Radiation Dose to Upper Airways from Inhaled Oxygen-15 Carbon Dioxide

Ernst Meyer, Lucas Y. Yamamoto, Alan C. Evans, Jane L. Tyler, Mirko Diksic, and William Feindel

Brain Imaging Center, Montreal Neurological Institute and Hospital; and Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada

According to Powell et al. (5), significant retention of ^{15}O in the tracheal mucosa results in a radiation absorbed dose of 75 to 200 rad upon breathing of $^{15}O\text{-}CO_2$ for one hour at 1 mCi/liter. Such a high dose would seriously compromise the $^{15}O\text{-}CO_2$ inhalation method for positron emission tomographic (PET) measurement of cerebral blood flow (CBF). In order to verify these results, we have assayed ^{15}O activity in the tracheal region of three volunteers by PET during inhalation of $^{15}O\text{-}CO_2$ and $^{15}O\text{-}O_2$. Using methods similar to those of the above authors for estimating absorbed dose in the tracheal mucosa, we have obtained a value of 14–38 rad, which is more in keeping with 3–5 rad found by Bigler et al. (12) from direct assay of mucus and saliva. We conclude that the $^{15}O\text{-}CO_2$ inhalation method is a safe and practical means of measuring CBF by PET.

Oxygen-15- (^{15}O) labeled carbon dioxide is frequently used in positron emission tomography (PET) for the measurement of regional cerebral blood flow (rCBF). Several models have been developed for that purpose. In the widely used steady state method originally proposed by Jones et al. (1) and adapted to quantitative PET by Frackowiak et al. (2), the tracer is administered by way of inhalation. Careful radiation dosimetry calculations have therefore been carried out particularly for the lungs which were considered to be the tissue at highest risk for this procedure (3,4). The calculated dose estimates to the respiratory pathways, so far, were found to be acceptably low (2). However, a recent report by Powell et al. (5) suggested that the mucosal layer of the trachea, about 50 microns thick, might absorb a considerable radiation dose during the inhalation of $^{15}O\text{-}CO_2$ due to significant biological uptake and retention of ^{15}O in the tracheal wall. Using longitudinal tomography, Powell et al. (5) reported that after a single-breath inhalation of $^{15}O\text{-}CO_2$, ~30% of the label was retained in the tracheal wall. During a short $^{15}O\text{-}CO_2$ continuous inhalation experiment they have measured radioactivity concentrations in the tracheal region of interest (ROI) and extrapolated the

results to obtain estimates of the concentrations found after 12 min of continuous inhalation in a typical steady state study. In order to measure tracheal activity from the inhaled radioactive gas alone, the procedure was repeated with $^{15}O\text{-}O_2$, where no biologic retention had been observed (5). The ratio of the steady state $^{15}O\text{-}CO_2$ and $^{15}O\text{-}O_2$ concentrations was found to be 29:1. Using either thermoluminescent dosimetry (TLD) measurements or theoretical calculations (6), these authors then estimated an absorbed dose to the tracheal mucosa of 75 to 200 rad, assuming an $^{15}O\text{-}CO_2$ inhalation concentration of 1 mCi/l of air over an hour. The dose estimate to the lungs as published by Bigler and Sgouros (3) for the same experimental conditions is 1.2 rad.

Since the steady state CBF method is routinely used at our Institute, the possibility of a substantial radiation absorbed dose to the tracheal wall was of concern to us. We therefore decided to measure tracheal radioactivity concentration as a function of time during short continuous-breathing tests with $^{15}O\text{-}CO_2$ and $^{15}O\text{-}O_2$ as described by Powell et al. (5) on three young volunteers using transaxial PET and the radioisotope administration procedure used at our institution (7). For the tracheal ROI, the mean ratio of the peak radioactivity concentration during the $^{15}O\text{-}CO_2$ test and the steady activity level during the $^{15}O\text{-}O_2$ test is compared to the ratio published by Powell et al. (5). Based on the calculations and TLD measurements of these authors,

comparative estimates of radiation absorbed dose to the tracheal wall are derived for the continuous inhalation of $^{15}O\text{-}CO_2$. It has to be stressed that the dose estimates derived here are of strictly relative nature with reference to the data due to Powell et al. (5), since an absolute assessment of ^{15}O activity in the tracheal mucosa is not feasible with the resolution offered by PET imaging.

