MIRD DOSE ESTIMATE REPORT NO. 9

Estimates of Radiation Absorbed Doses from Radioxenons in Lung Imaging

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J Nucl Med 21: 459–465, 1980

RADIOPHARMACEUTICAL

The principal xenon radioisotopes used in lung imaging are xenon-127 and xenon-133, which are available as the elemental gas or in a sterile saline solution. Other radioxenons, Xe-129m and Xe-131m, may be contaminants of Xe-127, but because of their shorter half-lives their relative contamination decreases with time. The radiation dose for each of these isotopes of xenon is calculated separately.

NUCLEAR DATA

Xenon-127 decays to I-127 by electron capture, with a half-life of 36.4 days. Xenon-133 decays to Cs-133 by β^-, with a half-life of 5.31 days. Xenon-129m and xenon-131m decay by isomeric transition with half-lives of 8.89 and 11.8 days, respectively. Decay data and radiation dose constants for those isotopes are given in Table 1.

BIOLOGIC DATA

The human uptake and retention functions for radioxenon are based on data supplied by the authors and supplemented by published data (*3–5*). These are listed in Table 2. The whole-body data show five identifiable exponential components, suggesting the simplified six-compartment spirometer-lung-tissue model shown in Fig. 1. The parameters appearing in the model will vary according to the procedure used for administering the radiopharmaceutical.

PROCEDURES

Ventilation study (Fig. 2). For the purpose of these calculations of radiation absorbed dose a typical ventilation study is considered to be performed as follows. The patient breathes through a mouthpiece or mask connected to a spirometer. The average volume of the spirometer is maintained at a constant level by replenishment of absorbed carbon dioxide with oxygen. Initially, 100% of the administered radioxenon is in the spirometer. The patient rebreathes the mixture of radioxenon and air from the spirometer for 5 min, at which time the concentration of radioxenon (mCi/l) in the patient's lung spaces is approximately the same as that in the spirometer. Five minutes is not long enough for the xenon to reach equilibrium concentration in the patient's other tissues, which would require up to 30 hr of rebreathing (*3*).

After 5 min of rebreathing from the spirometer, the patient breathes room air. The xenon in the lungs and other body tissues is eliminated from the body by exhalation. This is called the washout phase of the study.

Perfusion study. The radioxenon perfusion study is performed by the i.v. administration of a saline solution containing radioxenon; this is given during a breathhold at maximum inspiration, which is maintained for 0.5 min, after which the patient exhales and breathes room air. In the dose calculations it is assumed that 100% of the injected activity is in the lung space during the breathhold period.

Perfusion-Ventilation Study (Fig. 3). An alternative perfusion study starts as above, with radioxenon given i.v. during a breathhold at maximum lung capacity. This is maintained for 0.5 min, but the patient then rebreathes from a spirometer for 5 min, equilibrating the concentration of xenon in the lungs with that in the spirometer. Following this the patient breathes room air, washing out the xenon. This procedure is used clinically because in some conditions, particularly in pulmonary embolism, the perfusion and equilibrium activity distribution patterns are different. For these radiation dose calculations,

Received Oct. 9, 1979; accepted Nov. 26, 1979.

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TABLE 1. NUCLEAR DATA*

Radionuclide	Xe-127		Xe-129m		Xe-131m		Xe-133	
Physical half life (days)	36.4		8.89		11.8		5.31	
Decay constant	0.000793 hr^{-1}		0.00325 hr^{-1}		0.00245 hr^{-1}		0.00544 hr^{-1}	
Mode of decay	electron capture		isomeric transition		isomeric transition		beta minus	
Mean energy emitted per unit cumulated activity, $\Sigma\Delta i$, for nonpenetrating radiation (g-rad/μCi-hr)	0.0713		0.3937		0.3098		0.2928	
Principal Photons	E_i(MeV)	n_i	E_i(MeV)	n_i	E_i(MeV)	n_i	E_i(MeV)	n_i
	0.0291†	0.8820	0.0304†	1.1798	0.0304†	0.4989	0.0316†	0.4735
	0.0576	0.0137	0.0396	0.1026	0.164	0.0195	0.0809	0.3603
	0.1452	0.0413	0.1966	0.0580				
	0.1721	0.2504						
	0.2028	0.6756						
	0.3749	0.1797						

