PHYSICS AND RADIATION BIOLOGY

Biological Analysis and Dosimetry for ^{15}O-Labeled O_2, CO_2, and CO Gases Administered Continuously by Inhalation

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Estimates of radiation absorbed dose have been determined for the steady-state distribution of oxygen-15 ($T_{1/2}$ = 122 sec) from inhalation of molecular oxygen, $^{15}O_2$; carbon dioxide, $C^{15}O_2$; and carbon monoxide, $C^{15}O$. Biodistribution data for ^{15}O-labeled water, produced by the metabolism of oxygen and from CO_2 by pulmonary carbonic anhydrase, were used. Lung gas and intravascular activities are also included. The total oxygen utilized was taken to be 14.4 l/hr. Seventeen tissues were included as source organs. The radiation dose is directly proportional to the duration of inhalation. Air containing a constant level of ^{15}O is provided in excess of need to the patient, who breathes under his own control. The lung, which is known to be a particularly radiosensitive tissue, appears to be the dose-limiting or critical tissue. The radiation dose estimates for lung, based upon 1 hr of breathing air with an activity concentration of 1 mCi/l, are 3.6, 1.2, and 2.8 rads, respectively, for $^{15}O_2$, $C^{15}O_2$, and $C^{15}O$.

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Clinical studies of steady states induced by inhalation of gases labeled with oxygen-15 (*1*,*2*) are currently using a model suggested by Jones et al. (*3*) in conjunction with positron tomography (*4–6*). The inhaled air is labeled with gases such as $^{15}O_2$, $C^{15}O_2$, or $C^{15}O$, and is maintained at a constant proportion of activity while the subject breathes under his own control. The activity-containing air is supplied in excess of need, with the excess by-passing the subject. Due to the rapid decay of ^{15}O ($T_{1/2}$ = 122 sec) a steady-state (sometimes referred to as equilibrium) distribution of activity is obtained within the subject in ~6–10 min. The steady state is maintained during the time required to image the subject (typically up to one hour) and when administration stops, the activity within the subject decays away rapidly. Estimates of radiation risk for this procedure are needed. The purpose of this paper is to provide these estimates using a consistent model and providing sufficient detail so that the estimates can be easily renormalized to the conditions of any particular steady-state procedure.

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METHODS

Radiopharmaceuticals. Molecular oxygen, carbon dioxide, and carbon monoxide are labeled with oxygen-15 ($T_{1/2}$ = 122 sec), which emits 99.98% positrons (*7*) with a mean energy of 0.72 MeV (*8*). It is normally prepared by means of the $^{14}N(d,n)^{15}O$ reaction using a compact medical cyclotron. The chemical procedures used to prepare the three gases have been described (*9*). The nitrogen target gas, after chemical processing, is diluted with appropriate amounts of oxygen and air to provide the desired activity concentration in the patient's intake supply (normally about 1 mCi per l of air).

Absorbed-dose equations. A modified version of the schema described by Loevinger and Berman (*10*) was used for the absorbed-dose calculations. The modification provides an added residual term that accounts for the activity contained in the remainder of the body (*11*).

The equations used are:

$$\bar{D}_v = \sum_{r=a}^{v} \tilde{A}_r S_{v\leftarrow r} + \tilde{A}_{res} S_{v\leftarrow res}, \quad (1)$$

$$S_{v\leftarrow res} = \frac{m_{tb}}{m_{res}} \left(S_{v\leftarrow tb} - \sum_{r=a}^{v} \frac{m_r}{m_{tb}} S_{v\leftarrow r}\right), \quad (2)$$

$$\tilde{A}_{res} = \tilde{A}_{tb} - \sum_{r=a}^{v} \tilde{A}_r, \quad (3)$$

$$m_{res} = m_{tb} - \sum_{r=a}^{v} m_r, \quad (4)$$

where $\bar{D}$ = absorbed dose (rad), $\tilde{A}$ = cumulated activity (μCi-hr), S = S-factor (rad/μCi-hr), m = organ mass (grams), r = source tissue, v = target tissue, tb = total body, and res = residual body.

