Absorbed Dose Estimates for Positron Emission Tomography (PET): $C^{15}O$, ^{11}CO, and $CO^{15}O$

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Regional cerebral blood volume and blood flow may be determined using PET and $C^{15}O$, ^{11}CO, and $CO^{15}O$. Detailed estimates of radiation absorbed dose for 22 organs and the whole body are reported and compared for these gases administered by continuous or bolus inhalation and by infusion techniques.

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Positron emission tomography (PET) makes possible the in vivo regional determination of a large number of physiological parameters. The positron-emitting gases $C^{15}O$, ^{11}CO, and $CO^{15}O$ are not only easily produced in a cyclotron but have half-lives, decay schemes, and biological properties that make them particularly suitable for PET imaging. Regional cerebral blood volume (rCBV) has been measured in humans using bolus inhalation of ^{11}CO (*1–3*). The use of $C^{15}O$ administered by continuous inhalation has also been suggested for such studies (*4*). Bolus inhalations of $C^{15}O$ have been used to study lung function (*5*), but to date no rCBV studies have been reported using $C^{15}O$ administered in this way. $CO^{15}O$, inhaled continuously (*4,6*), may be used for measuring regional cerebral blood flow (rCBF). Bolus inhalations of $CO^{15}O$ have been used for cardiac and lung studies (*7–10*). Bolus injections of [^{15}O]carboxyhemoglobin (*11–13*) and $H_2{}^{15}O$ (*12,14*), equivalent to the inhalation of $C^{15}O$ and $CO^{15}O$ gases, have also been used to estimate cerebral blood volume and blood flow.

Before techniques using $C^{15}O$, ^{11}CO, and $CO^{15}O$ can become clinically useful, complete, comparative estimates of radiation absorbed dose for these gases should be considered. This paper presents detailed calculations using the most recent computational techniques to estimate radiation absorbed doses for 22 different organs from radioactivity assumed to be contained in either blood or in body water after $C^{15}O$, ^{11}CO, and $CO^{15}O$ are administered in a variety of ways.

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THEORY

Computational methods for radiation absorbed dose. The absorbed dose was estimated using the standard MIRD approach (*15–18*) and included contributions from radioactivity within the organ, separately identified organs, and the remainder of the body. The following equation explained in ORNL-5000 (*18*) was used:

$$\bar{D}_k = \sum_h [\tilde{A}_h S(r_k \leftarrow r_h) + \tilde{A}_{RB} S(r_k \leftarrow RB)] \quad (1)$$

in which the subscripts h, k, and RB are used to represent the source organ, target organ, and remainder of body; $\bar{D}$ is the average radiation absorbed dose (rad), $\tilde{A}$ is cumulated radioactivity (μCi-hr) and S is the radiation absorbed dose per unit cumulated radioactivity (g-rad/μCi-hr). The S-factor for the remainder of the body was computed as recommended by Coffey et al. (*19*).

For the brain, S-factors were computed using absorbed fraction data from the original version MIRD Pamphlet No. 5 (*20*) as this organ is not included in MIRD Pamphlet No. 11 (*17*). S-factors for the heart and heart contents were derived from specific absorbed-fraction data (*21*) and the radionuclide decay schemes and nuclear parameters (*22*). Reciprocity (*15*) was used to derive S-factors for the uterus and walls of the gastrointestinal and bladder as source organs.

Estimations of whole-body cumulated radioactivity. For bolus injection with an administered radioactivity $A_o(\mu Ci)$, the whole-body cumulated radioactivity, $\tilde{A}_{TB}(\mu Ci\text{-hr})$, was estimated as A_o/λ, where λ is the tracer's physical decay constant per hr (*23*). Biological excretion from the body would be small relative to physical decay for the short-lived PET radionuclides considered, and was neglected.

Under bolus inhalation, only a fraction, f, of the inhaled bolus may remain in the body after exhalation following breath-holding. The whole-body cumulated radioactivity was therefore computed from fA_o/λ.

