PRODUCTION AND CHARACTERISTICS OF ^{125}Xe: A NEW NOBLE GAS FOR IN VIVO STUDIES

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Radionuclides of the noble gases are extensively used to assess ventilation and blood flow in clinical and investigative studies. Xenon-133 is most commonly used but is not optimal for these in vivo studies. Xenon-125 has better physical characteristics and can be produced with a cyclotron by a $^{127}I(p,3n)^{125}Xe$ reaction; this reaction results in a maximum of 25 mCi/gm/cm²/μA-hr for 31-MeV protons. Under actual production conditions, 11 mCi/μA-hr were collected. Xenon-125 decays by electron capture with a 17.2-hr half-life and contributes less radiation per dose of radioactivity than ^{133}Xe. The radiation dose to the lungs from ^{133}Xe and ^{125}Xe is 5.0 and 1.8 mrads/mCi-min, respectively. The radiation dose per usable photon for ^{125}Xe is only 0.3 of ^{133}Xe. The principal photons of ^{125}Xe, 188 keV (55%) and 243 keV (29%), are more intense and are in an energy range that is more advantageous for imaging than the 81 keV (35%) of ^{133}Xe. These physical properties of ^{125}Xe result in better spatial resolution at the same information density and with less radioactivity administered to the patient. Phantom studies showed that 12.7-, 9.5-, and 6.4-mm lead bars were resolved with ^{125}Xe using a 410-keV diverging collimator whereas only the 12.7- and 9.5-mm lead bars were resolved using ^{133}Xe and either a 410-keV or 140-keV diverging collimator.

Radioactive inert gases such as ^{133}Xe, ^{79}Kr, and ^{85}Kr are commonly used to measure ventilation of the lungs and blood flow to many organs and tissues including the brain, kidneys, liver, lungs, heart, and muscle (*1–6*). However, none of these radionuclides is ideally suited for these purposes. Newhouse (*7*) reported using reactor-produced ^{135}Xe and Hoffer (*8*) proposed the use of cyclotron-produced ^{127}Xe. These radionuclides have certain advantages but are not ideal in all respects. We would like to describe a method for producing large amounts of ^{125}Xe, which has physical properties more suitable for in vivo studies than the radionuclides of krypton and xenon used until now.

METHODS AND MATERIALS

Research irradiation procedure. The threshold for the $^{127}I(p,3n)^{125}Xe$ reaction was calculated to be 18.9 MeV using Wapstra and Gove's "Atomic Mass Table" (*9*). Six sealed, thin (1 MeV) elemental iodine targets were irradiated with 24.5–36.0 MeV protons using the Crocker Nuclear Laboratory isochronous cyclotron to determine the yield as a function of proton energy.

The ^{125}Xe yields were determined to ±10% by comparing the sealed targets to an International Atomic Energy Agency ^{22}Na calibrated standard source in a constant geometry with a 30-cc Ge (Li) detector coupled to a 1,024-channel analyzer and by correcting for variations in detector efficiency and average number of photons per disintegration. Radionuclidic contaminants of the separated xenon were determined in a similar fashion at 0, 1, and 6 days after irradiation.

Production irradiation procedure. After the yield curve was determined, oval-shaped production boats were pressed from 0.004-in. tantalum sheets; these boats had an area of 6.0-cm² and were 1.9 mm in depth. About 6 gm of $^{127}I_2$ were melted into the boat and sealed with a 0.002-in. tantalum foil and epoxy. The target was irradiated with a defocused, 5-μA proton beam swept across the target to prevent overheating. Thirty-seven MeV protons were used since

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the protons lose 10 MeV in the target so that the yield was averaged over a 37–27-MeV proton energy range.

After the irradiation, the target was placed into a sublimation flask attached to a closed circulating system to separate the xenon from the iodine (Fig. 1). The target was heated with a radiofrequency heater opening the target and vaporizing the iodine. The sublimation flask was then cooled to −20°C to contain the iodine and the xenon was collected in a trap cooled with liquid nitrogen. The collecting trap was monitored and circulation was stopped after the radioactivity in the trap reached a plateau.

