jnm / PRELIMINARY NOTES

Absolute Measurement of Total-Body Calcium by the Ar-37 Method—Preliminary Results: Concise Communication

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Measurements of exhaled Ar-37 produced by total-body neutron irradiation of Ca-40, were used to determine total-body calcium in ten human subjects. There was a good correlation between the Ar-37 yield and total-body calcium determined by measurement of Ca-49.

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We have recently developed a low-dose method that uses neutron activation to measure total-body calcium (TBCa) in humans. The principle of the method was first described by Palmer (*1*); it uses 14-MeV neutrons to produce argon-37 in bone by the $^{40}Ca(n,\alpha)^{37}Ar$ reaction, and the resulting argon is then recovered from the exhaled breath (*1*). Argon-37 radioactivity is measured in a small low-background gas proportional detector.

Under the appropriate conditions of irradiation, the amount of Ar-37 produced is proportional to the amount of calcium present. Since 98–99% of the body's calcium is contained in the skeleton in constant proportion, measurement of TBCa is in effect a measure of bone mass.

Single as well as serial measurements of TBCa (in effect calcium balance) are extremely valuable for the study of a variety of metabolic bone abnormalities. In our laboratory bone-wasting diseases such as osteoporosis are under detailed study to elucidate the natural history of the disease and to evaluate the effect of drugs that inhibit loss of bone mass. The neutron activation analysis (NAA) technique is ideally suited to this type of drug evaluation.

Measuring TBCa by in vivo total-body NAA is not new, but has been limited to the $^{48}Ca(n,\gamma)^{49}Ca$ thermal neutron reaction. In this case the gamma-emitting, 8.8-min Ca-49 is measured by whole-body counting immediately following activation (*4*).

The Ar-37 method has a major advantage of reducing the total-body dose to 10 mrads or less per measurement, as opposed to the 60–200 mrads required for Ca-49 studies. Thus, selected population studies of TBCa will be quite acceptable, as well as long-range repetitive studies in various disease groups.

The purpose of this paper is to report the first quantitative measurements of total-body calcium in ten human subjects using the new Ar-37 TBCa system, and to indicate accuracy and basic design features of the method.

METHODS

Fast neutrons (14 MeV) are produced by a neutron generator* placed 5 m in front of a patient-irradiation enclosure. The enclosure is an aluminum water tank, 213 cm high, 61 cm wide, and 30.5 cm thick, mounted on a turntable. Uniformity of activation was ±2.7% for a bilateral irradiation (front and back), as determined by measuring the yield of Ar-37 from small vials containing known amounts of Ca-40 in solution at 45 positions within the water-filled tank.

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For the TBCa measurement, the patient is placed within the tank with shoulders level with the top. The tank is filled with water and a face mask is fitted to the patient. The mask is connected to a closed-circuit breathing system containing 30% oxygen and 70% helium.† An equally timed bilateral (front-and-back) irradiation is then performed for the desired whole-body dose (10 mrad for the studies presented in this report). The dose is standardized from one irradiation to another by the activation of four aluminum disks placed near the patient during irradiation. After a counting period of 1,000 sec, 50,000 counts can be obtained from the Na-24 produced, limiting the random counting error to 0.5%. The Na-24 is detected by placing the disks between two 9-in.-diam by 4-in.-thick NaI(Tl) detectors. The irradiation time is no more than 3 min. After irradiation the patient relaxes on a reclining chair until the end of the breath collection period.

During breath collection, variably timed samples of breath can be removed without disturbing the integrity of the closed system. When a sample is to be withdrawn, the system is flushed with O_2–He and all gases (except helium) are trapped on type 5-A molecular sieve material in a steel sampling cylinder cooled to liquid nitrogen temperature. The cylinder is then stored until it is processed for counting by a system recently described (*2*).

This initial study was designed primarily to explore the accuracy of the argon-37 method. To determine accuracy, ten volunteer subjects were irradiated with 14-MeV neutrons and Ar-37 was collected from their exhaled breath for periods of 0–1 hr, 1–3 hr, and 3–5 hr following the irradiation. The same subjects were also measured with the Ca-49 total-body activation and counting system at the University of Washington cyclotron. That system was calibrated by chemical analysis of the ash of five cadavers and, thus, gives an absolute value for total-body calcium after corrections for height and weight, as has been discussed in a previous publication (*4*).