S-factors. For oxygen-15 these were obtained largely from MIRD Pamphlet No. 11 (*12*). Values not listed there were either obtained from other sources (*13–15*), or calculated from the specific absorbed fractions listed in MIRD Pamphlet No. 5, Revised (*16*). In the few cases when none of the available references provided the S-factor for a particular combination of source organ and target organ, the S-factor of a different but geometrically similar organ pair was used. In some cases, when S-factors for two distinct parts of an organ were not available, the total-organ S-factor was used in calculating the dose from that organ to other tissues. Gray and white cerebral matter, for example, were considered source organs only for white and gray matter as targets; for other tissues, the total-brain S-factors were used.

Biological distribution of $^{15}O_2$. *1. Water of metabolism distribution.* The model-derived biodistribution data of Bigler et al. (*17*) were used to determine the redistribution of ^{15}O-labeled water produced by the metabolism of molecular oxygen in each tissue. The total-body rate of oxygen utilization in the resting state was taken to be equal to 14.4 l/hr (*18*). The model for water distribution provided the steady-state concentrations of activity due to redistributed water for each of five compartments (*17*). In order to determine the correspondence between the model compartments and the various body tissues, the following procedure was used. The water content of each tissue (*19*) was divided according to estimates of extra- and intracellular water content. The extracellular water was assumed to be included within the central compartment of the model. The intracellular water was assigned to either the rapidly or slowly exchanging water compartments of the model, depending on the clearance rate characteristics of the tissue (*19*). The intracellular percentages of the total water content of each organ and tissue were assumed to be 70%, except for muscle (75%) and bone (90%) (*21*). The cumulated activities in each organ and tissue due to water are the product of the time duration (1 hr) with the sum of the activity due to extracellular water (extracellular water volume multiplied by the concentration in the central water compartment) and the activity due to intracellular water (intracellular water volume multiplied by the concentration in the slowly or rapidly exchanging water compartment).

2. Blood. The cumulated activities due to molecular oxygen, both dissolved and hemoglobin-bound, in blood were calculated using the average concentration of oxygen in blood (0.16 ml-O_2 per ml blood) (*22*) and the blood volume of each tissue (*19*). These calculations assumed a 1-hr inhalation period and an oxygen specific activity of 4.8 μCi per ml-O_2. This specific activity is equal to the specific activity of oxygen in the inhaled air (1 mCi per l of air = 4.8 μCi per ml of O_2). The cumulated activities due to blood thus derived were added to the cumulated activities due to water of metabolism to give the total cumulated activity due to administered ^{15}O-labeled molecular oxygen for each tissue.

3. Lung oxygen. The cumulated activity for the lungs, as obtained from the activities of water and blood does not include the cumulated activity due to gaseous tracer. These values are the product of the inhalation duration, the specific activity (4.8 μCi per ml of O_2), the oxygen concentration in each lung region, and the respective lung volume. The oxygen concentration for the dead space was obtained by taking the average of the oxygen concentration before and after inspiration (17.3%). The alveolar oxygen concentration (14.6%) was obtained from Guyton (*23*). The dead-space volume remains constant at 150 ml throughout breathing (*18*). The average volume for the alveolar region is the sum of the functional residual capacity and half of the alveolar tidal volume, namely 2400 ml + 350/2 ml (*18*).

Table 1 shows the cumulated activity for eleven tissues due to ^{15}O-labeled molecular oxygen, broken down according to cumulated activity due to water of metabolism (metabolic) and that due to oxygen in blood (vascular) in each organ. A total of 23 tissue accumulated activities were used in our calculations.