MATERIALS AND METHODS

Three healthy young volunteers, all nonsmokers, were selected for the study. Their neck circumference just above the level of the laryngeal prominence of the thyroid cartilage was measured and the scanning level marked on the skin.

For this study, the gantry of the positron emission tomograph (Therascan 3128 by Atomic Energy of Canada Limited) (8) was tilted into a horizontal position. The subjects were seated under the gantry with the head extended as far as possible through the scanner port, thereby locating the respiratory pathway, from the laryngeal prominence to the upper larynx, in the imaging field. The head was retained in a fixed position both laterally and vertically by means of Velcro tape straps, styrofoam restraining blocks fixed on top of the gantry and a rigid metal angle against which the subject was asked to continuously press his vertex.

The radioisotopes $^{15}O\text{-}CO_2$ and $^{15}O\text{-}O_2$ were produced with a Japan Steel Works BC-107 medical cyclotron and supplied to the scanning site at a rate of 6 to 8 mCi/min and a flow of 70 ml/min, held constant by means of a feedback control system. (Assuming a tidal volume of 0.5 l and a respiratory rate of 12 respirations per minute, breathing $^{15}O\text{-}CO_2$ at a concentration of 1 mCi/l corresponds to a supply rate of 6 mCi/min). Upon admixture of 200 ml/min of medical air, the radioisotope was administered into a light fitting face mask from which the subject breathed freely.

In order to get a relative measure of the supplied radioactivity concentration, the section of the supply line immediately distal to the face mask was routed through the patient port parallel to the axis of the tomograph, close to the periphery of its visual field, and imaged at the same time as the subject's neck region (Fig. 1). This information was required to normalize the ^{15}O-activity concentration in the tracheal ROI for

identical inhaled radioactivity concentrations in the $^{15}O\text{-}CO_2$ and $^{15}O\text{-}O_2$ tests. An absolute calibration of the $^{15}O\text{-}CO_2$ supply was obtained by bubbling the radioactive gas for 1 min into a vial containing 10 ml of one normal sodium hydroxide (NaOH) solution.

Following the procedure described by Powell et al. (Fig. 3 of Ref. 5) the imaging session consisted of two dynamic studies, one with the subject breating $^{15}O\text{-}O_2$ at a regular rate followed by one with $^{15}O\text{-}CO_2$. Each study was composed of a total of 20 frames of 30 sec duration each. Imaging was started as soon as the total coincidence count rate sharply increased, indicating arrival of the tracer gas at the face mask level. Tracer supply was maintained during the first ten frames (5 min buildup phase) and then stopped while continuing imaging for the remaining ten frames (5 min washout phase).

The spatial resolution of the tomograph in the dynamic (low resolution) mode is 19.5 mm FWHM in the transverse and 11 mm FWHM in the axial direction with a separation between the three simultaneous image planes of ~12 mm. Between 75,000 and 300,000 image-forming counts were collected in each frame of the buildup phase. The raw data was corrected for the presence of random and scattered coincidences, for deadtime and for variations in detector efficiency (8,9). Owing to the highly localized distribution of activity in the trachea, the outline of the neck, required to carry out the proper attenuation correction, was derived manually rather than by the usual thresholding technique (10). An ellipse with a circumference equal to the one measured around the subject's neck at the selected slice level was carefully placed over the image with the highest number of counts. This outline was then used for all frames of the study without changing its position.

After reconstruction, time-activity curves were derived from the serial images. Assisted by an MRI image obtained at the same level as the PET scan, the tracheal ROI was identified as the area slightly anterior to the region of the large neck vessels showing up as a half-donut shaped structure on the PET image (Fig. 2). A diameter of 2.4 cm was chosen for the size of the tracheal ROI which was about equal to the average diameter of the trachea (11). Selection of a larger diameter would have led to a significant contamination from ^{15}O radioactivity in the neighbouring large neck vessels.