* For complete compilations of nuclear data the reader is referred to Refs. *1* and *2*. Table 1 lists only photons with mean yield per nuclear transformation >0.01; photons of energy <0.0115 are considered nonpenetrating; E_i is photon energy; n_i is mean number of photons per nuclear transformation.

† Weighted mean energy of K x-rays.

however, uniform distribution is assumed for both phases.

Single-breath ventilation study. A bolus of radioxenon gas may be introduced into the airway at functional residual capacity, and the patient then inhales to maximum lung capacity. (Here 100% of the administered activity is in the lung space at full inspiration.) After breathhold for 0.5 min, the subject rebreathes from a spirometer for 5 min, then washes out with room air as described above. Alternatively, the washout phase can follow the breathhold phase directly. The calculations of radiation absorbed dose for these methods are nearly identical with those used for the perfusion or the perfusion-ventilation studies.

Absorbed dose calculations. The radiation absorbed dose estimates are calculated by the formula

$$\bar{D}(k) = \sum_h \tilde{A}_h S(k \leftarrow h),$$

which is based on Eq. 6 in MIRD Pamphlet No. 1, revised (*6*).

Except for Xe-129m, the required S values are available in MIRD Pamphlet 11 (*7*). The S values for Xe-129m have been provided for this report (M. Ford, personal communication). The physical half-lives of all the radioxenons under consideration are more than ten times the biological half-times. Therefore, the physical half-lives have a relatively small effect in these calculations (Table 3).

The masses of source and target organs used in this

TABLE 2. BIOLOGIC PARAMETERS OF DISTRIBUTION OF XENON IN THE BODY AFTER INHALATION FOR 5 MIN*

Compartment (j)	Biological disappearance half-time (T_j)	Biological disappearance constant λ_j(hr^{-1})	Fractional distribution function (α_j)
1	21.7 sec	115	0.782
2	3.1 min	13.4	0.079
3	24.0 min	1.73	0.068
4	2.7 hr	0.257	0.047
5	10.5 hr	0.066	0.024

* Derived from data in Ref. *3* for a 10-liter spirometer and normal subjects. The fractional distribution at equilibrium was calculated from the washout rates assuming washin and washout rates to be identical. From these values the fractional distribution after 5 min of washin was calculated. Compartment (j) − 1 refers to lung space (L).

