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THE FEASIBILITY OF DETERMINING TOTAL BODY CALCIUM BY MEASURING ^{37}Ar IN
EXPIRED AIR AFTER LOW LEVEL IRRADIATION WITH 14 MeV NEUTRONS*

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MASTER

Abstract

During the irradiation of bone by 14 MeV neutrons a small quantity of the calcium is converted to ^{37}Ar by an (n, α) reaction. The ^{37}Ar leaves the bone and is released from the body through the expired air. This small amount of ^{37}Ar can be separated and purified from the other gaseous components and the quantity can be determined very efficiently by counting internally in a small proportional counter. The time required for more than 95 percent of the ^{37}Ar to leave the body is about 1 hour for rats, 1 1/2 hours for dogs, and is expected to be no more than 2 hours for humans. Satisfactory total body calcium measurements in humans should be possible with a radiation dose as small as 0.001 rad. This would be a factor of 50 to 200 times lower dose than that used for present in vivo neutron activation methods for total body calcium. This article describes the techniques and apparatus developed to perform these studies, discusses the results of experiments with rats and dogs, and predicts the usefulness of this technique for use with human patients.

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1. PRODUCTION OF ARGON RADIOISOTOPES FROM FAST NEUTRON INTERACTION WITH CALCIUM

Two argon radioisotopes, ^{37}Ar and ^{41}Ar , are produced during fast neutron irradiation of calcium. The decay half-lives of these radioisotopes are 35.1 days and 1.83 hours respectively. The 97 percent abundance stable isotope ^{40}Ca produces ^{37}Ar by the reaction $^{40}\text{Ca}(n,\alpha)^{37}\text{Ar}$ and the 2 percent abundance ^{44}Ca produces ^{41}Ar by the reaction $^{44}\text{Ca}(n,\alpha)^{41}\text{Ar}$. The cross section for these reactions for 14 MeV neutrons are approximately 110 millibarns for $^{40}\text{Ca}(1)$ and 30 millibarns for $^{44}\text{Ca}(2)$. From these cross section values and the natural abundances of ^{40}Ca and ^{44}Ca it can be calculated that about 180 times more ^{37}Ar is produced than ^{41}Ar . However, since the half life of ^{37}Ar is 460 times longer than ^{41}Ar , the initial activity of ^{41}Ar would be about 3 times that of ^{37}Ar . Since it takes 1 to 2 hours for argon to be excreted from the body, the activity of the two isotopes would be nearly the same at the time of counting. For longer counting times, i.e., several hours or days, ^{37}Ar would provide a much higher total count.

A problem in using ^{41}Ar as a measure of total body calcium is that an (n,p) reaction on ^{41}K also produces ^{41}Ar and, therefore, the potassium in the

body produces an interference for the calcium measurement. There are no apparent interferences in the use of ^{37}Ar as a calcium measurement except that ^{41}Ar must be allowed to decay away before counting. When comparing ^{37}Ar and ^{41}Ar for use in total body calcium measurements in regards to the lowest radiation dose, interferences, and counting sensitivity, the ^{37}Ar appears to be by far the best isotope to collect and measure.

2. COLLECTION AND PURIFICATION OF ^{37}Ar FROM THE BODY

The components of normal expired air are approximately 79% nitrogen, 16% oxygen, 4% carbon dioxide and a 1% fraction consisting of small quantities of water vapor, argon, hydrogen, etc. The boiling point and adsorption characteristics of nitrogen are so similar to those of argon that it is very difficult to separate a small quantity of ^{37}Ar from a large volume of nitrogen. The actual volume of ^{37}Ar gas which will be produced, collected, and purified is less than 1×10^{-13} cc (3×10^6 atoms) whereas the normal volume of expired nitrogen would be approximately 500 liters per hour from a human.

By substituting for inspired air a gas mixture of 80% helium and 20% oxygen such as that used by deep sea divers, the separation of ^{37}Ar is greatly simplified. The use of this gas mixture eliminates nitrogen and stable argon except for the small quantities which are adsorbed in the body tissue. The amount of adsorbed argon in the human body is negligible and that fraction of the 800 to 900 cc of adsorbed nitrogen⁽³⁾ which is expired during the ^{37}Ar collection period can be removed by reacting with hot calcium or lithium.

The ^{37}Ar is easily separated from oxygen, carbon dioxide, and water vapor and the apparatus and procedure for doing this with animals is shown in Figure 1. Larger animals such as a dog can be fitted with a hood with an air-tight connection at the neck. Smaller animals such as rats are placed completely inside an air-tight container. The helium-oxygen mixture flows through the hood or container at a rate of 2 liters per minute for an adult beagle dog and about 200 cc/minute for a rat. When a hood is used, expansion bags and an air pump are used to keep pressure the same both inside and outside of the hood. The expansion bags and pump can be eliminated when the animal is completely enclosed in the container.

The gas leaving the hood is bubbled through a solution of 30 to 50% NaOH or KOH to remove CO_2 , passed through hot copper at 400°C to remove oxygen, through an ice bath trap, CaSO_4 and P_2O_5 to remove water vapor and through a trap containing activated charcoal at liquid nitrogen temperature which quantitatively collects all the ^{37}Ar and allows the helium to pass through. Except for the nitrogen which also adsorbs on the activated charcoal the ^{37}Ar is pure enough to be transferred directly into a proportional counter for measuring the activity. Figure 2 shows the apparatus for transferring the ^{37}Ar into the counter. Hot calcium removes nitrogen and any remaining oxygen and the gas is transferred to a small activated charcoal trap which leads directly into the counter. This trap is warmed up and all the ^{37}Ar is swept into the counter with a counting gas composed of 90% argon and 10% methane.