Radioisotope Supply Line

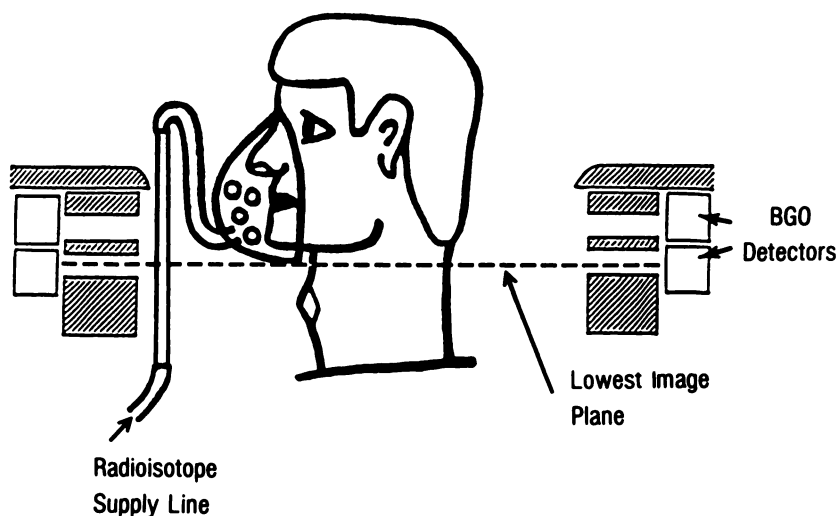Lowest Image Plane

BGO

Detectors

FIGURE 1
Schematic cross section of imaging situation indicating position of neck relative to lowest image plane and radioisotope supply line fed perpendicularly through patient port of tomograph.
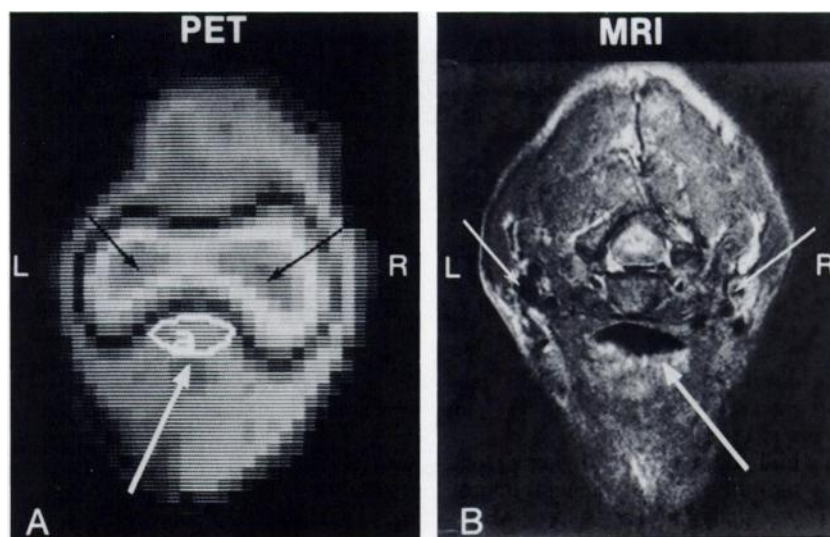
FIGURE 2
$^{15}O\text{-}CO_2$ PET image (A) and MRI image (B) obtained at identical levels indicating tracheal ROI (large arrows) anterior to large neck vessels (small arrows).

RESULTS

The time-activity curves of the relative ^{15}O activities in the tracheal ROI for one of the three $^{15}O\text{-}O_2$ and $^{15}O\text{-}CO_2$ experiments are presented in Figure 3. Upon initiation of the breathing period (0 sec), the $^{15}O\text{-}O_2$ curve rapidly rose to a level which remained constant until the radioisotope supply was turned off (300 sec). This constant $^{15}O\text{-}O_2$ level, calculated as the average of the ^{15}O-activity in the tracheal ROI over the first ten 30-sec frames of the study, was normalized to one. The
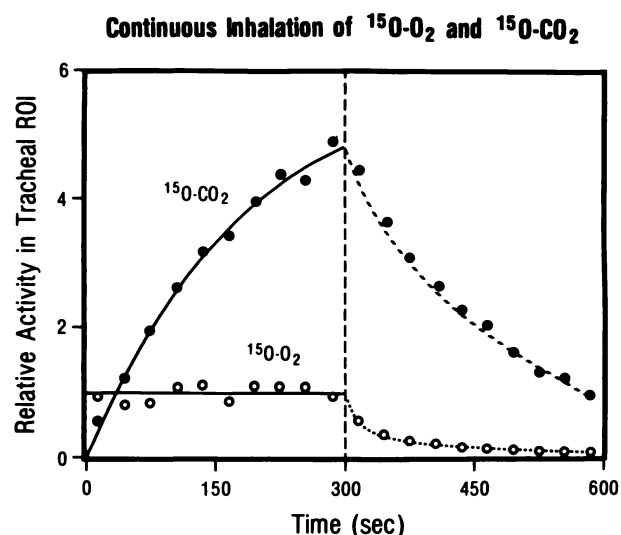
Continuous Inhalation of $^{15}O\text{-}O_2$ and $^{15}O\text{-}CO_2$

