CLINICAL STUDIES OF TOTAL BODY NITROGEN IN AN AUSTRALIAN HOSPITAL

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INTRODUCTION

The first reports of the measurement of Total Body Nitrogen (TBN) by In Vivo Neutron Activation Analysis (IVNAA) using a cyclotron date from the early 1970's (Harvey et al., 1973). By the late 1970's other laboratories were using the prompt gamma IVNAA technique with isotopic neutron sources (Mernagh et al., 1977; Vartsky et al., 1979a). The prompt IVNAA method is a relatively simple, non-invasive test which requires approximately 20 minutes of the patient's time. The radiation dose is minimal, and both capital and running costs are small. Clinically, Total Body Protein (TBPr) can be reliably estimated from TBN (TBPr = 6.25 x TBN). The many clinical applications of the technique are described by Wahlqvist and Marks elsewhere in this volume, and by McNeill (1988). It is therefore surprising that so few hospitals are currently using the technique.

A Body Composition Laboratory has been established recently at the Monash Medical Centre in Melbourne, Australia, and a clinical facility for the measurement of TBN has been available for patients since early 1988. This paper reviews all of the results from the first 18 months of operation.

Costing of this facility shows that the measurement of TBN by IVNAA is an inexpensive test. The total cost of the equipment was approximately A$40,000, which is less than the cost of refurbishing a suite of clinical rooms to accommodate it. Staffing costs, which include a full-time physicist and nurse, and a part-time physician, are the major cost.

EQUIPMENT

Fig. 1 is a cross sectional view of the equipment. The neutron source is 10 micrograms of ^{252}Cf. Preliminary design work for this system was carried out at the University of Melbourne and the Toronto General Hospital (McNeill et al., 1989) where the advantages of a relatively small ^{252}Cf source were demonstrated. The source is positioned in a borated wax collimator, and there is 7 cm of lead on top of the collimator to shield the detectors. The source is approximately 38 cm below bed level. The aperture is 24 cm wide and 43 cm long when projected to bed level.

Advances in In Vivo Body Composition Studies
Edited by S. Yasumura *et al.*, Plenum Press, New York, 1990

Two 12.5 x 10 x 10 cm NaI detectors are located on either side of the bed; they are surrounded by 3 cm of borated wax, and there is 50 cm of clear space between them. Standard electronics are used.

The patient is positioned on a sliding wooden stretcher mounted on a long bench. The section of the stretcher exposed to the neutron beam was replaced by a thin panel of aluminium because the chipboard top was contributing to the nitrogen background.

TECHNIQUE

The patient is placed in a supine position with the mid point between the iliac crests and the umbilicus over the centre of the neutron aperture. The nitrogen and hydrogen capture gamma rays are then counted for 1000 s without moving the patient. The data are analysed using the Toronto method (Harrison et al., 1984) which uses H as an internal standard (Vartsky et al., 1979). The precision of the measurements is limited by the number of counts in the nitrogen window and by the background in this window; a precision of 4% is obtained with a 1000s patient count.

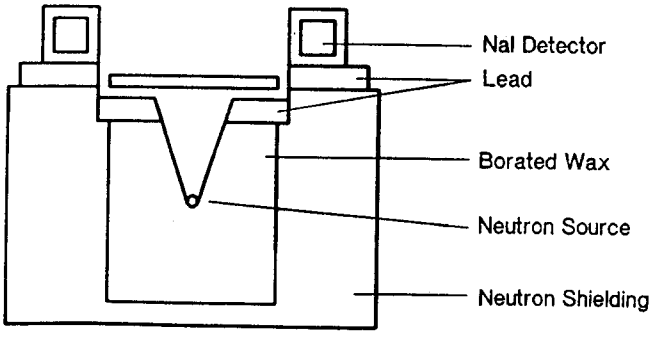

Fig. 1. Cross sectional view of the total body nitrogen facility at the Monash Medical Centre, Melbourne, Australia.

Techniques have not yet been finalised in this laboratory for applying various corrections to the measured results. Preliminary measurements with phantoms indicate that chlorine in the body of the patient increases the background in the nitrogen window by approximately 3%. This background also depends on the width of the patient, but this effect has been minimised by using phantoms that are 29 cm wide, a width that is very close to the average patient width. Finally, in the present technique it is assumed that 10% of the body weight is hydrogen; Harrison et al (1984) have shown that this assumption can lead to errors of $\pm$ 5% in extreme cases.

For obese patients, the magnitude of two of these corrections has been determined by preliminary phantom measurements. The N/H ratio increases by 10% when the width of the phantom is increased from 27 to 45 cm, because the hydrogen gamma rays are absorbed more than the nitrogen gamma rays.