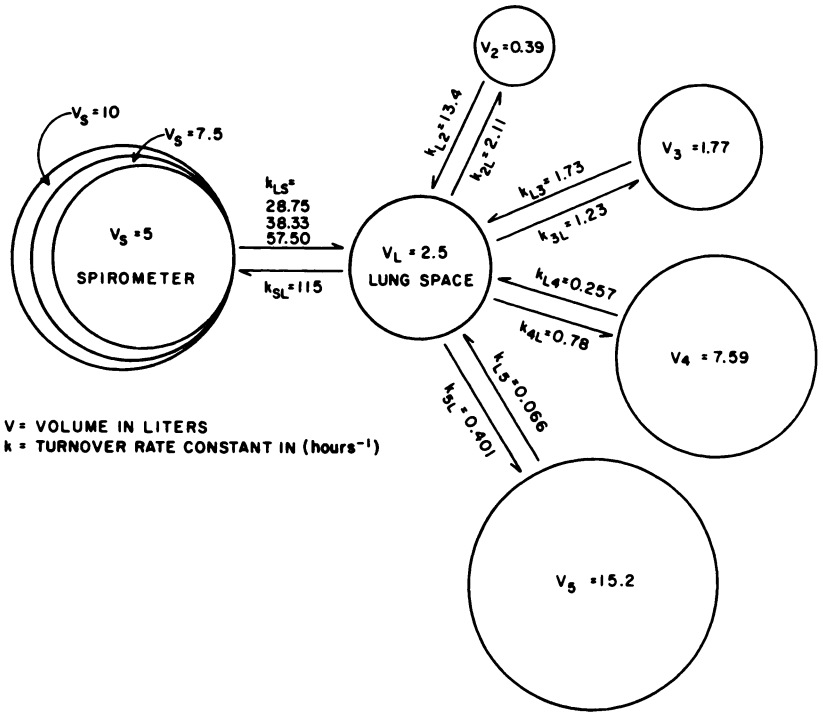

FIG. 1. Model used for radioxenon dose estimates.

dose estimate are listed in Table 4. For each of the source organs, cumulated activity, $\tilde{A}_h$, is obtained by integrating the xenon retention equation over time.

For the studies involving rebreathing, the spirometer and the fast-turnover compartment in the lung are considered to be an isolated two-compartment system, i.e., the effects of the other compartments on the retention curve of the fast lung compartment, indicated by { } in the following equations, are suppressed. However, in calculating the activity in the tissue compartments, exchange with the fast lung compartment is assumed.

The model is described by the following system of linear differential equations (see Appendix for definition of symbols).

Breathhold.

$$\frac{dA_L}{dt} = 0 \qquad (1)$$

Approach to equilibrium (rebreathing).

$$\frac{dA_S}{dt} = -k_{LS}A_S + k_{SL}A_L \qquad (2)$$

$$\frac{dA_L}{dt} = k_{LS}A_S - k_{SL}A_L + \left\{\sum_{j=2}^{5}(k_{Lj}A_j - k_{jL}A_L)\right\} \qquad (3)$$

Washout.

$$\frac{dA_L}{dt} = -k_{OL}A_L + \left\{\sum_{j=2}^{5}(k_{Lj}A_j - k_{jL}A_L)\right\} \qquad (4)$$

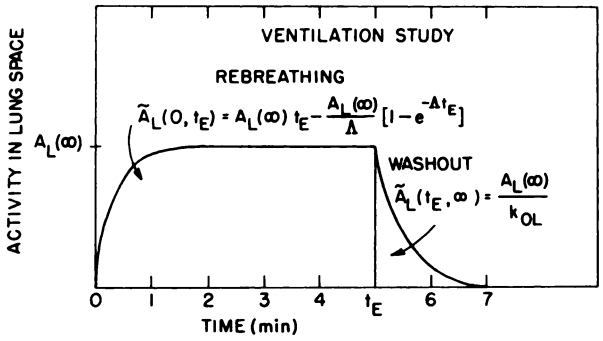

FIG. 2. Time course of radioactivity in lung space during radioxenon ventilation study.

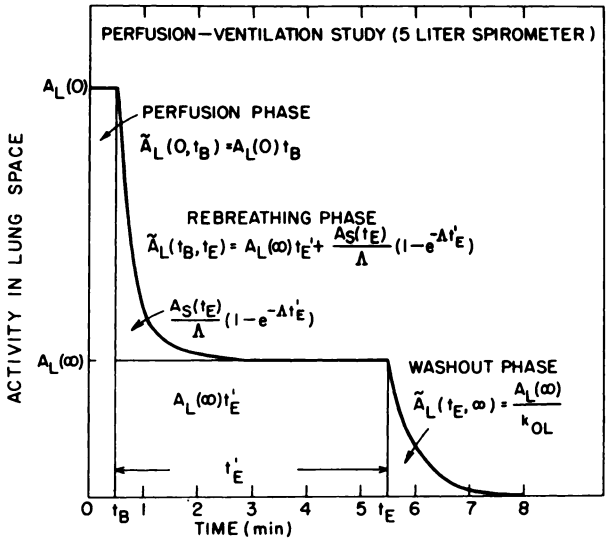

FIG. 3. Time course of radioactivity in lung space during a perfusion-ventilation study using a 5-liter spirometer.

