmonary arteries, and upper tracheobronchial tree has been achieved. Also it has been possible to watch the changing distribution of activity as inhalation proceeds. Abnormalities have been demonstrated in patients. Krypton-81m should be particularly useful to explore the variations in distribution of activity within the lungs in various lung disorders with changing patterns of inhalation. The inability to follow washout patterns and to achieve an equilibrated condition by breathing a fixed concentration of radioactive gas, as has been done with ^{133}Xe, limits the type of study which can be performed, but how important this limitation will be remains to be investigated. Unlike ^{133}Xe, which must be washed out of the lungs for

periods of up to 15 minutes in abnormal cases, ^{81m}Kr rapidly decays within 2 to 3 minutes, so that multiple studies can be completed in a short time.

Acknowledgments

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Figure Captions

Fig. 1. Decay scheme for ^{81}Rb - ^{81m}Kr.

Fig. 2. Radioisotope generator system for ^{81m}Kr.

Fig. 3. Ventilation studies of two normal subjects.

Fig. 4. Normal distribution of ^{81m}Kr in perfusion (L) and ventilation (R) studies.

Fig. 5. Impaired ventilation (L and R top) and perfusion (R bottom) of a patient with unresolved pneumonia.

Fig. 6. Ventilation and perfusion study of a patient with severe asthma.

Fig. 7. Ventilation and perfusion studies showing poor ventilation and perfusion to the right lung.