Biological distribution of $C^{15}O_2$. *1. Water.* The activity in inhaled $C^{15}O_2$ is rapidly transferred to bicarbonate within the lungs (*24–26*). The resultant steady-state distribution of oxygen-15-labeled water was calculated from a compartmental model by Bigler et al. (*17*). The production rate for total-body water was calculated by assuming that of the 500 ml of gas inspired with each breath (*18*), the total amount of carbon dioxide reaching the alveolar region (350 ml) (*18*) is completely converted to water (*24–26*). Given the total-body absorption efficiency, the model provided the concentrations of activity in each of its compartments. This activity was apportioned to each tissue according to its extracellular and intracellular water volumes, as was done for the water of metabolism in the case of molecular oxygen.

2. Lung carbon dioxide absorption and water clearance. The cumulated oxygen-15 activity assigned to the lung due to the inhalation process can be reduced

TABLE 1. VASCULAR AND METABOLIC COMPONENTS OF THE CUMULATED ACTIVITIES OF THE $^{15}O_2$ STEADY STATE

Tissue	Cumulated activity (μCi-hr)* Vascular	Metabolic	Sum
Lung	400	100	500
White matter	10	140	150
Gray matter	10	140	150
Spleen	70	20	90
Ovaries	2	1	3
Testes	1	4	5
Heart wall	40	30	70
Heart contents	370	30	400
Kidneys	53	32	85
Liver	190	170	360
Muscle	530	1030	1560
Residual body	1440	1260	2700
Alveolar lung gas	—	—	1670
Dead space gas	—	—	120
Total†	4000	3400	9100

* Assumes the gas is administered by inhalation for 1 hr at a concentration of 1 mCi per l of air.

† Cumulated activities for 12 tissues are not shown.

to two components: that due to gaseous carbon dioxide in the lungs, and that due to the water derived therefrom (via carbonic anhydrase) clearing the lungs. This water does not include the water returning to the lung, which is accounted for in the section above. The data of West and Dollery (*24*) for lung disappearance of carbon dioxide were fitted with a single exponential to obtain a biological half-time of $T_{1/2} = 1.0 \pm 0.1$ sec for carbon dioxide absorption by the lungs. The cumulated activity was then obtained by following the clearance of a single inhalation of the radioactive gas through successive expirations and inhalations until the amount initially breathed in had been effectively removed. For instance, after the first breath, the activity content of the alveolar lung volume has been reduced by absorption to 2.6% of its initial value, and then further by exhalation to 2.3%. Integrating the activity over the effective removal time gave the effective cumulated activity due to a single inhalation. To obtain the total alveolar cumulated activity due to 1 hr's inhalation of radioactive gas, the effective cumulated activity for a single breath was multiplied by 720, the average number of times a person at rest breathes in an hour (*18*). The cumulated activity assigned to the dead space was calculated by obtaining an average concentration of activity during the respiratory process. We assume, therefore, that the peak concentration of activity during inhalation in the 150 ml anatomical dead space is at the delivered gas concentration. After expiration no activity was assumed in the dead space, since essentially all of the radioactive carbon dioxide reaching the alveolar lung region is completely absorbed.

The second component of the cumulated activity assigned to the lung comes from the activity due to the water that is produced in the lungs by the carbonic anhydrase reaction. This contributes significantly to the dose to the lungs before it is cleared. The clearance data of West et al. (*25*), and Kenny et al. (*26*) were used to calculate a biological half-time of 3.2 sec for the water cleared from the lungs. The cumulated activity due to water produced in and clearing the lungs (200 μCi-hr) is added to the cumulated activity due to the gas (175 μCi-hr), together with that due to the model-derived recirculated water (320 μCi-hr), to give the total cumulated activity for the lungs.

Biological distribution of $C^{15}O$. *1. Blood.* Essentially all of the inhaled carbon monoxide is bound to hemoglobin once it has been absorbed. The total amount absorbed is then assumed to be uniformly distributed throughout the blood and bound to the hemoglobin. The total blood activity is calculated by determining the rate of transfer of activity into the body in the lung (see below). An activity concentration for blood (1.69 μCi per ml of whole blood) is obtained by assuming a total-body blood volume of 5.2 l (*19*). Given the activity concentration for the blood, the cumulated activity for each organ is calculated by multiplying the organ's blood volume (*19*) by the blood activity concentration and the time.

