PRELIMINARY OBSERVATIONS ON EXCRETION OF ^{37}Ar FROM MAN FOLLOWING WHOLE-BODY NEUTRON ACTIVATION—AN INDICATOR OF TOTAL-BODY CALCIUM

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Measurements of exhaled ^{37}Ar produced by total-body neutron irradiation of ^{40}Ca were used to determine total-body calcium in 16 human subjects. There was a good correlation between body calcium using the 30-min postirradiation breath sample of ^{37}Ar and body calcium determined by measurement of ^{49}Ca.

For the past 5 years the technique of in vivo neutron activation analysis has been successfully used at the University of Washington to measure total-body calcium in a variety of patients (*1–4*). The method employs uniform total-body irradiation with 200 mrads of cyclotron-produced neutrons followed by total-body counting of the gamma rays emitted by ^{49}Ca ($T_{1/2}$ = 8.8 min) (*1,2*). The ^{49}Ca is formed by slow neutron capture by stable ^{48}Ca in the skeleton (93–99% of total-body calcium is in the skeleton). We have been interested in finding techniques to significantly lower the patient radiation dose while maintaining the precision and accuracy of measurement. A possible method of accomplishing both of these goals is to quantitate ^{37}Ar which is produced from a fast neutron reaction (n,α) on ^{40}Ca. The long-lived radioargon ($T_{1/2}$ = 35 days) can be recovered from the exhaled breath and counted inside a small, low-background gas proportional detector.

Palmer has shown that the amount of radioargon exhaled is a quantitative indicator of total-body calcium (*5*). In rats, total-body calcium was measured with an accuracy of ±3%. These data also suggested that measurements of total-body calcium in humans can be obtained with a neutron exposure of 10 mrads or less.

The reduction of the patient dose could be accomplished for two reasons. First, ^{40}Ca comprising 99.7% of naturally occurring calcium is approximately 500 times more abundant than ^{48}Ca. A neutron is more likely, therefore, to be within the interaction distance of a ^{40}Ca nucleus. The reduction in the number of neutrons needed for activation (i.e., the dose) is somewhat counterbalanced by the lower average cross section for the (n,α) reaction (approximately a factor of 5) (*6,7*). Despite this, a significant dose reduction is possible. The second reason for dose reduction is the efficiency of the proportional detector. Argon-37 decays producing 2.62-keV Auger electrons that have a range of less than 0.02 mm resulting in proportional counterdetection efficiency of essentially 100%. In comparison, the sodium iodide counter used in the ^{49}Ca technique has an efficiency of 2–6% for the 3.1-MeV ^{49}Ca gamma photon. The advantage of the 100% efficiency is somewhat offset by the slow rate of decay of the ^{37}Ar nuclide. However, since it is convenient to count the ^{37}Ar for 4–16 hr, the net result is still a major reduction in the patient dose.

This report presents the initial findings in an investigation of the feasibility of using exhaled ^{37}Ar to quantitate body calcium in man. Thus far, the investigation has focused on determining the excretion rate of ^{37}Ar as a function of time after irradiation.

TECHNIQUE

Sixteen patients who were undergoing serial examinations of body calcium with the cyclotron facility by the ^{49}Ca technique (*1,2*) were used for these studies. The neutron beam produced by the cyclotron has a mean energy of 8 MeV with a full width at half maximum of 8 MeV and thus produces both the ^{48}Ca(n,γ) ^{49}Ca thermal reaction and the ^{40}Ca(n,α)

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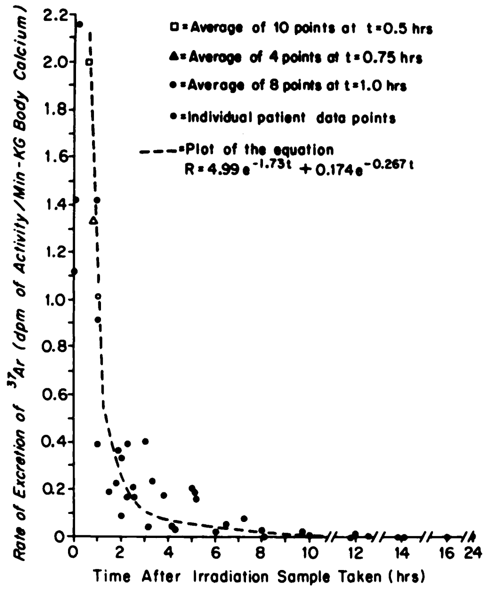

FIG. 1. Argon excretion rate versus time after irradiation. The data displayed are results of sampling 16 patients at one or more time periods following neutron irradiation at cyclotron facility. Excretion rate (vertical axis) is expressed in relation to total-body calcium of each patient.

