# TOTAL BODY COMPOSITION MEASUREMENTS USING IN VIVO NEUTRON ACTIVATION AT THE UNIVERSITY OF WASHINGTON

by

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ABSTRACT

The University of Washington Division of Nuclear Medicine has been using in vivo irradiation to study whole body calcium since 1969. Over 350 patients have been studied and currently five patients per week are being measured in support of research programs on bone wasting disease.

## 1. INTRODUCTION

In the late 1960's the University of Washington and the Battelle Northwest Laboratories began work on establishing a total body neutron activation facility at the University of Washington. The principal element studied has been total body calcium, although studies have also been carried out on non-exchangeable sodium, phosphorus, and nitrogen. The original developers of the system included H.E. Palmer (Battelle Northwest), W.B. Nelp, R.B. Murano, G.M. Hinn, J.L. Williams, T.G. Rudd, and J.D. Denney (University of Washington). The application of the in-vivo calcium measurement system to clinical studies of bone disease has been carried out under the direction of C.H. Chesnut and W.B. Nelp. In 1972, T.K. Lewellen joined the group to study the use of $^{37}Ar$ for calcium measurements as well as assist in the operation and development of the existing neutron activation system based on $^{49}Ca$.

This paper will briefly summarize the University of Washington's program. Due to the large number of studies which have been carried out on the system, many of the details of the system operation and clinical results will only be referenced.

## 2. $^{49}Ca$ ACTIVATION SYSTEM

### 2.1. General system description

The $^{49}Ca$ system is based on the activation of $^{48}Ca$ by slow neutrons to produce $^{49}Ca$. The $^{49}Ca$ is measured in-vivo utilizing a whole body detection system. Neutrons are produced by bombarding beryllium with 22MeV neutrons from the University of Washington 152 cm cyclotron. The average neutron energy is 8 MeV in the forward direction. The position for patient irradiation is 6 m in front of the beryllium target where the neutron flux is uniform within plus or minus 7 % over an area 2 m high by .9 m wide. Since activation of $^{48}Ca$ occurs primarily at energies below 0.04 eV, uniform calcium activation in the skeleton can be achieved by moderating certain parts of the body. The University of Washington system utilizes moderating devices for the head and extremities. A 1.9 cm thick lucite helmet covers the head and neck to moderate neutrons prior to the entry into the bone of the outer skull and cervical spine. Each arm is inserted to the level of axillia into an 11.4 cm diameter lucite cylinder and the subject stands in a lucite boot, 15.2 cm thick and 76.2 cm high. The arm and leg fixtures are filled with water to provide additional hydrogenous material over the bones in the hands, forearm and lower leg. The system also utilizes bilateral irradiation, rotating the patient half way through the activation procedure. With this procedure, uniformity of activation as measured in a series of cadavers was plus or minus 5.6%.

The time for irradiation is typically 1.5 minutes. The patient exposure is 200 millirads. Accumulative dose is measured both by a tissue equivalent ion chamber and a scintillator system. The cyclotron beam and the patient rotation system are both controlled automatically.

Immediately following irradiation, the patient is counted on a whole body detector system and the net $^{49}Ca$ counts induced in the subject are compared to those induced in a simultaneously irradiated fixed calcium comparative standard. The calcium comparative standard consists of four lexan containers containing 12.4 litres of 3.32 M Ca $(NO_3)_2 \cdot 4H_2O$. Each standard contains 1600 grams of calcium and are positioned around the patient during the irradiation procedure. The standards contain iron string bars which are covered with teflon. Following irradiation, the standards are stirred for 10 minutes by an automatic stirrer and then counted by the same detector system used on the whole body counter.

Counting begins within four minutes post irradiation. The patient lies supine in a 3 mm thick alluminum trough while an annular array of NaI (Tl) crystals (10 cm thick, 24 cm in diameter) pass over the patient from head to foot. A multichannel analyzer records the gamma spectra from each crystal from 1.825 MeV. The total body count lasts 12.5 minutes, and at 20 minutes after irradiation, a 10 minute count of the calcium comparator standards begin.

Prior to irradiation a background count of the patient is performed in the same detector system and for the same counting time. An hour after irradiation, a second post irradiation count is taken. The data is then analyzed by an Apple Computer System, and the results in terms of absolute counts, counts relative to the calcium standards, and an estimate of the total body calcium is printed out.