Rubidium-81, Krypton-81m Decay

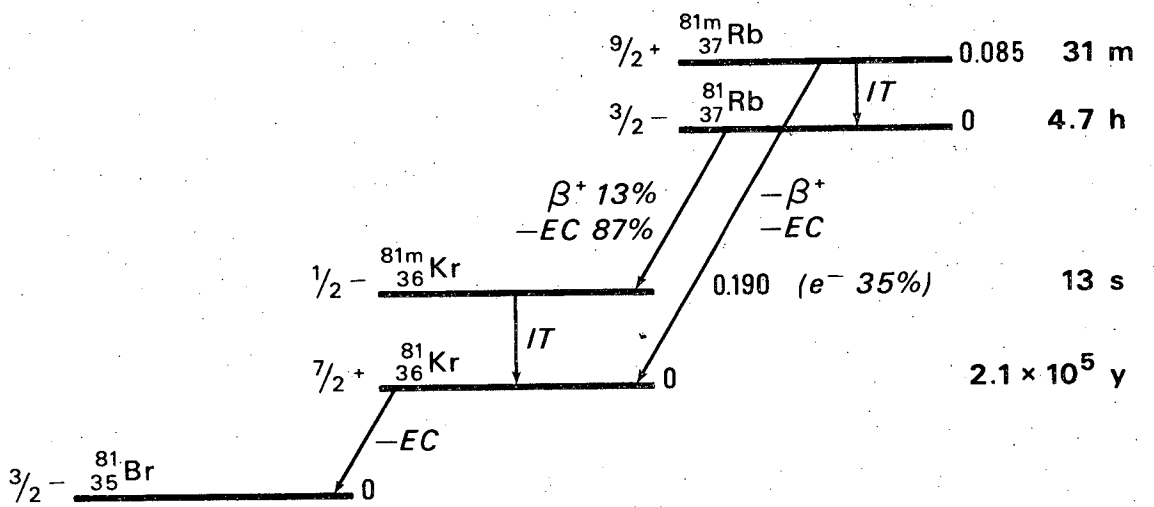

Fig. 1

DBL 696-4751

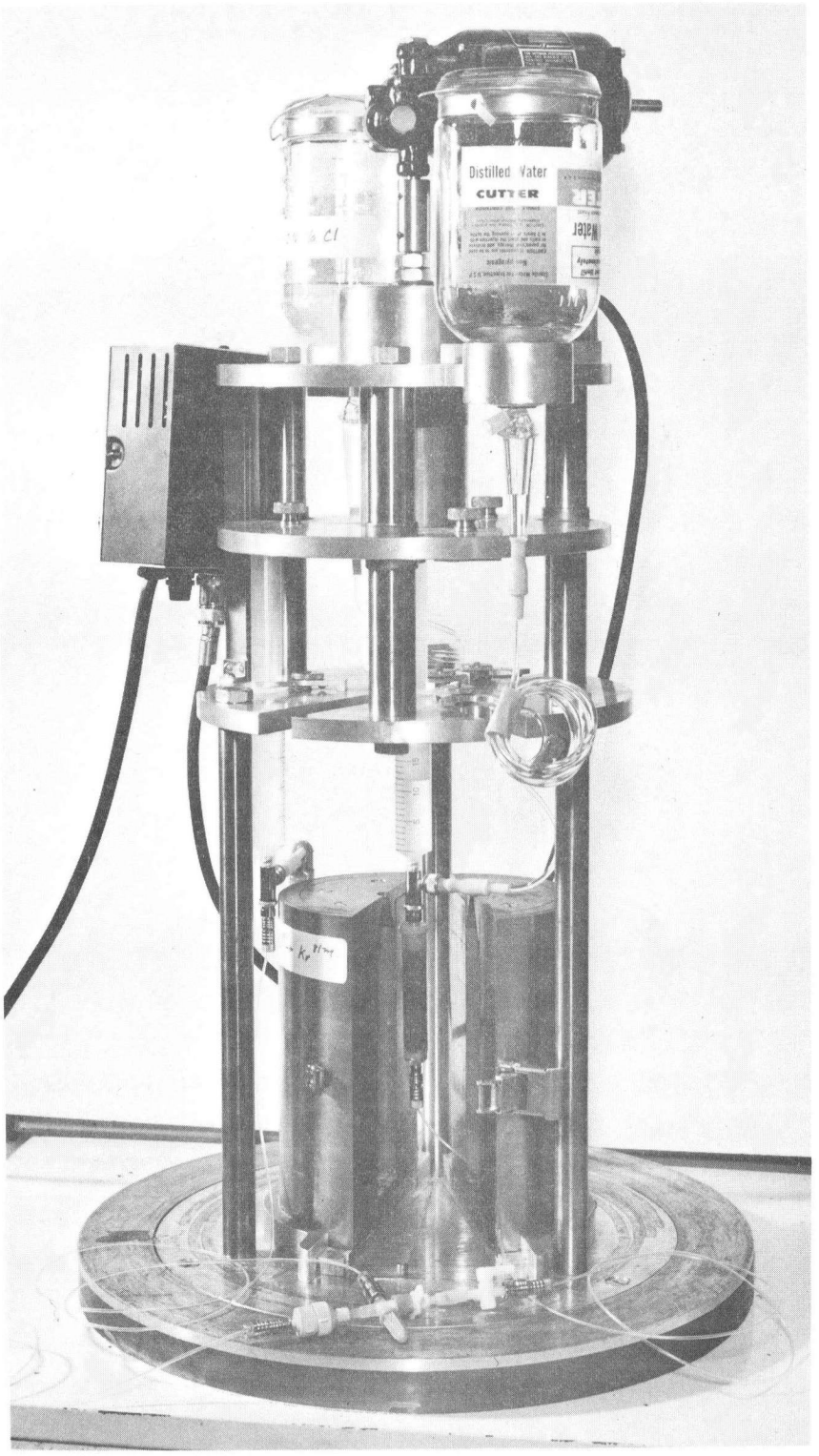

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Fig. 2