The half-time of $CO^{15}O$ in alveolar gas was measured as approximately 0.32 sec (*8*). The half-time of $CO^{15}O$ in the lungs, which includes both transfer from alveolar gas to blood and the washout from blood, was measured as 3.2 sec (*24*). Hence essentially all radioactivity should remain in the body if 30-sec breath-holding is used for $CO^{15}O$ (f = 1.0). Jones et al. (*9*) note that 5-sec breath-holding ensures total diffusion of $CO^{15}O$ from blood. For ^{11}CO, f is found to be ~0.3–0.5 for bolus inhalation (*3*), but breathholding was not demanded of the subject (Dr. M. Raichle, personal communication). Alveolar transfer rates ranging from 0.08 to 0.28 per sec have been observed (*25*), with an average of ~0.13 per sec. At this rate, practically all the $C^{15}O$ or ^{11}CO in an inhaled bolus should leave the alveolar gas with 30-sec breath-holding; hence f = 1 was used. Virtually complete uptake of an 8-mCi bolus of ^{11}CO with 10–15 sec breath-holding has been observed (Dr. J. Correia and co-workers, unpublished data).

Considering physical decay as the only mode of loss of radioactivity from the body for continuous infusion or inhalation protocols with radioactivity administered at a rate of $R(\mu Ci/hr)$, the whole-body steady-state radioactivity was estimated to approach a value of R/λ (μCi).

Assuming that the uptake and retention periods were equivalent to a single exposure at the steady-state burden, the whole-body cumulated radioactivity for continuous inhalation or infusion techniques of duration $t_i(hr)$ was computed from Rt_i/λ, where Rt_i represents the effective total administered radioactivity (μCi) for continuous inhalation or infusion. (Note that this is larger than the amount present at any given time.)

Any regional or pathological variations of uptake or retention of radioactive gases in the lungs was neglected.

Estimates of distribution of radioactivity in the body (excluding lungs). For a bolus inhalation of ^{11}CO, investigators allowed 2–6 min for equilibration of radioactivity in the body (*1–3*). Virtually all ^{15}O from $CO^{15}O$ labels H_2O before leaving the capillary bed (*10*). Radioactivity was therefore assumed to distribute rapidly for bolus techniques and instantaneously for steady-state techniques.

Since CO is rapidly taken up by red blood cells and remains firmly bound to hemoglobin, the distribution of radioactivity in the body should follow that of blood. The cumulated radioactivity in a specific organ "h" for $C^{15}O$ or ^{11}CO was therefore estimated from

$$\tilde{A}_h = \frac{m_b(h)}{m_b(TB)}\tilde{A}_{TB}, \qquad (2)$$

where $m_b(h)$ and $m_b(TB)$ represent the masses of blood (g) in the organ and whole body from ICRP 23 (*26*). Differences in tissue hematocrit were neglected, which should not introduce much error except for the spleen, which concentrates red blood cells. The in vivo spleen hematocrit has been found to be ~1.8 times the venous hematocrit in dogs (*27*), hence 1.8 times the cumulated radioactivity computed using Eq. 2 was used for this organ (venous and arterial hematocrit differences were neglected). Using these data, 3.1% of the total injected radioactivity was estimated to be present in the spleen.

The $CO^{15}O$ radioactivity follows the distribution of water in the body (*8*). The cumulated radioactivity in an organ "h" for $CO^{15}O$ was therefore estimated as

$$\tilde{A}_h = \frac{m_{H_2O}(h)}{m_{H_2O}(TB)}\tilde{A}_{TB}, \qquad (3)$$

where $m_{H_2O}(h)$ and $m_{H_2O}(TB)$ represent the water contents (g) of the organ and whole body respectively, from ICRP 23 (*26*).

For $C^{15}O$ and ^{11}CO, negligible amounts of radioactivity should enter the urine and feces. With $CO^{15}O$, however, $H_2{}^{15}O$ may enter the urine and feces from blood. The cumulated radioactivity in urine following a bolus administration of $CO^{15}O$ was estimated by solving a simple compartmental model with radioactivity entering at a rate determined by the product of the urine production rate and the blood radioactivity concentration, and leaving by physical decay. The result was

$$\tilde{A}_{u,b} = \frac{\tilde{A}_b U}{\lambda V_b}. \qquad (4)$$

where $\tilde{A}_b$ and V_b represent blood cumulated radioactivity in μCi-hr and volume in ml, respectively, and u represents the urine production rate in ml/hr.