The total dose for the Ar-37 procedure was 10 mrad, as measured by a tissue-equivalent ion chamber. While the dose includes a small contribution ($\simeq$10%) from gamma photons, for radiation safety purposes we assume that the dose is delivered by neutrons only.

RESULTS

The results of the argon-37 TBCa measurements in the volunteers are given in Table 1 and Fig. 1. The data are shown for each breath-collection interval and are expressed as picocuries of Ar-37 excreted per kg total-body calcium for 10-mrad dose.

During the first hour following irradiation, nine subjects excreted 6.9 ± 0.4 (mean ± s.d.) pCi of Ar-37 per kg of TBCa per 10 mrad. For 0–3 and 0–5 hr intervals this value increased to 8.8 ± 0.5 (ten subjects) and 10.4 ± 0.3 (four subjects). The relative standard deviation of these measurements was 5.8% for 0–1 hr, 5.7% for 0–3 hr, and 6.8% for the 0–5 hr interval, and was comparable with that of the Ca-49 measurement, i.e., ±5.3% (*3*). Based on the summation of errors present in this type of comparative analysis, these data indicate that the Ar-37 method will have an accuracy at least as good as the Ca-49 method with which it was compared.

COMMENT

These studies show very consistent excretion of Ar-37 in the subjects as a function of their TBCa. In particular, the data indicate that a single 1-hr

TABLE 1. RESULTS OF ARGON-37 NEUTRON-ACTIVATION ANALYSIS FOR TOTAL-BODY CALCIUM IN NORMAL SUBJECTS

Identification No.	Age (years)	Weight (kg)	Height (cm)	Sex	TBCa* (kg)	Ar-37 yield (pCi/kg TBCa per 10 mrad) 0–1 hr†	0–3 hr†	0–5 hr†
G-1	45	76.8	183	M	1.099	7.4	9.6	11.1
G-2	26	77.3	166	F	0.820	7.1	9.5	11.0
G-3	49	88.7	171	M	1.138	6.9	9.1	10.6
G-4	79	60.9	155	F	0.594	6.9	8.4	N.A.
G-5	75	101.5	177	M	1.005	—	8.8	—
G-6	66	81.6	178	M	1.147	6.3	8.3	—
G-7	60	58.6	168	F	0.767	7.1	8.8	—
G-8	67	80.5	171	M	1.167	6.6	8.5	9.3
G-9	55	79.9	175	M	1.116	7.5	9.3	10.2
G-10	59	55.5	161	F	0.712	6.4	8.0	
Mean						6.9	8.8	10.4
s.d.						±0.4	±0.5	±0.7

* As determined by the Ca-49 method.
† Breath collection interval after irradiation.

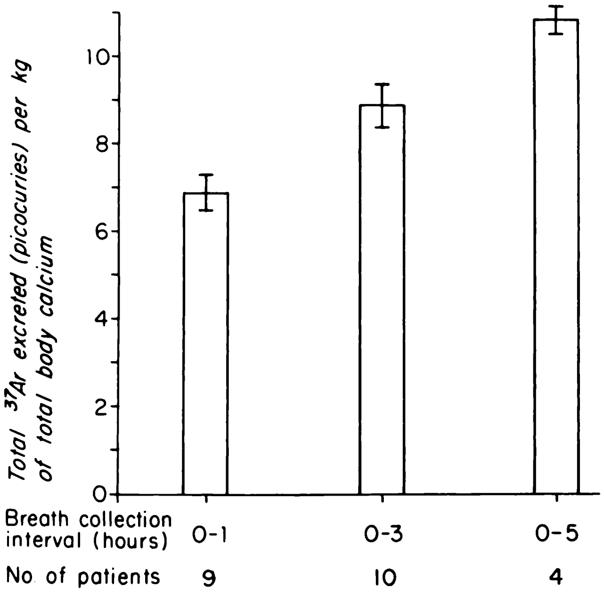

FIG. 1. Argon-37 yield after total-body irradiation (14-MeV facility). Mean yield of Ar-37 per kg total-body calcium, as independently measured by Ca-49 technique, is shown for three breath-collection intervals. For each data group vertical bar indicates standard deviation for that group.

breath collection may be sufficient for the measurement. Our previous qualitative analysis of the excretion rates of Ar-37 following neutron activation by cyclotron (*2*) indicated there was a two-component exponential type of excretion pattern with an initial excretion $t_{1/2}$ of 27 min and a second component with 156 min. On this basis, approximately 67% of the total Ar-37 to be excreted from the body will be collected during the first hour following irradiation.