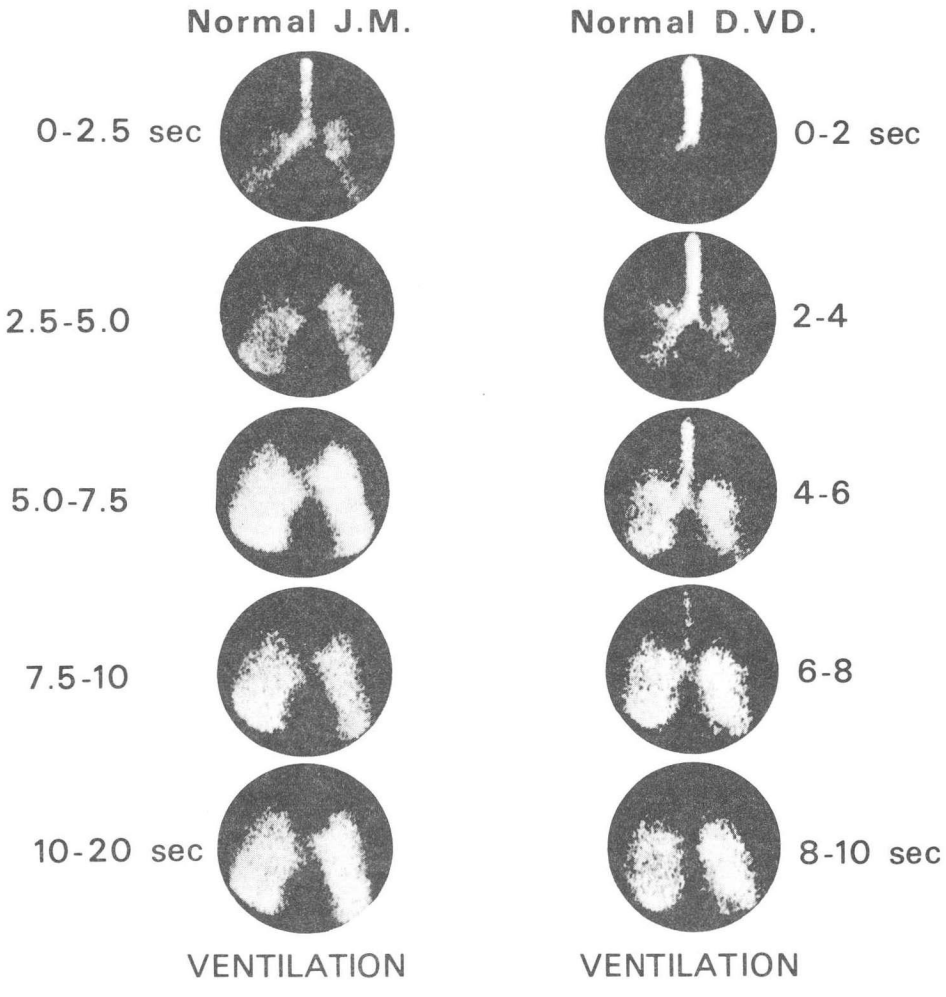

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Fig. 3

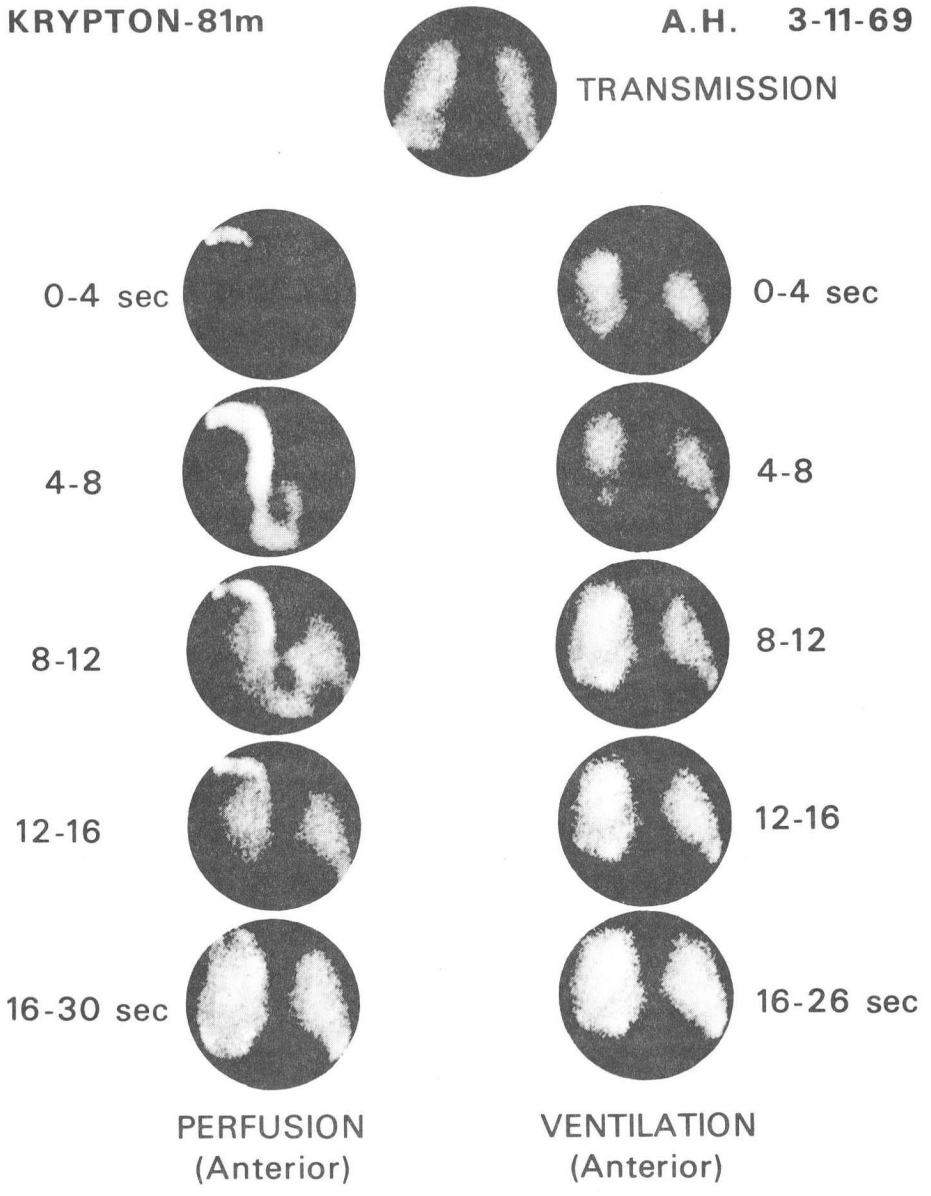

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Fig. 4