For continuous administration the urine cumulated radioactivity was estimated from

$$\tilde{A}_{u,c} = \frac{U\tilde{A}_b}{\lambda V_b}(\lambda t_i + e^{-\lambda t_i} - 1). \qquad (5)$$

which was obtained by solving the simple urine compartmental model mentioned above for steady-state conditions. For urinary production rates of 60 ml/hr (*26*), urinary cumulated radioactivities were estimated to be <30% of total-bladder cumulated radioactivity.

TABLE 1. CUMULATED RADIOACTIVITY FOR ^{11}CO, $C^{15}O$, and $H_2{}^{15}O$ INFUSION TECHNIQUES (μCi-hr/mCi ADMINISTERED)

	^{11}CO	$C^{15}O$	$CO^{15}O$ ($H_2{}^{15}O$)
ADRENALS	0.31	0.031	0.0093
BLADDER (WALL)	0.19	0.019	0.034
BLADDER (URINE)	0.	0.	0.017
BONE (CORTICAL)	19.	1.9	0.70
BONE (TRABECULAR)	4.7	0.47	0.27
BRAIN	2.9	0.29	0.34
FAT	21.	2.1	2.2
STOMACH	0.57	0.057	0.13
SMALL INTESTINE	59.	5.9	0.59
UPPER LARGE INTESTINE	20.	2.0	0.20
LOWER LARGE INTESTINE	15.	1.5	0.15
HEART	5.0	0.50	0.28
HEART CONTENTS	47.	4.7	0.47
KIDNEYS	6.6	0.66	0.28
LIVER	24.	2.4	1.5
MARROW	7.6	0.76	0.70
MUSCLE	66.	6.6	26.
OVARIES	0.21	0.021	0.010
PANCREAS	1.9	0.19	0.083
SKIN	6.1	0.61	1.9
SPLEEN	15.	1.5	0.16
TESTES	0.12	0.012	0.033
THYROID	0.34	0.034	0.018
UTERUS	0.76	0.076	0.074
TOTAL BODY	490.	49.	49.

The cumulated radioactivity for the heart was considered to be the sum of that in the heart walls and that in atrial and ventricular blood.

Cumulated radioactivity in the various organs used to estimate the radiation absorbed dose is summarized in Table 1 for infusion techniques. For inhalation techniques these numbers should be multiplied by the appropriate fractional uptakes. The individual organs listed account for 75–85% of the total body radioactivity.

Estimates of cumulated radioactivity in the lungs. For infusion techniques the cumulated radioactivity in the lungs is due only to the radioactivity in lung blood for $C^{15}O$ and ^{11}CO and in lung water for $H_2{}^{15}O$. Unfortunately, radioactivity in lung gas (both alveolar and nonexchanging) contributes significantly to the dose for inhalation studies.

For bolus inhalation with 30-sec breath-holding, the cumulated radioactivity in the alveolar gas of the lungs was computed from

$$\tilde{A}_a = \frac{A_o f_a (1 - e^{-0.5(\lambda+\lambda_j)})}{0.5(\lambda + \lambda_j)}, \quad (6)$$

where λ and λ_j represent constants in per hour for physical decay and biological excretion, and f_a represents the fraction of the bolus gas that is in the alveoli [with a volume equal to the functional residual capacity and one-half the tidal volume, from ICRP 23 (*26*)]. For $C^{15}O$, ^{11}CO, and $CO^{15}O$, biological half-times of 3.5 sec were used for the lung; equal lung and whole-body blood radioactivity concentrations were assumed. A dead space of 150 ml (*26*), containing $(1 - f_a)A_o$ for the duration of breath-holding, was included in the cumulated radioactivity estimate.

For estimates of the pulmonary cumulated radioactivity for continuous inhalation studies with $C^{15}O$ and $CO^{15}O$, a dead-space volume containing the radioactivity concentration of the inhaled gas was included. The alveolar volume was arbitrarily assumed to contain gas with half the administered radioactivity concentration (estimated using a steady-state compartmental model for the lungs and preliminary measured brain and blood radioactivity concentrations). This assumption appears reasonable since radioactivity enters blood quite rapidly from the alveolar gas.