The precision of the system has been established as 2.0% (plus or minus one standard deviation). The accuracy of this system, as determinated by measuring cadavers, has been established as 5.2% (plus or minus one standard deviation).

## 2.2 Total Body Calcium Clinical Studies

The system is used primarily for drug efficacy studies in the treatment of osteoporosis. All the clinical studies to date involve only measurements of total body calcium. We have studied over 350 patients, and are currently studying patients at the rate of five per week. Discussions of the clinical results can be found in the literature, and the references summarize a great deal of the clinical experience at the University of Washington.

## 2.3 Other Body Composition Studies.

There has been interest at the University of Washington in applying neutron activation procedures for studying sodium, phosphorus, and nitrogen in-vivo. There has been preliminary feasibility and clinical investigations of measurements of non-exchangeable sodium in normal man and feasibility studies of measuring phosphorus and nitrogen in-vivo. However, the clinical demand within the University of Washington has been primarily for total body calcium, thus our current facilities have been optimized for measurements of calcium, and at this point in time no other elements are routinely measured for clinical purposes. We do routinely analyze the patient's spectra for the presence of other elements, in particular sodium, but at this point in time the results are not being utilized.

## 2.4 Quality Assurance Procedures.

A major concern in the use of a total body calcium system for serial study, is the stability of this system with time. Many other potential problems in terms of the operation of the total body counter are kept under control by making a relative measurement. The data is always reported out as the patient's counts versus the counts in the comparator standard. During the activation process, a strip chart recorder is used to record the neutron flux density versus time. In that matter, any rapid changes in neutron flux, which could affect the ultimate result of the study, can be measured and appropriate corrections made in the data. Routine quality insurance of the system is primarily based on the activation of the three lexan tubes filled calcium nitrate, which are suspended within the patient enclosure inside larger tubes filled with water. The lexan tubes are 5 cm in diameter and 183 cm long. The outer PVC tubes are 15 cm in diameter and 183 cm long. These tubes are activated using the standard patient activation protocol, including the bilateral irradiation and automatic control. These tubes are then counted in the whole body counter along with the comparator standards. The total counts in these phantoms versus the calcium standard counts per unit dose provide us with a quality insurance check of the whole body counting system: the motor control for the scanning detector (which slows down with the half life of calcium) as well as the detector electronics. The absolute value of the phantom count versus unit dose gives us a quality assurance check of the quality of the neutron beam being delivered from the cyclotron. These phantoms are measured once a week, and the results are compared week to week as well as to the average results accumulated over the course of years the system has been in operation. Over the past ten years, the phantom counts to standard counts has been constant to with ± 1.5%. Overall, the system has provided a high degree of reproducibility, within the plus or minus 2% as established in the early phase of the project.

## 3. ARGON SYSTEM

### 3.1 General Description.

Use of $^{37}Ar$, produced by a fast neutron reaction on $^{40}Ca$ was originally suggested as a possible method to measure total body calcium in vivo by H.E. Palmer at the Battelle Northwest Laboratory. Initial results in rats looked extremely encouraging. A system to investigate the feasibility of this technique in humans was established at the University of Washington. Since the reaction required fast neutrons, a facility using a 14 MeV DT neutron generator was constructed. The neutron generator was placed inside a shield constructed of concrete blocks, and a patient enclosure was positioned 503 cm away from the generator target. The patient enclosure consisted of an alluminum tank with an adjustable platform inside so that the patient could be immresed in water to the level of his shoulders. Irradiation was carried out bilaterally, and took 5 minutes. Dose was measured with a tissue equivalent ion chamber and a scintillator detector. The control of the generator was done automatically on preset dose delivered to the patient. Since the technique was based on the collection of $^{37}Ar$ exhaled by the patient, the patient was connected to a closed circuit breathing system during the entire irradiation procedure and up to six hours post irradiation. Exhaled gas was collected from the patient, and collected on molecular sieve material cooled with liquid nitrogen. The gas samples are then purified using selective absorption, and the small amount of argon recovered was placed inside a 15 cc proportional detector which was counted from one to three days.

Because of the high abundance of $^{40}Ca$ and the ability to count the exhaled gas samples for long periods of time, it was possible to place the patient enclosure far enough away from the neutron generator to achieve good neutron field uniformity. A neutron flux at the patient site was ± 2% throughout the irradiation field. The in-vivo uniformity was estimated by irradiating a series of vials filled with a calcium nitrate solution suspended within the water filled patient enclosure. These vials were subsequently broken in a gas tight container and analyzed for the $^{37}Ar$ produced by the neutron irradiation. With bilateral irradiation, data taken both at the University of Washington and Battelle Northwest Laboratories indicated that an in-vivo uniformity of ± 2.7% could be achieved.