The data derived from this study also provide information about the possible long-term in vivo retention of Ar-37 in bone. The total amount of Ar-37 that would be excreted from a patient out to infinite time after irradiation can be estimated by using the mean yields of Ar-37 from Table 1 (for both 0–1 and 0–3 hr) and the formula for the total excretion rate curve presented in Ref. 2. This result, 9.7 pCi/kg TBCa for a 10-mrad dose can then be compared with the observed yield of 12.1 pCi of Ar-37 per kg calcium per 10 mrad dose, which was obtained from solutions of calcium nitrate exposed to the same activation uniformity and fluence as the patients. The values suggest that approximately 20% of the Ar-37 produced in vivo may be retained. Recent investigations by others of irradiated dead bone also suggest that approximately 20% of the Ar-37 produced may be retained in the bone crystal. The percent retained also varied linearly with age from a low 20% to a high of 30% over eight decades, but was the same for all types of bone in any individual (*8,9*).

Our data (Table 1) also suggest a slight decrease with advancing age for the Ar-37 released from bone in vivo. A linear regression analysis yields a rate of change with age essentially the same as that derived from the data of Bigler et al. Thus, the data suggest that the small variability of long-term Ar-37 retention with age will have a minimal effect on predicting the TBCa from the Ar-37 excreted. This is to say that representative quantitative sampling of the total-body calcium is observed.

At this time we are planning continuing measurements in a large number of patients whose TBCa has also been determined independently by the Ca-49 cyclotron method, in order to establish more precisely the accuracy of the Ar-37 method. In addition, the reproducibility (precision) of the argon-derived TBCa in any one individual will be established by repeated measurements in the same individual. Good precision is essential to the measurement of serial changes (calcium balance) in the same patient. We have measured TBCa argon in two subjects on three separate occasions and have obtained a coefficient of variation of ±2%.

The total-body neutron dose for these experiments was 10 mrad, but this level can be lowered by simply lengthening the counting time for Ar-37. For example, the dose could be lowered to 1 mrad if the counting time were increased from 10 hr (this study) to 2½ days.

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FOOTNOTES

* Kaman Nuclear Model 711.

† This mixture eliminates nitrogen from the system, since it would interfere with the processing of the Ar-37 (*2*). The gas used is of ultra-high purity, containing less than 0.001% argon by volume.

REFERENCES

1. Palmer HE: Feasibility of determining total body calcium in animals and humans by measuring ^{37}Ar in expired air after neutron irradiation. *J Nucl Med* 14: 522–527, 1973

2. Lewellen TK, Chesnut CH, Nelp WB, et al: Preliminary observations of excretion of ^{37}Ar from man following whole body neutron activation—an indicator of total body calcium. *J Nucl Med* 16: 672–675, 1975

3. NELP WB, PALMER HE, MURANO R, et al: Measurement of total body calcium (bone mass) in vivo with the use of total body neutron analysis. *J Lab Clin Med* 76: 151–162, 1970

4. NELP WB, DENNEY JD, MURANO R, et al: Absolute measurements of total body calcium (bone mass) in vivo. *J Lab Clin Med* 79: 430–438, 1972

5. COHN SH, DOMBROWSKI CS: Measurement of total body calcium, sodium chlorine, nitrogen and phosphorus in man by in vivo neutron activation analysis. *J Nucl Med* 12: 499–505, 1971

6. CHAMBERLAIN MJ, FREMLIN JH, PETERS DK, et al: Total body calcium by whole body neutron activation: New technique for study of bone disease. *Br Med J* 2: 581–583, 1968

7. PALMER HE, LEWELLEN TK, CHESNUT CH, et al: Body composition determination by measurement of total body activation products in expired air. In *Proceedings of the Third Conference on Application of Small Accelerators*, AEC, 1974

8. BIGLER RE, LAUGHLIN JS: Quantitative analysis of the fate in man of ^{37}Ar produced in body calcium by fast neutron exposure. *Rad Res* 67: 266–276, 1976

9. BIGLER RE, WOODARD HQ, LAUGHLIN JS: Age dependence in bone crystal—trapping of Radon and Argon. *Rad Res* 62: 590, 1975

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