2. Lung gas absorption. By using the uptake for carbon monoxide (53.0 ± 2.2%), as measured by Bates (*27*) in the model used in the previous section for absorption and exhalation of pulmonary carbon dioxide gas, we derived a gas clearance half-time for carbon monoxide (10.8 sec). As described for carbon dioxide, we then obtained an effective single-breath cumulated activity for carbon monoxide. The total alveolar cumulated activity estimated by this method is 800 μCi-hr. The cumulated activity of the dead space was also obtained in a manner similar to that used for carbon dioxide. The average of the activity contents of the dead space after inspiration (150 μCi) and after expiration (92 μCi) was taken as the activity content of the dead space throughout the steady state.

The above procedures were also used in calculating cumulated activities for subjects with emphysema. However, the biological parameters were altered according to data from Bates (*27*) and from Bates and Christie (*28*). Normal values for the tidal volume, functional residual volume, and respiration frequency are 500 ml, 2400 ml, and 12 breaths per minute respectively (*18*). In subjects with emphysema, these are 535 ml, 4630 ml, and 21 breaths per minute (*28*). The fraction of carbon monoxide absorbed from that inspired, for patients with medically diagnosed emphysema, is 29.0 ± 1.0%. This decrease in fractional uptake is compen-

TABLE 2. CUMULATED ACTIVITIES FOR $C^{15}O$ AT STEADY STATE IN HEALTHY SUBJECTS AND PATIENTS WITH EMPHYSEMA*

Tissue	Cumulated activities (μCi-hr) Healthy	Emphysema
Lung	900	820
White matter	30	25
Gray matter	25	20
Spleen	150	140
Ovaries	5	4
Testes	2	2
Heart wall	90	80
Heart contents	840	770
Kidneys	120	100
Liver	420	390
Muscle	1180	1080
Residual body	3220	2940
Alveolar lung gas	800	3080
Dead space gas	120	190
Total	9700	11300

* Assumes the gas is administered by inhalation for 1 hr at a concentration of 1 mCi per l of air.
† Cumulated activities for 12 tissues are not shown.

sated for by the increased respiration rate. The cumulated activity to tissues other than the lungs, therefore, is not drastically altered, whereas the cumulated activity in the alveolar region is significantly increased due to the increased breathing frequency and lung volumes. Values for the cumulated activities in body organs and tissues for normal subjects and for patients with emphysema are shown in Table 2.

TABLE 3. CUMULATED ACTIVITIES (μCi-hr) AT STEADY STATE FOR HEALTHY RESTING HUMANS FOR ^{15}O-LABELED O_2, CO_2, AND CO*

Tissue	O_2	CO_2	CO
Lung	500	530	900
White matter	150	200	30
Gray matter	150	300	25
Spleen	90	60	150
Ovaries	3	3	5
Testes	5	10	2
Heart wall	70	100	90
Heart contents	400	300	840
Kidneys	85	100	120
Liver	360	540	420
Muscle	1560	5000	1180
Residual	2700	4200	3200
Alveolar lung gas	1670	100	800
Dead space gas	120	75	120
Total	9100	12300	9700

* Assumes the gas is administered by inhalation for 1 hr at a concentration of 1 mCi per l of air.
† Cumulated activities for 12 tissues are not shown.

TABLE 4. ESTIMATED RADIATION DOSES AT STEADY STATE FOR HEALTHY RESTING HUMANS FOR ^{15}O-LABELED O_2, CO_2, AND CO*

Target tissues	Dose (mrads) O_2	CO_2	CO
Lung	3600	1150	2800
White matter	430	600	80
Gray matter	420	800	75
Spleen	950	700	1570
Ovaries	580	580	900
Testes	290	650	170
Heart wall	670	780	880
Kidneys	580	700	790
Liver	470	650	540
Muscle	180	400	170
Total body (mean)	300	400	320

* Assumes the gas is administered by inhalation for 1 hr at a concentration of 1 mCi per l of air.