Studies of resolution and photon flux. The spatial resolution and photon flux of ^{125}Xe and ^{133}Xe were evaluated using a Searle Radiographics Pho/Gamma III HP scintillation camera. The photon flux of ^{125}Xe and ^{133}Xe was compared by measuring the length of time required to obtain 500,000 counts using equal amounts of each radioisotope. Spatial resolution was evaluated by taking scintillation photographs of a "bar phantom," which consisted of 12.7-mm, 9.5-mm, 6.4-mm, and 4.7-mm lead bars with spacings between the bars equal to the width of the respective bar. Scintillation photographs of the bar phantom were obtained without a collimator to test the camera's intrinsic resolution with ^{125}Xe and ^{133}Xe.

Resolution studies were performed with collimators to simulate clinical situations. The bar phantom was placed between the collimator and a sheet source containing 10 mCi of either ^{125}Xe or ^{133}Xe. Scintillation photographs reflecting ^{133}Xe resolution were recorded using the 410-keV or 140-keV diverging collimators and the 81-keV photopeak. Scintillation photographs reflecting ^{125}Xe resolution were recorded with the 410-keV diverging collimator and either the 188-keV photopeak or a combination of the 188- and 243-keV photopeaks with 20% windows around all photopeaks.

Clinical model. A clinical model was used to evaluate different radionuclides for ventilation studies. This model was used to compare the absorbed radiation dose per usable photon and the absorbed dose to the lungs from radioactivity in the lungs. The fraction of usable photons was calculated considering the photon yield of the radionuclide, the tissue attenuation of the photons, and the calculated gross photopeak absorption for a ½-in. scintillation camera (*10*). We assumed that ^{133}Xe and each of the other radionuclides were used with a 140-keV and a 410-keV diverging collimator, respectively. The ratio of the collimators' efficiencies was calculated by dividing the counting rate from a sheet source of ^{133}Xe with the 140-keV collimator on a scintillation camera by the counting rate with ^{133}Xe and the 410-keV collimator. The tissue attenuation was calculated using the mass attenuation coefficient of water at each photon's energy and assuming the photons were attenuated by 5 cm of lung tissue and 5 cm of soft tissue with respective densities of 0.3 and 1.0 gm/cm^3.

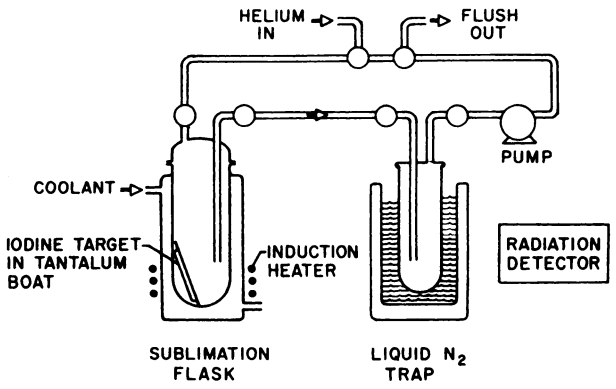

FIG. 1. Diagram of system for collecting xenon.

The absorbed radiation dose to the lungs from radioactivity in the lungs was calculated using the techniques described in *Diagnostic Nuclear Medicine* (*11*) and taking the absorbed fractions from MIRD (*12*). The physical decay information was taken from Geiger (*13*) and the *Table of Isotopes* (*14*). In these calculations, instantaneous uptake and clearance of the radionuclide were assumed. The absorbed dose relative to that from ^{133}Xe was calculated by:

$$RD = \frac{I_{81}\,\delta_{81}\,\alpha_{81}}{AD(133)} \times \frac{\epsilon_{140}}{\epsilon_{410}} \times \frac{AD(X)}{\sum_{1} I_{\gamma_1}\,\delta_{\gamma_1}\,\alpha_{\gamma_1}}$$

where RD is the absorbed dose relative to ^{133}Xe; I_γ is the intensity of photons of energy γ (percent per disintegration); δ_γ is the detector efficiency at energy γ; α_γ is the fraction of photons of energy γ reaching the collimator; $\epsilon_{140}/\epsilon_{410}$ is the ratio of the efficiencies of the 140-keV and 410-keV collimators, 1.85; AD(X) is the absorbed dose to the lungs per millicurie-minute from radionuclide X; AD(133) is the absorbed dose to the lungs per millicurie-minute from ^{133}Xe; $\sum_{1} I_{\gamma_1}\,\delta_{\gamma_1}\,\alpha_{\gamma_1}$ is the sum of the corrected photon intensity to be used in the study.