TABLE 3. RESIDENCE TIMES, τ, FOR XENON-127 (HOURS)*

Ventilation study

V_S (liters)	Compartment 1	2	3	4	5
5	0.02750	0.00433	0.01960	0.08370	0.166
7.5	0.02070	0.00326	0.01470	0.01290	0.125
10	0.01660	0.00261	0.01150	0.05030	0.100

Perfusion ($V_S = \infty$) and perfusion-ventilation studies (V_S = 5, 7, 7.5, and 10 liters)*

V_S (liters)	Compartment 1	2	3	4	5
5	0.0402	0.00633	0.0287	0.122	0.244
7.5	0.0344	0.00541	0.0245	0.105	0.207
10	0.0308	0.00486	0.0220	0.0938	0.187
∞	0.0168	0.00264	0.0120	0.0510	0.101

* Values given are for Xe-127. Compartment 4 may be lower by up to 2% and compartment 5 by up to 7% for Xe-133, with smaller variations for Xe-129m and Xe-131m.

All phases (other tissues).

$$\frac{dA_j}{dt} = k_{jL}A_L - k_{Lj}A_j \qquad (j = 2,5) \qquad (5)$$

Expressions for A in the various compartments are obtained as solutions of the above system of differential equations, and the integrals of these expressions yield $\tilde{A}$.

Summary of $\tilde{A}$ equations. *Ventilation study.*

1. Lung Space:
   Rebreathing

$$\tilde{A}_L(0,t_E) = A_L(\infty)t_E - \frac{A_L(\infty)}{\Lambda}[1 - e^{-\Lambda t_E}] \qquad (6)$$

   Washout

$$\tilde{A}_L(t_E,\infty) = \frac{A_L(\infty)}{k_{OL}} \qquad (7)$$

TABLE 4. MASSES OF SOURCE AND TARGET ORGANS (7)

Organ	Mass (g)
Lungs	999.2*
Whole body	69880
Fat	12500†
Red marrow	1500
Testes	37.08
Ovaries	8.27

* Volume of lungs is 3378 cm^3. The mean air space is 2500 cm^3 (8).

† Does not include yellow marrow and interstitial adipose tissue.

2. Tissues:
   Rebreathing

$$\tilde{A}_j(0,t_E) = k_{jL}A_L(\infty)\left[C_1 t_E - \frac{C_2}{\Lambda}(1 - e^{-\Lambda t_E}) + \frac{C_3}{k_{Lj}}(1 - e^{-k_{Lj}t_E})\right] \qquad (8)$$

   Washout

$$\tilde{A}(t_E,\infty) = \frac{A_j(\infty)}{k_{Lj}} + \frac{k_{JL}A_L(\infty)}{k_{Lj}k_{OL}} \qquad (9)$$

Perfusion study.

1. Lung space:
   Breathhold

$$\tilde{A}_L(0,t_B) = A_L(0)t_B \qquad (10)$$

   Washout

$$\tilde{A}_L(t_B,\infty) = \frac{A_L(0)}{k_{OL}} \qquad (11)$$

2. Tissues:
   Breathhold

$$\tilde{A}_j(0,T_B) = \frac{k_{jL}}{k_{Lj}}A_L(0)\left[t_B - \frac{1}{k_{Lj}} + \frac{1}{k_{Lj}}e^{-k_{Lj}t_B}\right] \qquad (12)$$

   Washout

$$\tilde{A}_i(t_B,\infty) = \frac{k_{jL}A_L(0)}{k_{Lj}k_{OL}} + \frac{A_j(t_B)}{k_{Lj}} \qquad (13)$$

Perfusion-ventilation study.