Table 1 - Measured Values of $TBN/HAS^{2.6}$ for Normals

	Melbourne			Toronto		
	No	Mean	Std Dev	No	Mean	Std Dev
Males	9	0.48	0.05	25	0.50	0.06
Females	6	0.43	0.03	63	0.42	0.04

The nitrogen background decreases by 14% when the width of a water-filled phantom is increased from 27 to 45 cm.

This supine-only, non-scanned technique was adopted only after measurements showed an invariant N/H ratio at several sites in a normal volunteer and in two pig carcasses. Further tests have been designed to discover those situations in which the assumption is invalid, and it has been demonstrated that the N/H ratio can vary significantly between the normal upper abdominal position and the thighs in obese patients.

PATIENT DOSE

The estimated patient dose is less than 0.15 mSv, based on the work of Allen et al (1985). The dose received by operators is approximately 0.004 mSv/h at 1 m from the patient; the equipment is located in a large room and the control console is positioned to minimise this dose.

VALIDATION

Fifteen healthy, non-obese volunteers (age range 21-59) have been measured, and the results compared with data published by Harrison et al (1984). The comparison technique is based on Harrison's definition of the Nitrogen Index, NI, viz.

$$NI = \frac{\text{Measured TBN}}{\text{Predicted TBN}}$$

where $\text{Predicted TBN} = \text{Constant} \times HAS^{2.6}$

HAS is the mean of height and armspan. By definition, the mean NI of the Toronto normals is 1.00. Harrison et al. (1984) determined the constant by calculating the mean value of $(\text{Measured TBN})/HAS^{2.6}$ from the Toronto data for males and females separately; this procedure has been repeated for the Melbourne data. There is good agreement between the results from both laboratories as shown in Table 1. (See footnote)

Fig. 2 is a histogram of all of the actual NI values for the Melbourne patients. The other data in Fig. 2 are discussed below.

Two tests have been designed to study the long-term reproducibility of the TBN results. Firstly, two normal volunteers have been measured on three

NOTE ADDED IN PROOF - More recent measurements on a larger group of normals suggest that with the Melbourne method normal patients have a mean NI of 0.86 rather than 1.00. The interpretation of the patient results presented below has been altered accordingly. Measurements on normals are continuing.

Table 2. Measured Values of the Ratio* $\frac{(N/H)_{am\ urea\ phantom}}{(N/H)_{pm\ urea\ phantom}}$

Measured Mean	= 1.004
Measured Standard Deviation	= 0.03
Calculated Statistical Error	= 0.033
Calculated Standard Error	= 0.005 (= $0.033/\sqrt{43}$)

*Based on the results of 43 paired measurements of the same phantom.

separate occasions, once in August 1987, and twice in June 1989. The measured values of TBN for Volunteer 1 are 2.20, 2.13 and 2.15, mean = 2.16, Std Dev = 0.03. Values for Volunteer 2 are 1.93, 1.83, 1.81, mean = 1.86, Std Dev = 0.05. The volunteers had no significant change in weight over the period that the measurements were performed. For each volunteer, the observed standard deviation of the three measurements is smaller than the predicted counting error; this indicates good reproducibility.

The second stability test was conducted with phantoms. When measuring TBN in patients a phantom containing an aequeous solution of urea is measured for standardisation before and after the patient(s). There is generally at least 3 hours between the measurements. The N/H ratio calculated from the morning (am) measurement should equal the N/H ratio from the afternoon (pm) measurement to within the precision of the measurement. To test the system reproducibility, the ratio of these N/H ratios, as shown in Table 2, was calculated for each of 43 studies during a period of 10 months. The

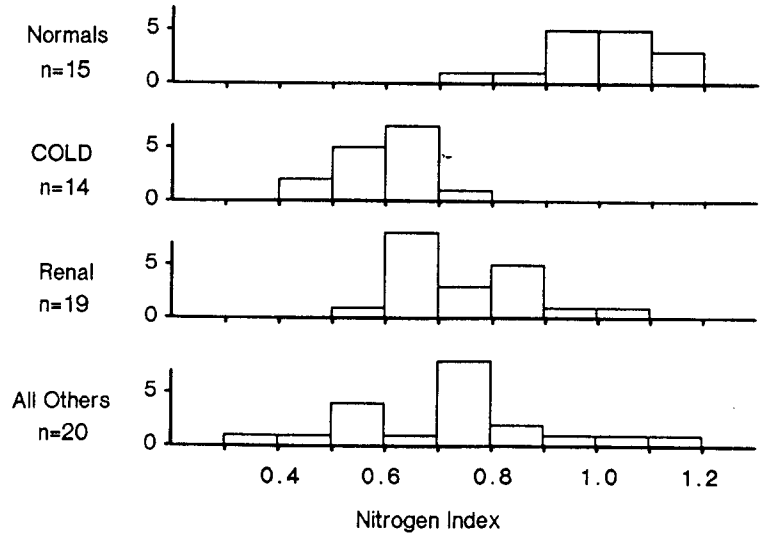

Fig 2 Histogram showing Nitrogen Index (NI = Measured TBN / Predicted TBN) for normals and for all patients.

measured mean should be unity. The standard deviation should approximate the calculated statistical error, and the calculated standard error should approximate the measured mean minus unity. The results indicate stability to within the precision of the measurement.