RESULTS

The absorbed radiation dose to the lungs from radioactivity in the lungs is lowest per millicurie for ^{122}Xe, ^{125}Xe, and ^{127}Xe (Table 1). Table 2 compares the usable photon yields of some of the xenon radioisotopes with 100% selected as 3.7×10^7 photons/sec. Xenon-125 and ^{127}Xe have usable photon yields of 23% and 27%, respectively, which is more than twice the yield of ^{133}Xe. The relative doses

TABLE 1. PHYSICAL AND BIOLOGIC CHARACTERISTICS OF RADIONUCLIDES OF XENON AND KRYPTON

Radionuclide	Photon energy (keV)	Intensity (No. per disintegration)	$T_{1/2}$	Disintegration mode	Radiation dose (Lungs ← lungs) $\left(\frac{mr}{mCi \times min}\right)$	Relative absorbed dose
^{122}Xe	350	0.077	19 hr	EC*	0.6	2.0
	149	0.027				1.1†
	417	0.019				
^{123}Xe	149	0.49	2.1 hr			1.5
	178	0.15		EC	6.4	1.1†
	329	0.09				
^{125}Xe	188	0.55	17.2 hr	EC	1.8	0.4
	243	0.29				0.3†
^{127}Xe	203	0.65	36.4 days	EC	1.8	0.4
	172	0.22				0.3†
	375	0.20				
^{129m}Xe	196	0.06	8.0 days	IT‡	6.5	12.8
^{131m}Xe	164	0.02	11.8 days	IT	5.7	30.5
^{133}Xe	81	0.35	5.3 days	β^-	5.0	1.0
^{135}Xe	250	0.92	9.2 hr	β^-	11.9	2.4
^{79}Kr	511	0.15				
	606	0.10	34.9 hr	EC	3.4	9.8
	398	0.09		β^+		6.3†
	261	0.07				
^{85}Kr	514	0.004	10.8 yr	β^-	8.7	108.4
^{85m}Kr	150	0.74	4.4 hr	β^-	12.3	1.9
	305	0.16				

Xenon radioisotopes with mass numbers from 118 to 121 and 137 to 144 have half-lives of 17 min or less.
Radionuclides ^{124}Xe, ^{126}Xe, ^{128}Xe, ^{130}Xe, ^{132}Xe, ^{134}Xe, and ^{136}Xe are stable.
* EC, electron capture.
† Combination relative dose using two best photons.
‡ IT, isomeric transition.

that take into account the usable photon yields and the absorbed dose to the lungs are given in Table 1. The clinical model showed that ^{125}Xe and ^{127}Xe have the lowest relative dose per usable photon; this is more than three times lower than ^{133}Xe. All other radionuclides listed in Table 1 have relative absorbed doses of one or more.

The thin target yield of ^{125}Xe as a function of proton energy reached a maximum of 25 mCi/gm/cm^2/μA-hr for 31-MeV protons (Fig. 2). The full width at half maximum for the radioactive yield curve was approximately 12 MeV. The final yield in the collection trap after the chemical separation was 11 mCi/μA-hr under the conditions given for production irradiations. The only radioactive contaminant other than the ^{125}I decay product in the collection trap was ^{127}Xe, which was less than 0.5% of the ^{125}Xe radioactivity at 1 hr after the irradiation.

The intrinsic resolution of the scintillation camera was better with ^{125}Xe than with ^{133}Xe (Fig. 3A). The 4.7-mm bars of the bar phantom were readily distinguished with either the 188-keV or the 243-keV photopeak of ^{125}Xe whereas the 6.4-mm bars were barely resolved with the 81-keV photopeak of ^{133}Xe. Resolution with the 410-keV diverging collimator was also better with ^{125}Xe. The 6.4-mm bars were clearly resolved using either the 188-keV or a combination of the 188- and 243-keV photopeaks

TABLE 2. PERCENT OF USABLE PHOTONS

Radionuclide	E_γ (keV)	I_γ (%)	Transmission (%)	Detector efficiency (%)	Percent usable photons (%)
^{125}Xe	149	49	38	92	17
	178	15	40	82	5
					22
^{125}Xe	188	55	40	78	17
	243	29	44	50	6
					23
^{127}Xe	203	65	42	70	19
	172	22	40	86	8
					27
^{133}Xe	81	35	29	100	10
^{135}Xe	250	93	44	47	19