All traps and absorbers were designed for a maximum flow of 2 liters per minute which is adequate for animal experiments but would have to be scaled up in size to handle human breathing rates. Another alternative would be to compress the expired air into tanks as it leaves the body and then slowly flow it through the present apparatus.

The copper used to remove oxygen was in the form of short lengths of wire less than 1/4 inch long and 0.025 inch diameter which can be purchased in the cupric oxide form and then reduced with hydrogen at 400°C. This makes a very reactive column for oxygen removal and the column can be easily regenerated from oxide to copper with hydrogen for indefinite reuse. The CaSO_4 is a commercial drying agent and the P_2O_5 is used as a covering on glass beads for the final removal of water vapor. The activated charcoal was a commonly available coconut charcoal, 6-14 mesh, which is outgassed under vacuum for about 10 minutes at a temperature of about 250 to 300°C before being used to absorb the ^{37}Ar .

3. MEASUREMENT OF ^{37}Ar ACTIVITY

A very sensitive method for measuring ^{37}Ar is to place it internally into a gas proportional counter. The fluorescent yield of the 2.63 keV chlorine X rays which are emitted during ^{37}Ar decay is only 6.5 percent. Therefore, in 93.5 percent of the disintegrations, the energy will be emitted as Auger electrons having an energy of 2.62 keV and these will be absorbed within a very small counter with essentially 100 percent efficiency. The calculated range of a 2.6 keV electron in argon gas at atmospheric pressure would be less than 0.02 mm. With such a short range and the very small amount of ^{37}Ar , the proportional counter can be made very small and a background of less than 0.1 count per minute is easily obtained. This low background coupled with the almost 100 percent counting efficiency and the relatively long half-life of 35.1 days allows a very sensitive measurement of ^{37}Ar activity.

4. RESULTS OF ANIMAL STUDIES

One of the problems anticipated with this method was that the ^{37}Ar might take several hours or possibly days to be released from the bone matrix. Also, since rare gases are known to be absorbed to some extent by body fat, there is the possibility that this would delay the transfer of the ^{37}Ar out of the body. Neither of these problems appear to be significant.

Early studies in which a live and dead rat were simultaneously irradiated and then whole body counted for ^{41}Ar with a Ge(Li) detector one hour after irradiation showed that more than 85% of the ^{41}Ar had been expired from the live rat within one hour. A similar experiment on sections of leg bone of both a live and dead dog gave the same results. These results are encouraging but not conclusive since some of the ^{41}Ar in the animals is formed from potassium in soft tissue and would be released more readily than from bone. However, in the dog study the rear knee joint was irradiated and the major content of the leg at this point is bone such that the ^{41}Ar from potassium is a small fraction of the total.

Subsequent studies have been performed in which the ^{37}Ar was collected from the expired air of rats and dogs during and following 14 MeV neutron irradiation. Figure 3 shows ^{37}Ar collected from a rat during the first and second 1/2 hour intervals after the beginning of a 5-minute irradiation and indicates that more than 90 percent of the ^{37}Ar leaves the body within the first 30 minutes. Figure 4 shows that only 1 or 2 percent as much ^{37}Ar expired from a rat during the first hour is expired during the second hour. The removal of ^{37}Ar from a 12 kilogram dog occurs only half as rapidly as in the rat. Figure 5 shows that from 1 1/2 to 2 hours are required for removal of essentially all the ^{37}Ar from the dog.

A correlation of ^{37}Ar production to calcium content of animals has not been accomplished. The present effort is being devoted to improving the techniques of collection, separation, purifying, and counting the ^{37}Ar to make the method accurate and precise.

5. APPLICATION TO HUMAN TOTAL BODY CALCIUM MEASUREMENT

This technique has been used only on rats and dogs to this date. The results of these studies show that the method is feasible for use with human patients and the application to human use will probably occur within the next year. In the very near future with Dr. Nelp at the University of Washington School of Medicine we plan to begin collecting ^{37}Ar from patients who are irradiated for total body calcium determination. This will allow us to study the excretion rate of ^{37}Ar from the bone and body of humans and to determine how much, if any, is lost through the skin of the body. This information will allow us to determine if the expired air from a human can be collected with just a hood over head or if complete enclosure of the body is necessary.

The radiation dose required for human use has been estimated by irradiating a phantom containing a known quantity of calcium with a known dose of 14 MeV neutrons and then collecting and counting the ^{37}Ar . For a person containing 1000 grams of calcium, a dose of 0.001 rad will produce about 200 disintegrations of ^{37}Ar per hour and a 2 days count would then give almost 10,000 net counts over a background of about 300 counts. This level of radiation dose should remove all doubts about the radiation hazard in total body calcium measurements and would allow many repeated measurements on the same patient.

The method should be very useful in studying and assessing bone disease and studying the apparent calcium loss in Astronauts. The method offers the advantages of much lower radiation dose and greater accuracy than existing methods in in vivo neutron activation analysis for calcium. The method does not require whole body counting with its inherent errors due to different counting efficiency for different size persons and interferences from other isotopes produced in the body.

The completeness of the removal of ^{37}Ar from the human body has not yet been determined. If it is found that there is a fraction of the bone which releases the ^{37}Ar more slowly, the method should still be of value since the ^{37}Ar which is released will probably come from the more metabolically active bone which would be of the most interest.

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Fig. 1

Apparatus for collecting and purifying ³⁷Ar from expired air of animals

Fig. 2

Apparatus for transferring purified ^{37}Ar from activated charcoal trap in to a proportional counter

Fig. 3

^{37}Ar in expired air from a rat irradiated with fast neutrons for 5 minutes

Fig. 4
 ^{37}Ar in expired air from a rat irradiated with
 ^{14}MeV neutrons for 5 minutes

Fig. 5

^{37}Ar in expired air from a dog irradiated with
14 MeV neutrons for 5 minutes