1. Lung space:
   Breathhold

$$\tilde{A}_L(0,t_B) = A_L(0)t_B \qquad (14)$$

TABLE 5. SELECTED S VALUES ABSTRACTED FROM MIRD 11, (rads/μCi-hr)

Target organ	Source organ: Lung				Whole body			
	Xe-127	Xe-129m*	Xe-131m	Xe-133	Xe-127	Xe-129m*	Xe-131	Xe-133
Lung	1.1E-04	4.14E-04	3.2E-04	3.0E-04	4.5E-06	6.8E-06	4.9E-06	5.0E-06
Red marrow	3.5E-06	1.17E-06	4.3E-07	1.1E-06	5.9E-06	7.72E-06	5.2E-06	5.8E-06
Ovaries	2.4E-07	1.25E-08	3.1E-09	1.8E-08	5.2E-06	6.81E-06	4.9E-06	5.1E-06
Testes	2.7E-08	1.14E-09	2.6E-10	9.0E-10	3.8E-06	6.46E-06	4.7E-06	4.8E-06
Total body	4.5E-06	6.80E-06	4.9E-06	5.0E-06	4.4E-06	6.70E-06	4.8E-06	5.0E-06

* Xe-129m data from M. Ford, personal communication.

Rebreathing

$$\tilde{A}_L(t_B,t_E) = A_L(\infty)t'_E + \frac{A_S(t_E)}{\Lambda}(1 - e^{-\Delta t'_E}) \quad (15)$$

Washout

$$\tilde{A}_L(t_E,\infty) = \frac{A_L(\infty)}{k_{OL}} \quad (16)$$

2. Tissues:

Breathhold

$$\tilde{A}_j(0,t_B) = \frac{k_{jL}}{k_{Lj}} A_L(0)\left[t_B - \frac{1}{k_{Lj}} + \frac{1}{k_{Lj}} e^{-k_{Lj}t_B}\right] \quad (17)$$

Rebreathing

$$\tilde{A}_j(t_B,t_E) = k_{jL}A_L(0)\left[C_4 t'_E + \frac{C_5}{\Lambda}(1 - e^{-\Lambda t'_E}) - \frac{C_6}{k_{Lj}}(1 - e^{-k_{Lj}t'_E})\right] \quad (18)$$

Washout

$$\tilde{A}_j(t_E,\infty) = \frac{A_j(t_E)}{k_{Lj}} + \frac{k_{jL}}{k_{OL}k_{Lj}} A_L(t_E) \quad (19)$$

The residence time, τ, for the different studies and for several values of spirometer volume, V_S, are given in Table 3. These are obtained by the following expressions:

for the ventilation study, $\tau = \tilde{A}_j(0,\infty)/A_S(0)$ and

for the perfusion and perfusion-ventilation studies, $\tau = \tilde{A}_j(0,\infty)/A_L(0)$.

Numerical values for k_{jL} are obtained through use of the following expression:

$$k_{jL} = \frac{\alpha_j/\alpha_1}{\frac{1}{k_{Lj}} + \frac{\Lambda}{k_{Lj}}\left(\frac{1}{k_{Lj} - \Lambda}\right)e^{-k_{Lj}t_E}} \quad (20)$$

TABLE 6. RADIATION ABSORBED DOSES (rads) PER MILLICURIE OF ADMINISTERED ACTIVITY IN THE VENTILATION STUDY*

Target organ	Spirometer volume (liters)	Xe-127	Xe-129m	Xe-131m	Xe-133
Lung	5	0.0047	0.015	0.011	0.011
	7.5	0.0036	0.011	0.0086	0.0082
	10	0.0028	0.009	0.0069	0.0065
Red marrow	5	0.0017	0.0020	0.0014	0.0015
	7.5	0.0013	0.0016	0.0010	0.0012
	10	0.0010	0.0012	0.0008	0.0009
Ovaries	5	0.0014	0.0018	0.0013	0.0013
	7.5	0.0011	0.0013	0.0010	0.0010
	10	0.0008	0.0011	0.0008	0.0008
Testes	5	0.0010	0.0017	0.0012	0.0012
	7.5	0.0008	0.0013	0.0009	0.0009
	10	0.0006	0.0010	0.0008	0.0007
Total body	5	0.0013	0.0020	0.0014	0.0014
	7.5	0.0010	0.0015	0.0011	0.0011
	10	0.0008	0.0012	0.0009	0.0009

* Administered activity is the initial activity introduced into the spirometer.