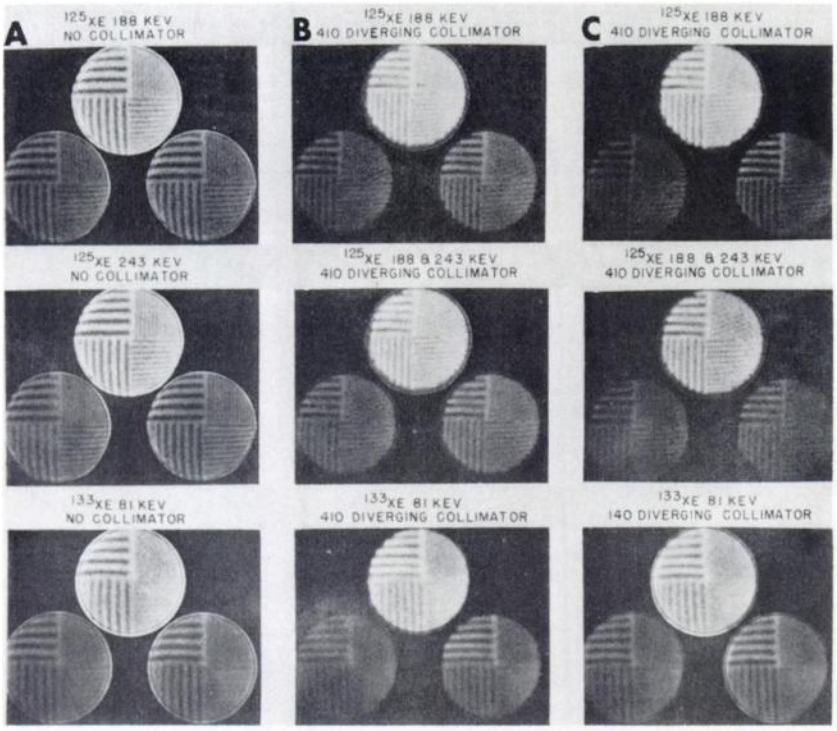

FIG. 2. (A) Intrinsic electronic resolution of scintillation camera for ^{125}Xe and ^{133}Xe evaluated with bar phantom; 12.7-, 9.5-, 6.4-, and 4.7-mm bars can be resolved with ^{125}Xe whereas 4.7-mm bar cannot be resolved with ^{133}Xe. (B) 410-keV diverging collimator resolution of the scintillation camera for ^{125}Xe and ^{133}Xe evaluated with bar phantom; 6.4-mm bar can be resolved with ^{125}Xe but not with ^{133}Xe. (C) 140-keV diverging collimator does not make it possible to resolve 6.4-mm bar with ^{133}Xe.

whereas only the 9.5-mm bars could be resolved with ^{133}Xe (Fig. 3B). Resolution with ^{133}Xe was not improved by a 140-keV diverging collimator (Fig. 3C).

The usable photon flux from 10 mCi of ^{125}Xe was higher than from an equal amount of ^{133}Xe. With the scintillation camera and the 410-keV diverging collimator, the 188-keV and 243-keV photopeaks yielded 2,300 and 1,400 counts/sec, respectively, while ^{133}Xe gave 1,670 counts/sec in the 81-keV photopeak. The more efficient 140-keV diverging collimator gave 3,100 counts/sec with ^{133}Xe. This was less than the combined 188–243 photopeaks of ^{125}Xe, which gave 3,700 counts/sec with the 410-keV diverging collimator.

DISCUSSION

The physical properties of ^{125}Xe make it better suited for in vivo imaging with the scintillation camera than other radionuclides of the inert gases. Xenon-125 and ^{127}Xe have the lowest relative absorbed radiation dose to the lungs per usable photon because of their good photon yields and low absorbed radiation dose from electron capture decay. By using a more efficient medium-energy collimator for ^{125}Xe or ^{127}Xe their relative dose could be further reduced.