FIGURE 3
Continuous inhalation of $^{15}O\text{-}O_2$ and $^{15}O\text{-}CO_2$. Time-activity curves of relative ^{15}O radioactivity in the tracheal ROI measured by PET for one of the three subjects breathing sequentially $^{15}O\text{-}O_2$ and $^{15}O\text{-}CO_2$ mixed with air. The constant level found when breathing $^{15}O\text{-}O_2$ (no fixation of oxygen in tracheal wall) was normalized to one. The data is further normalized for equal radioisotope supply and corrected for the virtual absence of $^{15}O\text{-}CO_2$ in the exhaled air.

$^{15}O\text{-}CO_2$ curve showed a gradual increase with a tendency to level off as the inhalation time progressed. The peak value reached at the end of the breathing period was expressed as the ratio of the activity in the tracheal ROI at 5 min (frame No. 10) and the constant level for the corresponding $^{15}O\text{-}O_2$ inhalation study on the same subject, normalized to equal supply concentrations and corrected for the virtual absence of $^{15}O\text{-}CO_2$ in the exhaled gas. The mean ratio for the three subjects studied was 5.3 (5.0, 3.1, 7.9). The figure derived from the study by Powell et al. (5) was ~27.5.

The results of the analysis of the three continuous breathing studies are summarized in Table 1. Concentric circular ROIs of diameters varying between 0.8 cm and 2.4 cm were first placed over the areas corresponding to the radioisotope supply tube. As seen from column 2 of Table 1, the ratio of the $^{15}O\text{-}O_2$ and $^{15}O\text{-}CO_2$ activities in the supply ROI, averaged over the ten 30-sec frames of the breathing phase, was constant and independent of the ROI diameter for each subject studied. This ratio was used to normalize the tracheal data for equal radioisotope supply rates. The mean $^{15}O\text{-}CO_2$ supply rate into the face mask for the three studies was 7.1 mCi/min.

The ratios of the $^{15}O\text{-}CO_2$ activity value at 5 min after onset of radioisotope breathing and the constant $^{15}O\text{-}O_2$ level, shown in the last column of Table 1, were normalized for equal radioisotope supply in the paired $^{15}O\text{-}CO_2$ and $^{15}O\text{-}O_2$ studies as described above. The data was further normalized for equal time averaged concentrations in the lumen of the trachea to account for the fact that $^{15}O\text{-}CO_2$ is virtually absent in the exhaled gas whereas only about 20% of the inhaled oxygen is retained in the lungs. This means that for each tomographic image (30-sec frame) of the $^{15}O\text{-}CO_2$ study and neglecting dead space, the tracheal ROI reflects on the average only ~50% of the $^{15}O\text{-}CO_2$ activity present during the inhalation phase (average of inhaled

TABLE 1
$^{15}O-O_2$ and $^{15}O-CO_2$ Continuous Inhalation PET Data

Subject no.	Radioisotope supply		Tracheal ROI	
	ROI diameter (cm)	$\left[\dfrac{^{15}O-O_2 \text{ activity}}{^{15}O-CO_2 \text{ activity}}\right]^*$	ROI diameter (cm)	$\left[\dfrac{^{15}O-CO_2 \text{ activity at 5 min}}{\text{average }^{15}O-O_2 \text{ level}}\right]^\dagger$
1	0.8	1.04	2.4	5.03
	1.6	1.03 mean: 1.030		
	2.4	1.02		
2	0.8	1.02	2.4	3.16
	1.6	1.02 mean: 1.023		
	2.4	1.03		
3	0.8	1.07	2.4	7.90
	1.6	1.07 mean: 1.070		
	2.4	1.07		

mean ratio: 5.36 (range: 4.74)
(Powell et al. (5): ~27.50)