For studies with ^{15}O-labeled gases, dead-space radioactivity accounted for only a small proportion of the estimate of total lung absorbed dose (9% and 4% for steady-state and 19% and 8% for bolus $CO^{15}O$ and $C^{15}O$ studies), whereas alveolar gas contributed more (66% and 31% for steady-state and 47% and 19% for bolus $CO^{15}O$ and $C^{15}O$). For ^{11}CO administered by inhalation, only 3.5% of the estimate of lung absorbed dose was due to lung gases.

Amount of administered radioactivity for equivalent count density PET techniques. For bolus techniques with initial equilibration period t_o(hr) and image periods t_f(hr), the number of counts detected for the brain will be given by

$$N_b \propto e^{-\lambda t_o}(1 - e^{-\lambda t_f})\beta\tilde{A}_B, \quad (7)$$

where $\tilde{A}_B$ is the cumulated radioactivity in the brain in μCi-hr, and β is the number of positrons emitted per disintegration (*23*).

Similarly, for steady-state techniques

$$N_c \propto (t_f/t_g)(1 - e^{-\lambda t_f})\beta\tilde{A}_B, \quad (8)$$

where t_g represents the total gas on-time (hr).

Typically, 5–15 mCi of ^{11}CO are used in PET protocols for bolus inhalation (*1–3*). Computations were done for 15 mCi of ^{11}CO, and the administered radioactivities for other studies were scaled using Eqs. 7 and 8 so that similar brain counts resulted. Equilibration times of 5 min and 7 min were allowed for bolus and steady-state techniques, with identical imaging times. Estimates of radiation absorbed dose for other protocols with different timing and administered radioactivity (required in part by camera sensitivity and statistical needs) may be made using Eqs. 7 and 8 and the estimates of absorbed radiation doses per mCi administered in Tables 2, 3, 4, and 5.

TABLE 2. ESTIMATES OF RADIATION ABSORBED DOSES TO LUNG FOR CEREBRAL BLOOD STUDIES WITH EQUIVALENT COUNT DENSITIES

	Brain cumulated activity†	Lung cumulated activity†	Lung absorbed dose mrad/mCi‡	Administered mCi¶	Total lung absorbed dose rad/study
^{11}CO					
bolus inhalation	2.92	51.7	55	15.0	0.83
bolus infusion	2.92	49.8	53	15.0	0.80
$C^{15}O$					
continuous inhalation	0.292	7.6	13	104.7*	1.36
bolus inhalation	0.292	6.8	11	32.5	0.36
continuous infusion	0.292	5.0	8.6	104.7*	0.90
bolus infusion	0.292	5.0	8.6	32.5	0.28
$CO^{15}O$					
continuous inhalation	0.343	3.56	6.2	89.3*	0.55
bolus inhalation	0.343	2.71	4.9	27.7	0.14
continuous infusion	0.343	0.91	2.0	89.3*	0.18
bolus infusion	0.343	0.91	2.0	27.7	0.055

* Product of administered (mCi/min) × min administered. Amount present at any given time during stable state is (ln 2)/λ = 0.34 times this amount.

† μCi-hr/mCi administered.

‡ Administered mCi.

¶ For equivalent count density.

TABLE 3. ^{11}CO RADIATION ABSORBED DOSE ESTIMATES

Organ	Bolus inhalation		Bolus infusion	
	mrad/mCi*	mrad/15 mCi*	mrad/mCi*	mrad/15 mCi*
ADRENALS	29.	435	29.	435
BLADDER	13.	195	14.	210
BONE (CORTICAL)	8.8	132	8.8	132
BONE (TRABECULAR)	7.7	116	7.7	116
BRAIN	4.5	68	4.5	68
FAT	6.7	101	6.7	101
STOMACH	15.	225	15.	225
SMALL INTESTINE	86.	1290	86.	1290
UPPER LARGE INTESTINE	62.	930	62.	930
LOWER LARGE INTESTINE	63.	945	63.	945
HEART	33.	495	33.	495
KIDNEYS	28.	420	28.	420
LIVER	21.	315	21.	315
MARROW	10.	150	10.	150
MUSCLE	6.7	101	6.7	101
OVARIES	27.	405	27.	405
PANCREAS	27.	405	27.	405
SKIN	4.8	72	4.8	72
SPLEEN	53.	795	53.	795
TESTES	8.5	128	8.6	129
THYROID	19.	285	19.	285
UTERUS	16.	240	16.	240
TOTAL BODY	19.	285	19.	285

* Administered mCi.