CLINICAL STUDIES

Chronic Obstructive Lung Disease Patients

A select group of patients suffering from Chronic Obstructive Lung Disease (COLD) has been studied as part of a randomised, placebo-controlled trial of an oral nutrient supplement. Subject selection criteria included the presence of severe COLD, less than 90% of ideal body weight (Metropolitan Life Insurance Table, New York 1978), and capability to perform respiratory function and exercise tests. Fourteen patients (Age Range 48-76) have been studied so far. Their mean Body Mass Index (BMI = Weight/Height^2) is 18. Their mean NI is 0.58 with a standard deviation of 0.08; this mean is approximately three standard deviations below normal. All of their NI values are shown in histogram form in Fig. 2; the distribution of NI values is rather narrow. The study is continuing.

Short Bowel Patients

TBN has been measured in two short bowel syndrome patients about to be transferred to home parenteral nutrition. Both were referred for TBN measurements immediately prior to discharge after many months in hospital and were clinically well. The first patient, age 37, had an NI = 0.72 which is low, but normal. The second patient, age 66, had NI = 0.66; this is also interpreted as normal since there is evidence of a decline in TBN in normals over the age of 60 (Harrison et al., 1984).

Renal Patients

Monash Medical Centre contains the largest renal dialysis unit in Australia. Because of concerns about their nutritional status, TBN has been measured in a slected group of patients consisting of 10 on Haemodialysis, 4 on continuous ambulatory peritoneal dialysis, and 5 approaching end-stage chronic renal failure. Dialysis patients were studied immediately after dialysis. The ages of these 19 patients range from 22 to 69, their BMI's range from 16 to 33, and their NI's have a mean value of 0.73 (SD = 0.16). Their mean NI is approximately 13% below that of normals. The histogram in Fig. 2 suggests a fairly broad distribution of NI values. A number of these patients display total body protein depletion, despite having a BMI in the normal range (20-25) or higher.

Obese Patients

TBN measurements are important in obese patients because protein malnutrition is a concern when dieting, and following surgery for Upper Gastric Reduction (UGR). However, it is difficult to measure TBN accurately in obese patients because of the limited penetration of the neutrons and because of the inhomogeneities caused by the thick outer layers of nitrogen-deficient adipose tissue. Siwek et al (1984) have successfully measured obese patients by constructing a phantom based on CT measurements for each individual patient. Such an approach is impractical except in a research environment. Preliminary measurements have been made on phantoms as described above, and patients in Melbourne to develop a more practical approach.

In patients, TBN has been measured by applying the method described above with no corrections. Measurements have been made at both the normal abdominal position and in the thigh, since the outer layer of adipose tissue may be thinner in the thigh. In six female patients with weight exceeding 100 kg the mean NI observed in the abdominal area is 0.86 ± 0.12 (Std Dev); the thigh measurement was, on average, 20% higher than the abdominal measurement. Further work is needed before it will be possible to measure TBN accurately in obese patients.

CONCLUSIONS

Our experience with various groups of patients shows that prompt IVNAA is a cheap, clinically useful and accurate method of assessing total body protein.

ACKNOWLEDGEMENTS

We wish to acknowledge generous assistance from B.J. Allen of the Australian Nuclear Science and Technology Organisation, and from G.L. Hill's group in Auckland. Financial assistance was received from Novo Laboratories Pty Ltd for the study of the COLD patients.

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IN VIVO BODY COMPOSITION STUDIES

Recent Advances

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PLENUM PRESS • NEW YORK AND LONDON

Library of Congress Cataloging-in-Publication Data

International Symposium on In Vivo Body Composition Studies (1989 : University of Toronto)
In vivo body composition studies : recent advances / edited by Seiichi Yasumura ... [et al.].
p. cm. -- (Basic life sciences ; v. 55)
"Proceedings of the International Symposium on In Vivo Body Composition Studies, held June 20-23, 1989, at the University of Toronto, Toronto, Ontario, Canada"--T.p. verso.
Includes bibliographical references and index.
ISBN 0-306-43618-3
1. Body composition--Congresses. I. Yasumura, Seiichi. II. Title. III. Series.
QP88.I53 1989
612'.01585--dc20 90-7551
CIP

Proceedings of the International Symposium on *In Vivo* Body Composition Studies, held June 20-23, 1989, at the University of Toronto, Toronto, Ontario, Canada