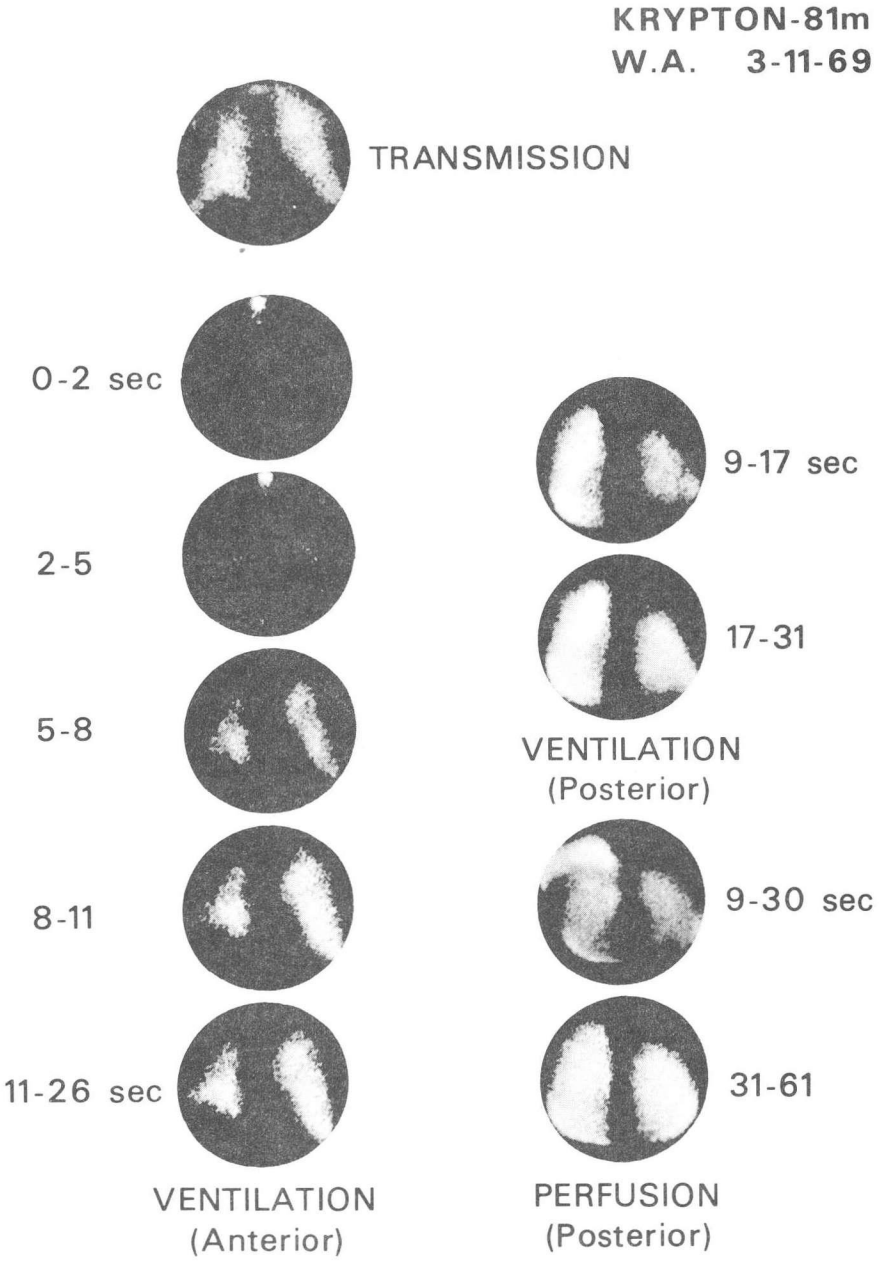
KRYPTON-81m
W.A. 3-11-69
TRANSMISSION
0-2 sec
2-5
5-8
8-11
11-26 sec
VENTILATION
(Anterior)
9-17 sec
17-31
VENTILATION
(Posterior)
9-30 sec
31-61
PERFUSION
(Posterior)
XBB 696-3854