TABLE 4. RADIATION ABSORBED DOSE ESTIMATES FOR $C^{15}O$

Organ	Continuous inhalation		Bolus inhalation		Continuous infusion		Bolus infusion
	Mrad/mCi*	mrad/105 mCi*	mrad/mCi*	mrad/32.5 mCi*	mrad/mCi*	mrad/105 mCi*	mrad/32.5 mCi*
ADRENALS	4.4	461	4.4	143	4.4	461	143
BLADDER	1.5	157	1.6	52	1.8	188	59
BONE (CORTICAL)	1.2	126	1.2	39	1.2	126	39
BONE (TRABECULAR)	1.1	115	1.1	36	1.1	115	36
BRAIN	0.60	63	0.60	20	0.60	63	20
FAT	0.94	98	0.93	30	0.91	95	30
STOMACH	1.8	188	1.8	59	2.0	209	65
SMALL INTESTINE	14.	1466	14.	455	14.	1466	455
UPPER LARGE INTESTINE	9.1	953	9.2	299	9.3	974	302
LOWER LARGE INTESTINE	10.	1047	10.	325	10.	1047	325
HEART	4.5	471	4.5	146	4.4	461	143
KIDNEYS	4.3	450	4.3	140	4.3	450	140
LIVER	3.0	314	3.0	98	3.0	314	98
MARROW	1.5	157	1.5	49	1.5	157	49
MUSCLE	0.99	104	0.98	32	0.96	101	31
OVARIES	4.2	440	4.2	137	4.2	440	137
PANCREAS	4.1	429	4.1	133	4.1	429	133
SKIN	1.1	115	1.1	36	1.0	105	33
SPLEEN	15.	1571	15.	488	15.	1571	488
TESTES	1.0	105	1.0	33	1.1	115	36
THYROID	3.1	325	3.1	101	3.1	325	101
UTERUS	2.1	220	2.1	68	2.1	220	68
TOTAL BODY	1.6	168	1.6	52	1.6	168	52

* Administered mCi.

RESULTS

For inhalation techniques the absorbed-dose estimate for lungs is higher than for most other organs. Table 2 includes the brain cumulated radioactivity and lung radiation absorbed dose per mCi administered and for a PET protocol giving equivalent count density.

As seen in Table 2, the replacement of inhalation with an infusion technique yielding equivalent count density may result in the reduction of estimated lung absorbed dose from 4–67%, with the largest reduction being for steady-state $CO^{15}O$ ($H_2{}^{15}O$) studies. Only a very small reduction in the estimate of lung absorbed dose results from the infusion of ^{11}CO, since for bolus inhalation the lung half-time for CO is large with respect to the physical decay constant of C-11.

In general, bolus techniques result in lower radiation absorbed doses than steady-state techniques. For the determination of cerebral blood volume with CO, a 33-mCi infused bolus of $C^{15}O$ will give the lowest radiation absorbed dose for the lungs (280 mrad), while bolus inhalation of $C^{15}O$ results in the lowest lung radiation absorbed doses for all inhalation techniques (360 mrad). An injected bolus results in a 1/3.3 reduction in estimated lung absorbed dose over steady-state infusion techniques for $CO^{15}O$, whereas a bolus $CO^{15}O$ inhalation results in approximately one-fourth of a similar estimate for a continuous inhalation protocol resulting in equivalent image statistics (140 mrad compared with 550 mrad).

Radiation absorbed dose estimates for 22 organs and the whole body are listed in Tables 3, 4, and 5 for ^{11}CO, $C^{15}O$ and $CO^{15}O$, respectively; these include the absorbed-dose estimates per mCi administered and for equivalent count-density protocols. The results suffer from considerable uncertainty: the coefficient of variation (20–50%) in the absorbed-fraction data (*17,20*) alone may result in errors of 28–70% in the absorbed-dose estimates.