RESULTS

The cumulated activities for oxygen-15-labeled molecular oxygen, carbon dioxide, and carbon monoxide administered to healthy resting subjects are summarized in Table 3.

TABLE 5. ESTIMATED RADIATION DOSES FOR $C^{15}O$ AT STEADY STATE IN HEALTHY SUBJECTS AND PATIENTS WITH EMPHYSEMA*

Target tissues	Dose (mrads) Healthy	Emphysema
Lung	2800	6300
White matter	80	80
Gray matter	70	70
Spleen	1570	1470
Ovaries	900	830
Testes	170	160
Heart wall	880	900
Kidneys	790	740
Liver	540	540
Muscle	170	180
Total body (mean)	320	370

* Assumes the gas is administered by inhalation for 1 hr at a concentration of 1 mCi per l of air.

TABLE 6. RADIATION DOSE SOURCE DISTRIBUTION FOR O-15-LABELED GASES AT STEADY STATE FOR THE *LUNG**

Source tissues	Dose (mrad) O_2	CO_2	CO
Lung	3500.	1020.	2700.
Lung dead space	1.	0.7	1.
Brain	0.4	0.7	0.1
Spleen	1.4	0.9	2.4
Heart contents	18.	13.	37.
Heart wall	3.	4.	4.
Kidneys	0.6	0.7	0.8
Liver	6.6	9.7	7.6
Muscle	15.6	50.	11.8
Residual body	37.	55.7	41.7
Total dose	3600.	1150.	2800.

* Assumes the gas is administered by inhalation for 1 hr at a concentration of 1 mCi per l of air.

Analogous absorbed-dose estimates are summarized in Table 4. The gas is assumed delivered at a concentration of 1 mCi per l of air and for a 1-hr duration. Table 5 contains the absorbed-dose estimates for inhaled carbon monoxide for patients with emphysema. The dose to the lung—the critical organ for all the gases—is increased considerably. In obtaining the dose to each organ or tissue, the contribution from 19 tissues (20 for white and gray matter) was individually considered and summed to obtain the total dose. Table 6 shows an example of the dose to a particular target organ (lung) from those source organs that contributed a significant amount to the total dose.

DISCUSSION

The increased interest in the steady-state use of oxygen-15-labeled gases, to study human metabolic and physiologic functions with positron tomography, renders an estimate of the absorbed doses due to such procedures both timely and necessary. We have performed a detailed biological analysis in order to obtain accurate cumulated activities for each tissue for this purpose.

In Table 7 we show how the tissue activity concentrations derived from the biological data can be broken down into their absolute and relative amounts in each gram of body tissue. Molecular oxygen activity concentrations for cerebral white and gray matter (rapidly exchanging tissues) and for muscle (slowly exchanging tissue) are broken down to their biological components. We can see that for rapidly exchanging tissues the final steady-state activity concentration is not directly proportional to the locally produced water of metabolism, as required for a direct measurement of oxygen utilization. For this purpose, the major loss due to clearance, along with the gains due to recirculation and vascular oxygen content, are effects that should be considered for correction of the observations. The contribution for oxygen in the blood is thought to be negligible by those using the theory suggested by Jones et al. (*3*). An analysis of this approximation—and of errors resulting from uncertainties in the partition coefficient of water—shows that regional cerebral oxygen utilization are overestimated by as much as 40% when these effects are ignored (*29*). In contrast, the corrections required to obtain the activity concentration due to oxygen metabolism from measurements of the final steady-state activity concentrations, for a slowly exchanging tissue (e.g. muscle), are large and are necessary for both vascular oxygen (34%) and extracellular water (27%). Water loss (−2%) and gain (6%) are of less importance.