^{37}Ar reaction in the patient. The (n,α) reaction for ^{37}Ar is most probable at neutron energies between 6 and 14 MeV.

Argon-37 excretion was measured by taking several samples of the exhaled breath at various times after irradiation (Fig. 1). Continuous collections were not possible because the breath collection apparatus could not be used during the three 12-min total-body counting procedures after irradiation (for ^{49}Ca) (*1*).

The techniques for collecting, purifying, and counting the samples of exhaled ^{37}Ar are essentially the same as those used for animal studies (*5*). During breath collection, the patient breathes a 25% O_2–75% helium mixture to minimize the amount of nitrogen in the samples. The patient is placed on a closed circuit rebreathing system during the sample collection interval (20–40 min). (The system has been used continuously up to 6 hr.) At the end of the interval, the gases in the breathing system are pumped through a stainless steel sampling cylinder which is immersed in liquid nitrogen. The sampling cylinder, filled with type 5-A molecular sieve, captures all gases except helium. To recover the ^{37}Ar, the gases in the cylinder are passed over copper at 400°C to remove oxygen, then through soda lime, $CaSO_4$ and Aquasorb to remove water and Co_2, and finally over calcium at 600°C to remove nitrogen and residual traces of oxygen. The remaining gas containing the ^{37}Ar is transferred into a 500-cc proportional detector which is then filled with a mixture of 90% argon and 10% methane to a pressure of 15 lb absolute. Finally, the sample is counted for 4–12 hr with the detector placed between two 9 in. diam × 4 in.-thick-NaI(Tl) detectors that act as a cosmic ray anticoincidence shield.

RESULTS

The combined data for the excretion of ^{37}Ar at various times after activation from the 16 patients are shown in Fig. 1. On the vertical axis the ^{37}Ar excretion is indicated as a rate normalized to the total-body calcium of each patient as measured independently by the ^{49}Ca technique. The data indicate that the maximum rate of ^{37}Ar excretion occurs immediately (5–20 min) after irradiation. By 6 hr the excretion rate has decreased to approximately 1% of the maximum value. The downward limb of the excretion curve can be described by a double exponential equation. The fast component of the descending limb has a $T_{1/2}$ of approximately 27 min, and the $T_{1/2}$ of the slow component is approximately 156 min.

Figure 2 represents plots of the serial ^{37}Ar excretion rates from two individuals and is typical of that seen in patients when three or more serial samples are obtained. (The curves in Fig. 2 represent the two extremes observed in the combined data plotted in Fig. 1). These excretion patterns could be described by the same equation used for the combined data, differing only in the values of the multiplicative constants of each exponential.

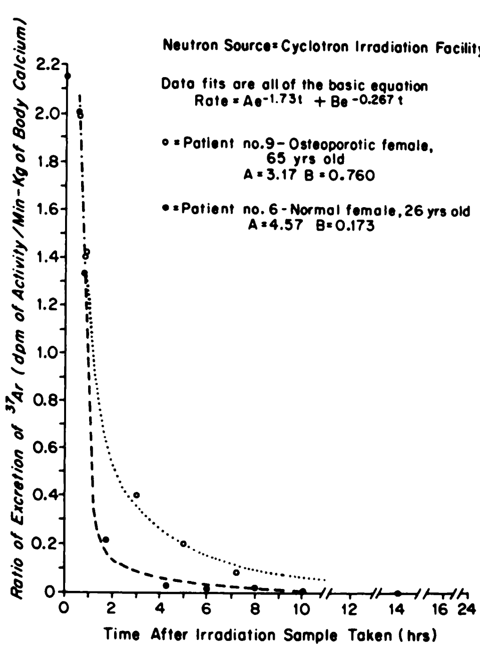

FIG. 2. Continuous argon excretion rate from two patients following irradiation. Rate is expressed in relation to total-body calcium. These patients represent fastest and slowest rates observed in combined data depicted in Fig. 1.

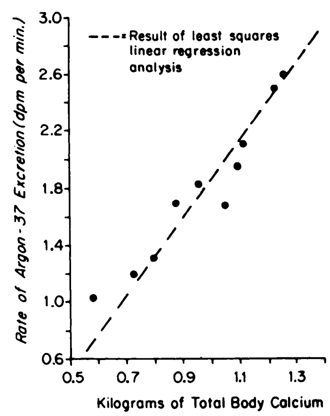

FIG. 3. Argon-37 excretion rate in humans at 30 min after irradiation compared with total-body calcium. Correlation is apparent with our r value of 0.97. Dashed regression line is described by $y = 2.74x - 0.87$.