* Activities averaged over ten 30-sec frames from start to stop of radioisotope supply.
† Ratio corrected for equal radioisotope supply rates and for almost complete absence of $^{15}O-CO_2$ in exhaled gas, neglecting activity in the dead space.

and exhaled activity). The corresponding percentage for the $^{15}O-O_2$ study is ~90%. A correction factor of 90%/50% = 1.8 was therefore included in the tracheal ($^{15}O-CO_2$)/($^{15}O-O_2$) ratio figures. The average ratio of 5.3 is ~5.2 times smaller than the figure measured by Powell et al. (5). Since the radiation absorbed dose to an organ is linearly related to its radioactivity concentration, our comparative estimates of radiation absorbed dose to the tracheal mucosa and the upper larynx (Table 2) were obtained by scaling down the figures published by Powell et al. (5) by a factor of 5.2. The derived estimates based either on the figures calculated by these authors or on their TLD-measurements are shown in Table 2. These values presume that the subject is inhaling air for 1 hr at an ^{15}O concentration of 1 mCi per liter of air. The figures given in brackets apply to a typical ^{15}O

TABLE 2
Radiation Absorbed Dose Estimates to the Upper Airways from Continuous Inhalation of $^{15}O-CO_2$ in Man*

Investigator	Absorbed dose estimate (rad)	Structure	Method	Remarks
Powell et al. (5)	200	tracheal mucosa	longitudinal PET, continuous inhalation of $^{15}O-O_2$ and $^{15}O-CO_2$	Dose estimate calculated according to formalism of Loevinger et al. (6).
	75			Dose estimate based on TLD-measurements on tracheal phantom.
Powell et al. (13)	3.3	equivalent to tracheal mucosa	direct TLD measurements on Lucite tracheal phantom	
Bigler et al. (12)	5.2	mouth	direct ^{15}O assay	Study in man
	2.8	nose	of saliva and	
	3.5	trachea	mucus samples	Derived from studies in dogs
Present study	38 (13)	upper larynx region	transaxial PET, continuous inhalation of $^{15}O-O_2$ and $^{15}O-CO_2$	Comparative dose estimates derived from calculated values by Powell et al. (5).
	14 (5)			Comparative dose estimates derived from TLD-measurements by Powell et al. (5). (Figures in brackets apply to a typical study involving continuous inhalation of air at an O-15 supply rate of 4 mCi/min or 0.66 mCi/liter for 30 minutes).

* Assuming inhalation of air for 1 hr at an ^{15}O concentration of 1 mCi/l of air.

steady-state blood flow study of 30 minutes duration with a continuous ^{15}O-CO_2 supply rate of 4 mCi/min, equivalent to a concentration of 0.66 mCi/l. For comparison, radiation absorbed dose estimates to the mouth, the nose and the trachea calculated by Bigler et al. (12) and based on direct measurements of ^{15}O activity in saliva and mucus in man and in dogs are given in Table 2 together with data of TLD measurements on a Lucite tracheal phantom by Powell et al. (13). The dose to the lungs as calculated by Bigler and Sgouros (3) is 1.2 rad involving the breathing of air at an ^{15}O concentration of 1 mCi per liter for 1 hr.

DISCUSSION

The present study was carried out with the aim of deriving relative figures of radiation absorbed dose to the trachea from ^{15}O-CO_2 steady state CBF studies with reference to the data of Powell et al. (5), using the equipment and methodology currently available at our Institute. The continuous breathing experiment performed by these authors was therefore duplicated and radiation absorbed dose estimates to the upper airways, applicable to our clinical procedures, derived indirectly.