There is some variation in absorbed-dose estimate for nonlung organs from protocol to protocol for the O-

TABLE 5. RADIATION ABSORBED DOSE ESTIMATES FOR $CO^{15}O(H_2{}^{15}O)$

Organ	Continuous inhalation		Bolus inhalation		Continuous infusion		Bolus infusion
	mrad/mCi*	mrad/89.3 mCi*	mrad/mCi*	mrad/27.7 mCi*	mrad/mCi*	mrad/89.3 mCi*	mrad/27.7 mCi*
ADRENALS	1.9	170	1.9	53	1.9	170	53
BLADDER	1.2	107	1.2	33	1.3	116	36
BONE (CORTICAL)	0.80	71	0.81	22	0.82	73	23
BONE (TRABECULAR)	0.73	65	0.73	20	0.72	64	20
BRAIN	0.59	53	0.59	16	0.59	53	16
FAT	2.0	179	2.0	55	2.0	179	55
STOMACH	1.9	170	1.9	53	2.1	188	58
SMALL INTESTINE	2.1	188	2.2	61	2.2	196	61
UPPER LARGE INTESTINE	2.0	179	2.1	58	2.2	196	61
LOWER LARGE INTESTINE	2.0	179	2.1	58	2.2	196	61
HEART	2.2	196	2.2	61	2.1	188	58
KIDNEYS	2.1	188	2.1	58	2.1	188	58
LIVER	2.0	179	2.0	55	2.0	179	55
MARROW	1.2	107	1.2	33	1.2	107	33
MUSCLE	2.0	179	2.0	55	2.0	179	55
OVARIES	2.1	188	2.1	58	2.1	188	58
PANCREAS	2.0	179	2.0	55	2.0	179	55
SKIN	2.2	196	2.2	61	2.1	188	58
SPLEEN	2.1	188	2.1	58	2.1	188	58
TESTES	2.1	188	2.1	58	2.2	196	61
THYROID	1.9	170	1.9	53	1.9	170	53
UTERUS	1.9	170	1.9	53	1.9	170	53
TOTAL BODY	1.6	143	1.6	44	1.6	143	44

* Administered mCi

15-labeled gases, with the estimate for infusion sometimes being slightly higher (<15%) than for inhalation. No such differences in nonlung estimates were noted for ^{11}CO.

For ^{11}CO and $C^{15}O$ the critical organ is the spleen, which receives a higher radiation absorbed dose than the lungs (1.4 rad/15 mCi administered ^{11}CO, and 0.49 rad/33 mCi administered $C^{15}O$). Because of their vascularity, the walls of the gastrointestinal tract should also receive significant radiation doses for ^{11}CO and $C^{15}O$ (1.3 rad/15 mCi administered and 0.46 rad/33 mCi for small intestine). The dose estimate for blood due to the positrons is approximately 1.2 rad/15 mCi administered ^{11}CO and 0.46 rad/33 mCi $C^{15}O$.

The distribution of $H_2{}^{15}O$ in the body is more uniform than for ^{11}CO and $C^{15}O$, and the estimated absorbed doses for the various organs for a bolus infusion varies from approximately 20 to 60 mrad/28 mCi administered.

CONCLUSIONS

For the measurement of either rCBV or rCBF with PET, bolus O-15-labeled gaseous inhalation or infusion techniques would result in the lowest lung radiation absorbed dose and would also circumvent stability problems inherent in steady-state protocols. However, detailed analysis of the quantitation of bolus $CO^{15}O$ rCBF techniques is needed. Certain applications such as neuropsychological studies requiring sequential baseline and stimulation studies may, by their nature, require steady-state techniques. Considerable reduction in the estimate for lung absorbed dose results if O-15-labeled gaseous inhalations are replaced by infusion. Unfortunately, infusion is more invasive than inhalation and requires additional steps in radiopharmaceutical preparation.

The estimates of radiation absorbed dose presented here for ten different inhalation/infusion PET protocols should serve as useful guidelines in the design of PET

experiments involving human subjects once specific requirements for timing and administered radioactivity have been determined.

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