To determine if ^{37}Ar excretion was correlated with the patient's body calcium content, the excretion rate at 30 min after irradiation was carefully determined in ten of the patients. (This interval was chosen as a convenient time near maximum excretion that would not interfere with the total-body counting procedure.) A plot of the 30-min ^{37}Ar excretion rate versus the body calcium of these ten patients is seen in Fig. 3. A good correlation is evident and an r value of 0.97 was obtained by least-squares linear regression analysis that took into account the precision of measurement of the ^{37}Ar activity for each point.

DISCUSSION

These initial studies describe the basic kinetics of the excretion of ^{37}Ar following neutron activation of skeletal ^{40}Ca in man. It is apparent that ^{37}Ar excretion is relatively rapid with the maximum rate occurring immediately; by 6 hr after activation 96–98% of the excretion has occurred (area under the curve seen in Fig. 1). It is of particular interest that the 30-min ^{37}Ar excretion rate is closely correlated with total-body calcium.

To measure total-body calcium by the ^{37}Ar method, it appears that a 3–6-hr total collection period after irradiation might suffice. This, however, remains to be determined by further experimentation.

The characteristics of the ^{37}Ar excretion rate data may be related to the various structural components of the skeleton (i.e., trabecular and cortical bone) and their proportionate mass. The fast excretion component may be derived primarily from trabecular bone which has relatively high blood flow, extracellular volume, and active bone surface. Thus, the ^{37}Ar produced in this bone would be delivered to the lungs more rapidly. Conversely, cortical bone (dense bone) with relatively less blood flow, extracellular volume, and total bone surface may release the ^{37}Ar more slowly and hence be responsible for the slow component of the ^{37}Ar excretion rate (Fig. 1). It is possible that the differential analysis of the ^{37}Ar excretion rates in a given patient may provide an index of the relative amounts of cortical compared with trabecular bone. Since trabecular bone is likely to show more alteration with disease, serial analysis may show important quantitative changes in the two components as a disease state progresses or remits.

Although most of the ^{37}Ar excreted in these studies appears in the first few hours, it is still unclear if small amounts of ^{37}Ar are retained in the bone over extended periods of time. In studies of rats and dogs, there is not any significant long-term retention of ^{37}Ar. In vitro studies by Bigler, et al (*8*) of dead bone irradiated with neutrons suggested that as much as 30% of the ^{37}Ar formed was not released, even after grinding the bone. Based on their estimate of specific activation (microcuries of ^{37}Ar produced per unit of neutron exposure) and a single human irradiation, they suggest that retention of similar amounts of ^{37}Ar may occur in vivo. If a retained fraction were quite constant, as is apparently the case with radon (*9,10*), then the counting of only the excreted fraction of the activated ^{37}Ar would not cause inaccuracies in total-body calcium measurements. At present, however, such retention remains a question and this point will be carefully explored as we proceed in our investigations.

The next human studies will be done with 14-MeV neutrons produced by a small $^{3}H(d,n)^{4}He$ generator. With a properly designed patient irradiation enclosure, the high-energy neutrons should provide a uniform activation of ^{40}Ca in the body (*11*). It will be possible to determine the minimum collection intervals needed to measure reproducibly body calcium content. Relating the amount of ^{37}Ar excreted from a patient to the grams of body calcium (quantitative calibration) will be possible by measuring ^{37}Ar excretion in patients who have had a recent total-body calcium measurement made by the established ^{49}Ca system.

The ^{37}Ar technique appears to offer several advantages over the ^{49}Ca technique currently in use. First, since a moderate flux neutron generator, a relatively uncomplicated gas-purifying system, and a simple proportional detector can be used, the cost of operation of the equipment is small. The accuracy and precision of the technique are potentially excellent due, in part, to the absence of any other radionuclides in the purified gas sample and to the elimination of inaccuracies produced by variations in patient geometry that are inherent in whole-body counting. The principal advantage of the ^{37}Ar technique, however, is the reduction of the patient dose. Our calculations from the current experiments confirm that an examination with 14-MeV neutrons resulting in a precision of 1% in determining the ^{37}Ar activity in a 3-hr sample should be possible with a dose of 10 mrads or less.

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