## 3.2 Patient Studies.

A limited number of patients were studied in order to determine the precision of measurement obtainable with the $^{37}Ar$ system and to correlate the $^{37}Ar$ results with total body calcium measurements using $^{49}Ca$ system. The precision of measurement in a group of six patients was in the order of 3.3% for a collection period of 1 hour and 2.4% for a collection period of 3 hours. The correlation with the $^{49}Ca$ system was also very good for 0 - 1, 0 - 3, and 0 - 5 hour breath collection intervals. There were several excretion half-lives noted during these studies, an indication that there was a long term retention of some fraction of the total body argon produced. Based on calculations of measured argon yield from calcium nitrate and irradiated bone samples in conjunction with total body calcium as determined by the $^{49}Ca$ system, the amount of argon which should have been collected versus the amount of argon actually collected in patients was estimated. In a group of 10 patients, the average amount of argon recovered after 3 hours blood collection was 85%.

## 3.3 Quality Assurance.

The argon technique requires strigent quality assurance procedures primarily due to the handling of small amounts of radioactive gas. A major concern was the ability to produce a gas tight seal between the patient and the face mask as well as maintaining system integrity throughout the collection and processing apparatus. Our routine technique was to produce large amounts of $^{41}Ar$ by irradiating a calcium nitrate solution, and introduce this gas into the closed circuit rebreathing system with the face mask replaced by a closed loop. The $^{41}Ar$ present in the calcium nitrate container was counted prior to introducing the gas into the rebreathing system. The amount of $^{37}Ar$ eventually introduced into the proportional detector was also determined. By comparing the ratio of these two isotopes it was possible to check the system for loss of argon. Each procedure was carried out once a week throughout the course of our development of the $^{37}Ar$ system. We experienced frequent gas leaks, and great care had to be exercised to perform proper system preventive maintenance procedures.

## 3.4 Discussion.

While the data we obtained regarding $^{37}Ar$ indicated that it would be possible to develop a total body calcium and perhaps a regional calcium system based on the technique, further development of $^{37}Ar$ at the University of Washington has been suspended. The technique is not being pursued primarily because of the cost involved and because of the several questions remaining about long term retention of the argon gas in-vivo, the reabsorption of argon when utilizing the close circuit breathing system, and potential problems of in-vivo gas transport with various kinds of disease states. The cost of operation on the argon system is high because of the large amount of preventive maintenance required and the rather complex gas handling, requiring a considerable amount of technician time for study.

## 4. OTHER COMPOSITION STUDIES

4.1 We have not implemented measurement of nitrogen as a standard clinical procedure primarily due to a lack of clinical interest within the University of Washington. We have done preliminary work for measuring total body nitrogen and phosphorus. These studies were performed in conjunction with H.E. Palmer of Battelle Northwest Laboratories, and indicated that such measurements would indeed be feasible. However at this point in time the University of Washington is not pursuing such studies.

### 4.2 Non Exchangeable Sodium.

A small number of patients were involved in a study of non-exchangeable sodium in the University of Washington. They have been reported in the literature and no further clinical use has been made of the basic technique. Sodium numbers are routinely analyzed from our total body calcium activations for patients. However, these numbers are currently not being used clinically.

### 4.3 Total Body Nitrogen.

Animal studies were conducted at Battelle Northwest by H.E. Palmer in order to assess the feasibility of measuring total body nitrogen in-vivo with neturon irradiation and the formation of carbon by a fast neutron reaction on nitrogen-14. The studies looked very promising in animals. However, when a series of three patients were studied at the University of Washington, the exhalation proved to be nine times larger than observed in animals. Due to the short life of the carbon isotope, it was decided this was not likely to be a viable clinical tool and further human experimentation was suspended.

## 5.0 General Discussion.

The University of Washington has been involved with in-vivo neutron activation since the late 1960's. Our primary thrust has been in the area of measuring total body calcium due to the larger clinical interests in osteoporosis and bone physiology within our School of Medicine. For the forseeable future, we will continue restricting our use of neutron activation analysis to measurements of total body calcium.

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