Fig. 5

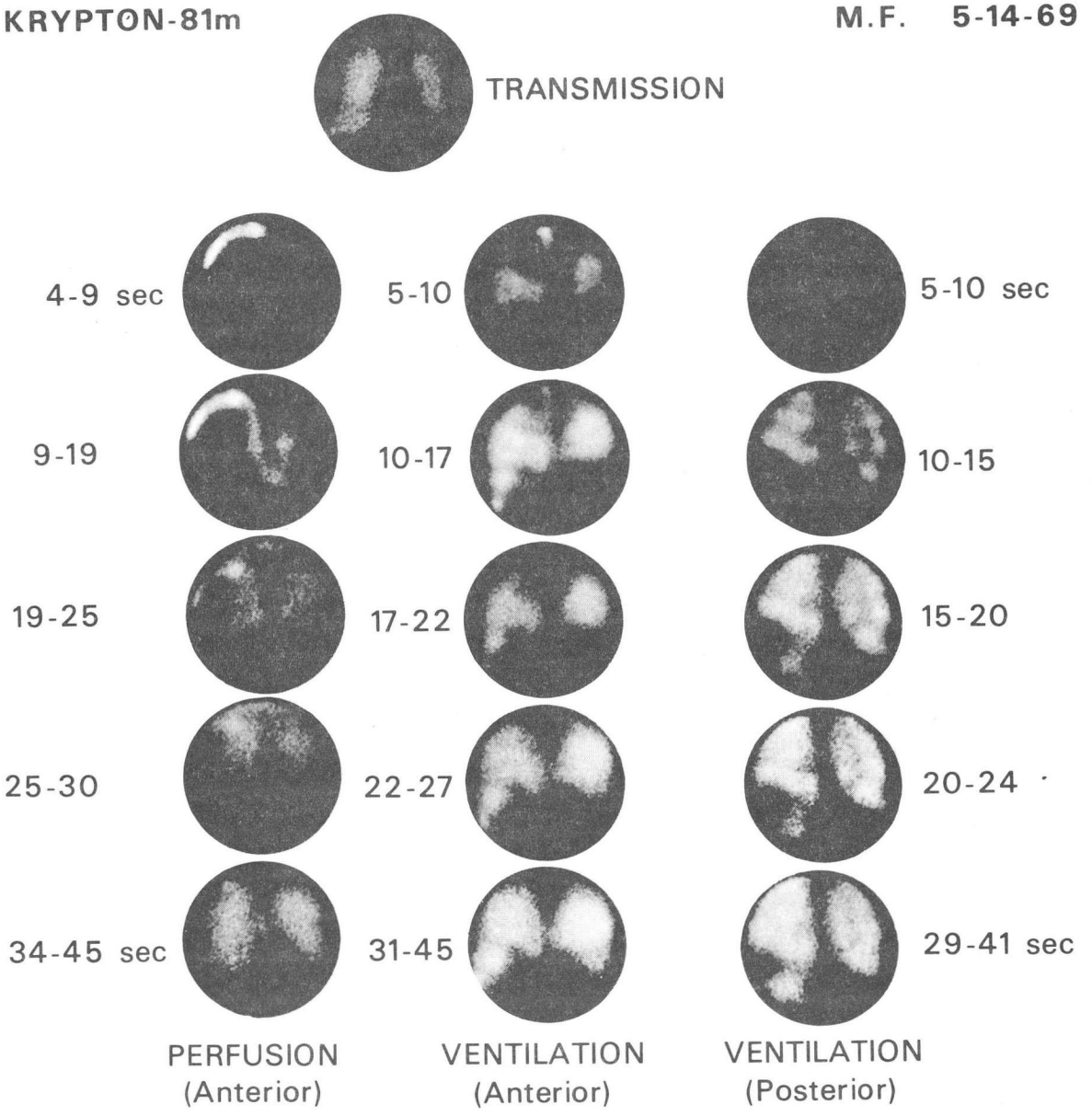
KRYPTON-81m
M.F. 5-14-69
TRANSMISSION
4-9 sec
9-19
19-25
25-30
34-45 sec
5-10
10-17
17-22
22-27
31-45
5-10 sec
10-15
15-20
20-24
29-41 sec
PERFUSION (Anterior)
VENTILATION (Anterior)
VENTILATION (Posterior)
XBB 696-3855