They are: $\frac{j}{2}\ \frac{k_{jL}}{2.11}\ (hr^{-1})$

3 1.23
4 0.78
5 0.40

Radiation absorbed doses. To utilize the values it is necessary to assign anatomical locations to the various components of the total-body curve. Components 1 and 2 are assumed to represent the lung space and lung tissues, respectively. In the absence of information, the other components are assigned a total-body distribution.

The absorbed-dose estimate is given in rads per millicurie of administered activity. This was obtained for each target organ by considering the lungs and total body as source organs, the former consisting of Compartments 1 and 2, and the latter of 3, 4, and 5. In each case the component compartments are regarded as being coextensive. The S values used are listed in Table 5.

Xenon and other noble gases are more soluble in lipids than in water, hence tissues with high fat content concentrate xenon more than do the other tissues. As a working hypothesis we may assume that Compartment 5, with the slowest turnover rate constant, represents fatty tissues. The measured half-life for washout from this compartment averages 10.5 hr. Therefore, during buildup in the studies under discussion, only a minimal amount of radioxenon enters into fatty tissue. If we assume that the xenon in Compartment 5 is uniformly distributed in body fat, the concentration, A/m, in the high-fat tissues will be obtained by dividing the activity, A, by the weight of the fat content of the body (12,500 g) instead of that of the total body (69,880 g) and multiplying by the fractional fat content of the organ or tissue of interest. For fractional fat contents of 50 to 100%, this procedure yields xenon concentrations in the high-fat tissues of 2.8 to 5.6 times that for the average as calculated for the total body. Because of unequal blood perfusion rates, the distribution of xenon among the fatty tissues will not in fact be uniform, and a somewhat higher ratio will be attained in organs such as the brain, adrenals, and gonads, these having relatively high blood perfusion rates. In the absence of data this effect cannot be assessed accurately.

The contribution from the 5th compartment to the total-body radiation dose from Xe-127 is about 28%. About 55% of the total-body radiation dose is from the activity in the lungs, and this will not be greatly affected by changes in local tissue xenon concentration ratios.

The listed absorbed dose estimates for the contaminants, Xe-129m and Xe-131m, must be multiplied by appropriate factors depending on the fraction of the

TABLE 7. RADIATION ABSORBED DOSES (rads) PER MILLICURIE OF ADMINISTERED ACTIVITY IN THE PERFUSION-VENTILATION OR PERFUSION-ONLY STUDIES ($V_S = \infty$)*

Target organ	Spirometer volume (liters)	Xe-127	Xe-129m	Xe-131m	Xe-133
Lung	5	0.0069	0.022	0.017	0.016
	7.5	0.0059	0.019	0.014	0.014
	10	0.0053	0.017	0.013	0.012
	∞	0.0029	0.009	0.007	0.007
Red marrow	5	0.0025	0.0030	0.0020	0.0022
	7.5	0.0021	0.0026	0.0017	0.0019
	10	0.0019	0.0023	0.0016	0.0017
	∞	0.0010	0.0012	0.0008	0.0009
Ovaries	5	0.0021	0.0026	0.0019	0.0019
	7.5	0.0018	0.0022	0.0016	0.0016
	10	0.0016	0.0020	0.0015	0.0015
	∞	0.0009	0.0011	0.0008	0.0008
Testes	5	0.0015	0.0025	0.0018	0.0018
	7.5	0.0013	0.0021	0.0016	0.0015
	10	0.0012	0.0019	0.0014	0.0014
	∞	0.0006	0.0010	0.0008	0.0008
Total body	5	0.0020	0.0029	0.0021	0.0021
	7.5	0.0017	0.0025	0.0018	0.0018
	10	0.0015	0.0022	0.0016	0.0016
	∞	0.0008	0.0012	0.0009	0.0009

* Administered activity is the activity injected into the patient's vein.

contaminant present at the time of administration of Xe-127.