The measured tracheal ^{15}O-O_2 and ^{15}O-CO_2 time activity curves (Fig. 3) show the same general behaviour as the ones recorded by Powell et al. (5) with the difference, however, that the peak value at 5 min on our ^{15}O-CO_2 curves is significantly smaller, indicating a substantially reduced retention of the label under our experimental conditions. Derived radiation dose estimates are therefore much lower than those due to Powell et al. (5) and within a factor of about four of the estimates of Bigler et al. (12) if one accepts the TLD results (Table 2).

The figures of 3 to 5 rad derived by Bigler et al. (12), which interestingly enough are in close agreement with TLD measurements on a Lucite tracheal phantom by Powell et al. (13), are based on radiation dose determinations using the method of direct sampling and ^{15}O-assaying of mucus and saliva from the linings of the airways in humans and dogs. These values are well within the accepted dose range for PET procedures (14). Since the method of direct sampling is more accurate than imaging techniques with their inherent problem of crosscontamination from neighboring structures due to the limited spatial resolution, the dose estimates derived in the present study are considered to be purely comparative with reference to the data of Powell et al. (5).

There are several factors which might contribute to the discrepancy between the data of Powell et al. (5) and the results of our study. Free breathing of the gas via a light fitting face mask instead of tubes introduced into mouth and/or nose, in our experience, gives the best result with regard to stability of arterial ^{15}O levels

and patient comfort. This procedure is also used by other workers in the field (2,15). No details are given about the gas administration method used by Powell et al. (5). The presence of significant amounts of water vapor in the inhaled gas would greatly facilitate physical adsorption of ^{15}O-labeled water on mucous membranes leading to larger tracheal activities than would result from our supply condition where special drying tubes (Matheson, Whitby, Ontario, Canada) were used to eliminate all traces of moisture. Another factor is the accurate assessment of the relative radioisotope supply rates which is essential in order to correctly normalize the data of the paired ^{15}O-O_2 and ^{15}O-CO_2 studies. Our method of simultaneously imaging the supply tube carrying the label at a constant flow allows us to monitor this parameter as close to the inhalation site as possible during the actual study. We further applied a single theoretical correction factor to all three studies to adjust the tracheal ROI information to the gas specific differences in the ^{15}O concentrations in the inhaled and exhaled air. The correction method used by Powell et al. (5) is not given explicitly. In the present study, transaxial tomography was used and the region referred to as tracheal ROI rather corresponds to the upper larynx area extending into the pharynx close to the opening of the esophagus since the restricted patient port opening did not allow selection of image planes below the level of the laryngeal prominence. This region contains saliva reflecting O-15 activities characteristic of the pharynx as well as mucus from the lungs prior to being swallowed. Since the direct sampling experiments by Bigler et al. (12) have shown the highest activity concentration in the oropharynx, variable amounts of this high activity might be wrongly assigned to the tracheal region due to the resolution and positioning limitations of the tomograph. This situation might explain the fact that our derived dose estimates to the trachea are still higher than the direct estimates due to Bigler et al. (12). The study by Powell et al. (5) is based on longitudinal tomography. The size and position of the analyzed tracheal region of interest, however, is not specified. Although the spatial resolution characteristics of the two tomographs involved most likely are different (no mention is made of the machine used by Powell et al. (5)), the dimensions of a resolution element and the size of the selected ROIs are much larger than the tracheal wall thickness making it impossible to determine the absolute ^{15}O activity in this structure. The experimental conditions, as far as imaging is concerned, are therefore considered to be comparable for the two studies. Since the ^{15}O activity in blood and tissues gradually builds up during the continuous inhalation process, the selected tracheal ROIs necessarily contain variable amounts of contaminating ^{15}O activity from neighboring structures due to the limited spatial resolution of the tomograph. In the present study great care was taken to minimize activity

contributions from the major neck vessels running alongside the respiratory tract.

No definite reason was given by Powell et al. (5) for the disagreement between the dose estimates based on theoretical calculations and those based on TLD-measurements on a tracheal phantom. The fact that our dose figures derived from their TLD results are closer to the direct dose estimates by Bigler et al. (12) than the theoretical values supports the TLD-measurements and the adequacy of the tracheal phantom used by Powell et al. (13).

Methods have been proposed to reduce the radiation dose to the respiratory system by choosing different ways of tracer administration. The intravenous infusion of ^{15}O-labeled water, either as a bolus (16,17) or continuously (18) are alternatives. Although the dose to the lung is reduced with these techniques (4), the dose to the blood vessel lining at the infusion site might be substantial (12).