Fig. 6

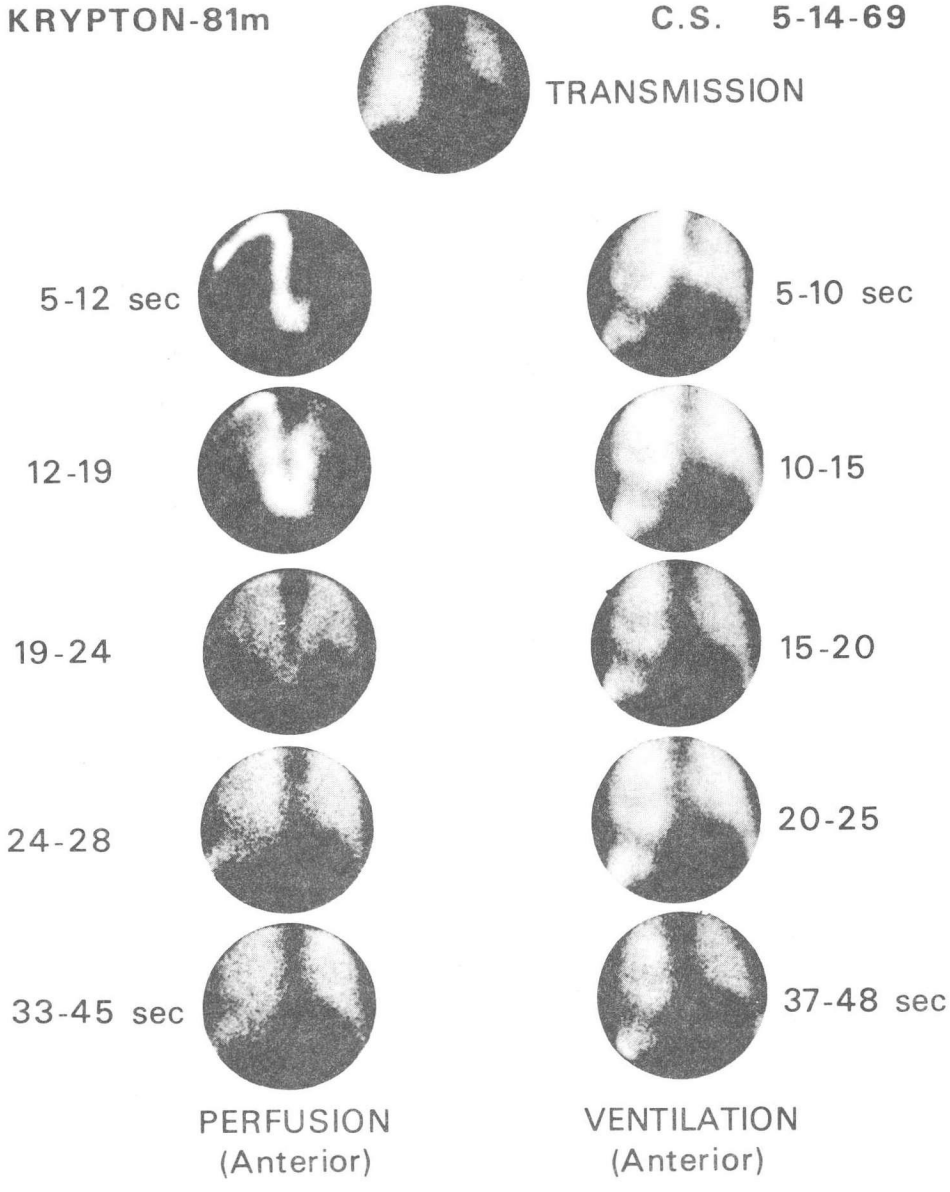

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Fig. 7.

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