Despite different assumptions, there is satisfactory agreement between previously published absorbed-dose estimates (*9–12*) and those of this report (Tables 6 and 7).

ACKNOWLEDGMENT

The work on which this publication is based was performed pursuant to Contract No. 223-75-6067 with the Public Health Service, Food and Drug Administation, DHEW.

APPENDIX

Definitions of Symbols

Symbol	Definition	Unit
$\bar{D}(k)$	Mean absorbed dose in organ k	rad*
$A_j(t)$	Activity at time t in jth organ or compartment; $A_S(t)$ = activity in spirometer; $A_L(t)$ = activity in lung spaces	μCi†
$\alpha_j(t)$	Fractional distribution function for the jth compartment	
τ_h	Average residence time in source organ h	hr
$\tilde{A}_h$	Cumulated activity in source organ h $\tilde{A}_h = \tau_h A_j(0)$ where $A_j(0)$ is the administered activity, initially in jth compartment, with j = lung or spirometer	μCi-hr
$S(k \leftarrow h)$	Mean absorbed dose in organ k per unit cumulated activity in source organ h	rad/μCi-hr
V_S	Volume of air in spirometer (or reservoir)	liters
V_L	Average volume of air in lung spaces	liters
k_{ji}	Turnover rate constant for xenon transfer into the jth compartment from the ith compartment: k_{OL} = turnover rate constant for lung to room air; k_{LS} = turnover rate constant for spirometer to lung; k_{SL} = turnover rate constant for lung spaces to spirometer	$(hr)^{-1}$
Λ	$k_{LS} + k_{SL}$	
t	time after administration of activity	hr
t_B	time at end of breathhold phase	
t_E	time at end of rebreathing (equilibration) phase	
t'_E	$t_E - t_B$	

For ventilation study:

$$A_S(\infty) = A_S(0)\frac{V_S}{V_L + V_S} = A_S(0)\frac{k_{LS}}{k_{LS} + k_{SL}}$$

= equilibrium activity in spirometer

$$A_L(\infty) = A_S(0)\frac{V_L}{V_L + V_S} = A_S(0)\frac{k_{SL}}{k_{SL} + k_{LS}}$$

= equilibrium activity in lung space

For ventilation-perfusion study:

$$A_S(\infty) = A_L(0)\frac{V_S}{V_L + V_S} = A_L(0)\frac{k_{LS}}{k_{LS} + k_{SL}}$$

= equilibrium activity in spirometer

$$A_L(\infty) = A_L(0)\frac{V_S}{V_L + V_S} = A_L(0)\frac{k_{SL}}{k_{SL} + k_{LS}}$$

= equilibrium activity in lung space

$$C_1 = \frac{1}{k_{Lj}}$$

$$C_2 = \frac{1}{k_{Lj} - \Lambda}$$

$$C_3 = \frac{\Lambda}{k_{Lj}}\left(\frac{1}{k_{Lj} - \Lambda}\right)$$

$$C_4 = \left(\frac{V_L}{V_L + V_S}\right)\cdot\left(\frac{1}{k_{Lj}}\right)$$

$$C_5 = \left(\frac{V_S}{V_L + V_S}\right)\cdot\left(\frac{1}{k_{Lj} - \Lambda}\right)$$

$$C_6 = \frac{k_{Lj} - k_{LS}}{k_{Lj}(k_{Lj} - \Lambda)}$$

* 1 rad = 1 centigray.

† 1 μCi = 3.7×10^4 becquerel.

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