Xenon-125 is preferable to ^{127}Xe, proposed by Hoffer (*8*), because ^{125}Xe is less expensive to produce. Theoretical calculations for ^{127}I(p,xn)Xe reactions show that the yield of ^{125}Xe is ten times greater per atom than ^{127}Xe (*15*). Furthermore, the ratio of the half-lives, 36.4 days to 17.2 hr, is about 50 so that an equal number of atoms of ^{125}Xe will give about 50 times more radioactivity than ^{127}Xe. Therefore, the ^{125}Xe yield should be 500 times greater per millicurie than ^{127}Xe. Xenon-125 should cost between $0.50 and $1.00 per millicurie to produce. This cost could be substantially reduced by irradiating two ^{127}I targets in tandem to produce ^{123}I by the ^{127}I(p,5n) ^{123}Xe 2.1 hr/E.C. → ^{123}I reaction (*16*) and ^{125}Xe by the ^{127}I(p,3n)^{125}Xe reaction. We are presently pursuing this possibility.

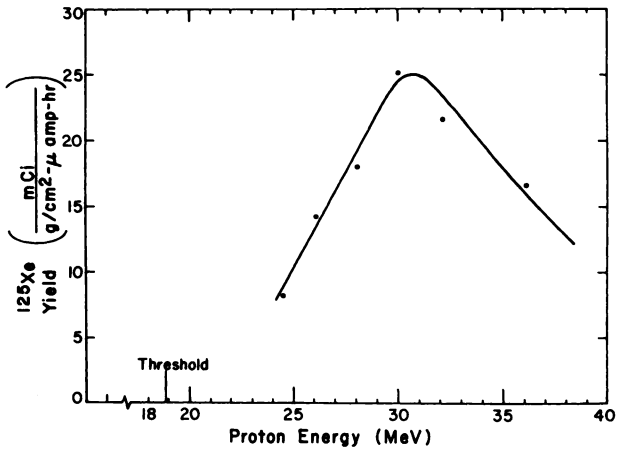

FIG. 3. Research irradiations reveal maximum yield of ^{125}Xe of 25 mCi/gm/cm^2/μA-hr at proton energy of 31 MeV; full width at half maximum of curve of radioactive yield extends from 25.5 to 37.5 MeV.

The 188-keV and 243-keV photons of ^{125}Xe may be accepted together with a wide-energy window or separately with two narrow-energy windows (*17*). Both photopeaks provide a total of 0.84 photons per disintegration as compared with 0.35 for the 81-keV photons of ^{133}Xe. Using the same collimation and a combination of the 188-and 243-keV photopeaks, ^{125}Xe provided more than twice as many counts per second as ^{133}Xe. When using the more efficient 140-keV diverging collimator for ^{133}Xe, ^{125}Xe gave about 20% more photons per millicurie than ^{133}Xe. However, this method of comparison takes into account the reduced detector efficiency for ^{125}Xe but not the increased attenuation of the 81-keV photons by soft tissue and bone since little absorbing material was present in the photon flux studies (Table 2). The usable photon flux of ^{125}Xe can be increased with the use of a medium-energy diverging collimator.

The photons of ^{125}Xe have an energy that is more advantageous for imaging with the scintillation camera than the 81-keV photons of ^{133}Xe. Improved spatial resolution with ^{125}Xe was demonstrated (Fig. 2). These scintillation photographs were recorded without scattering material, which would reduce the resolution of ^{133}Xe more than the resolution of ^{125}Xe.

Xenon-125 decays to ^{125}I and after two half-lives (34 hr) less than 1% of the original radioactivity will be ^{125}I, which adheres to the walls of the container. Thus, the ^{125}I contaminant is not available if the ^{125}Xe is used in its gaseous form or placed in solution in a secondary container. If the patient rebreathes 10 mCi of ^{125}Xe for 5 min and there is no subsequent substantial retention, then about 0.4 μCi of ^{125}I would be produced in the lungs. This can result in a few millirads to the thyroid unless it is blocked.

Xenon-135, proposed by Newhouse (*7*), has the advantage of intense 250-keV photons (92%), but has the disadvantages of a short physical half-life, (9.2 hr) and positron decay. The relative radiation dose of ^{135}Xe is about eight times that of ^{125}Xe.

Xenon-129m and ^{131m}Xe have photon yields that are too low in intensity to be used in in vivo clinical studies.

Thus, it would appear that ^{125}Xe is superior to other radionuclides of the noble gases for in vivo clinical studies although the moderately short physical half-life and ^{125}I contaminant represents some inconvenience.

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