Quantitative measurements of oxygen utilization in tumor and surrounding tissues have been reported in a spontaneous dog tumor model system (*30*). Such studies have been initiated in humans in our laboratory. This paper identifies the nature and magnitude of some of the biological and physiological problems we face in vali-

TABLE 7. BREAKDOWN OF THE RESULTANT ACTIVITY CONCENTRATION (μCi/g) IN SELECTED TISSUE DUE TO CONTINUOUSLY INHALED ^{15}O-LABELED OXYGEN*

Tissue†	Water of metabolism	−	Biological water loss	+	Recirculation water gain	+	Extracellular water	+	Vascular oxygen	=	Total
White matter	0.32 (152%)‡		0.15 (72%)		0.026 (12%)		—§		0.017 (8%)		0.21 (100%)
Gray matter	0.68 (315%)		0.53 (245%)		0.049 (23%)		—§		0.016 (7%)		0.22 (100%)
Muscle	0.019 (35%)		0.0014 (2%)		0.0035 (6%)		0.015 (27%)		0.019 (34%)		0.056 (100%)

* Activity concentrations shown assume that the gas is administered by inhalation for 1 hr at a concentration of 1 mCi per l of air to a steady-state (i.e. >10 min).

† Water contents for white matter, gray matter, and muscle are 0.73, 0.85, and 0.79 ml/g, respectively.

‡ The values in parentheses are in percent of the observed activity in each tissue.

§ The rate-limiting boundary for free diffusion of water for brain is assumed to be the blood-brain barrier, rather than the cell membrane as for all other tissues in the body.

dating a model for regional oxygen utilization per gram. It will be necessary to estimate all of the tissue activity contributions. In addition, the problem of correcting for necrotic tissue must be solved if we are to estimate the magnitude and extent of regional hypoxia of vital tissues. If this problem can be solved, it should then prove possible to select patients for therapy with radiation having high linear energy transfer (LET)—e.g., neutrons, heavy ions, and pi mesons—based upon their degree of hypoxia.

The only previous papers giving information adequate for comparison of the radiation dose estimates given here are a paper limited to $C^{15}O_2$ (*31*) and our recent conference paper (*32*). The former paper assumes that the water ($H_2{}^{15}O$) activity concentration is equal to the mean value determined by the ratio of the steady-state total-body activity to body water content (g). The steady-state activity content is equal to the administration rate into the body by absorption within the lungs divided by the decay constant of oxygen-15. The model of Bigler et al. for steady-state water distribution (*17*) was used in the second paper and here to account for the distribution kinetics in apportioning the water to the various intracellular and extracellular components of the body.

A more important difference in comparison to the body-water activity distribution among all three papers was in their treatments of the lung gas. The first paper assumed that the gaseous lung $C^{15}O_2$ activity concentration was equal to the average activity required in the inhaled gas to provide the defined level of activity within the body. The conference paper used the measured oxygen concentration values as also used here for the $^{15}O_2$ estimates. For the carbon dioxide and carbon monoxide estimates, the lung activity concentration was set equal to the activity concentration in the inhaled gas. As discussed earlier, measured values taken from the literature were used here for the lung. The overall effect of these differences causes the earlier studies (31,32) to overestimate the radiation doses, especially for the critical lung tissues. The normalized dose to the lung for the first study was almost six times that given here. The lung doses estimated in the conference paper were higher by factors of 1.2, 3.5, and 1.5, respectively, for oxygen-15-labeled molecular oxygen, carbon dioxide, and carbon monoxide.

The major variable in the radiation dose estimates for the oxygen-15-labeled gases arises from the determination of the amount of activity extracted by the patient from that in the incoming air. The person-to-person variability in the values of the biological and physiological parameters needed to estimate this extraction suggest that a direct measure of this parameter is needed in each patient study for reasonably accurate estimates of radiation dose. A simple procedure would be to measure the activity concentrations in the unused excess gas and the exhaled gas. The difference between the latter and the inhaled gas activity concentration, multiplied by the flow rate, would yield the needed extraction rate. An automatic system designed to provide these data for this and other purposes is currently under construction in our laboratory.

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