In conclusion, based on this comparative study, we estimate that for the continuous ^{15}O-CO_2 inhalation method, the radiation absorbed dose to the upper airways is of the same order of magnitude as the generally accepted dose of 1.2 rad for the lungs calculated by Bigler and Sgouros (3). Supported by the direct dose estimates of Bigler et al. (12), our results suggest that the tracheal radiation absorbed dose from inhaled ^{15}O-CO_2 is lower than the levels reported by Powell et al. (5). An absorbed dose of 3 to 5 rad seems more probable, which makes the steady state ^{15}O-CO_2 method a safe and practical means of measuring cerebral blood flow.

ACKNOWLEDGMENTS

REFERENCES

1. Jones T, Chesler DA, Ter-Pogossian MM. The continuous inhalation of oxygen-15 for assessing regional oxygen extraction in the brain of man. Br J Radiol 1976;49:339-343.

2. Frackowiak RSJ, Lenzi G-L, Jones T, et al. Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography. Theory, procedure and normal values. J Comput Assist Tomogr 1980;4:727-735.

3. Bigler RE, Sgouros G. Biological analysis and dosimetry for ^{15}O-labelled O_2, CO_2, and CO gases administered continuously by inhalation. J Nucl Med 1983; 24:431-437.

4. Kearfott KJ. Absorbed dose estimates for positron emission tomography (PET): $C^{15}O$, ^{11}CO, and $CO^{15}O$. J Nucl Med 1982;23:1031-1037.

5. Powell GF, Schuchard RA, Reff CS, et al. Radiation absorbed dose to tracheal mucosa from inhaled oxygen-15-labelled carbon dioxide. Ann Neurol 1984; (Suppl Vol 15):S107-S109.

6. Loevinger R, Japha EM, Brownell CL. Radiation dosimetry. New York: Academic Press, 1956:693-722.

7. Meyer E, Yamamoto YL, Evans AC, et al. Radiation dose to the trachea from inhaled oxygen-15 labelled carbon dioxide. J Nucl Med [Abstract]1985;26:P62.

8. Cooke BE, Evans AC, Fanthome EO, et al. Performance figures and images from the Therascan 3128 positron emission tomograph. IEEE Trans Nucl Sci 1984;NS-31:640-644.

9. Cooke BE, Evans AC. A phantom to assess quantitative recovery of positron tomographs. J Comput Assist Tomogr 1983;7:876-880.

10. Bergstrom M, Litton J, Eriksson L, et al. Determination of object contour from projections for attenuation correction in cranial positron emission tomography. J Comput Assist Tomogr 1982;6:365-372.

11. Gray H. Anatomy, descriptive and surgical. New York: Crown Publishers, 1977:965.

12. Bigler RE, Sgouros G, Zanzonico PB, et al. Radiation dose to the respiratory airway linings from inhalation of (^{15}O)-carbon dioxide [Abstract]. J Nucl Med 1985;26:P62.

13. Powell G, Reft C, Schuchard R, et al. Beta particle dose to the major airways from inhaled gas [Abstract]. J Nucl Med 1984;25:P39.

14. Yamamoto YL, Thompson CJ, Diksic M, et al. Positron emission tomography. Neurosurg Rev 1984; 7:233-251.

15. Baron JC, Comar D, Bousser MG, et al. Etude tomographique, chez l'homme, du débit sanguin et de la consommation d'oxygène du cerveau par inhalation continue d'oxygène 15. Rev Neurol 1978;134:545-556.

16. Herscovitch P, Markham, J, Raichle ME: Brain blood flow measured with intravenous $H_2^{15}O$. I. Theory and error analysis. J Nucl Med 1983;24:782-789.

17. Raichle ME, Martin WRW, Herscovitch P, et al. Brain blood flow measured with intravenous $H_2^{15}O$. II. Implementation and validation. J Nucl Med 1983; 24:790-798.

18. Jones SC, Greenberg JH, Dann R, et al. Cerebral blood flow with the continuous infusion of oxygen-15-labelled water. J Cerebr Blood Flow Metab 1985;5:566-575.