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Validation of a Normal Range for Trapping Index in Thyroid Scintigraphy

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Foot line: Validation of Thyroid Trapping Index

ABSTRACT

Introduction: Thyroid trapping index of ^{99m}Tc pertechnetate (neck to thigh ratio) has been used for several decades as a simple alternative to thyroid uptake. Using a trapping index normal range of less than 6, several patients with subjectively diffuse increase in thyroid trapping, biochemical hyperthyroidism and clinical features of thyrotoxicosis have been classified as normal.

Methods: Three thyroid function calculation methods were used in 43 patients:

- thyroid trapping index calculated from the total counts in the neck and thigh images – method A,
- thyroid trapping index calculated from thyroid ROI counts and ROI transposition over the thigh – method B,
- standard based percentage thyroid uptake - method C.

Results: Five patients (11.6%) were shown to be hyperthyroid by thyroid uptake while trapping index was within normal limits. Correlation amongst all three methods was excellent with methods A and B showing a 0.9870 correlation coefficient, methods A and C a 0.9859 correlation coefficient and methods B and C a 0.9804 correlation coefficient.

Conclusion: All 3 methods were shown to provide valid measures of thyroid function. The normal range for trapping index was modified after correlation with the standard thyroid uptake normal limits:

- Trapping index (total counts) = 1.9 - 5.1
- Trapping index (ROI) = 3.7 - 15.1

Key words: thyroid uptake, trapping index, neck to thigh ratio, validation, hyperthyroid

INTRODUCTION

Accumulation of radionuclides in the thyroid gland allows the scintigraphic evaluation of the size, position and function of the thyroid gland.[1,2] Historically, ^{131}I sodium iodide was the agent of choice for thyroid function determination via measurement of the percentage thyroid uptake of the radiopharmaceutical. Unfortunately, ^{131}I is associated with a high radiation burden due to the beta emission and its 8 day half life and has poor physical characteristics for scintigraphic imaging with a 364 keV gamma emission and poor count density (3). ^{123}I provides improved imaging and dosimetry characteristics but this cyclotron produced radionuclide is limited by availability and cost.[2] While thyroid function is primarily assessed by serum assays of hormone levels, radionuclide uptake by the thyroid gland has a number of useful clinical applications, including; ^{131}I therapy dose calculation in hyperthyroidism, confirmation of hyperthyroidism as a diagnosis, evaluating the response to ^{131}I or medical therapy and differentiating thyroid pathologies.[1]

The ability of the thyroid gland to trap ^{99m}Tc pertechnetate in a similar fashion to iodine provides an alternative radiopharmaceutical for both scintigraphic imaging and functional assessment.[4,5] Intravenous (IV) administration and favourable physical characteristics allows rapid and convenient functional assessment to be incorporated into scintigraphic imaging protocols. Unfortunately, ^{99m}Tc pertechnetate is neither bound nor organified in the thyroid resulting in more rapid washout from the thyroid gland than iodine radionuclides.[3] As a result, a narrower window of opportunity exists in which thyroid uptake can be reliably measured. Moreover, thyroid uptake determination using ^{99m}Tc pertechnetate is hindered by the need for measurement during the time interval when background activity in the neck is proportionally high.[3] This is further complicated by the relatively low absolute uptake of ^{99m}Tc pertechnetate by the thyroid gland.[3] Salivary gland activity is also prominent during this window of opportunity when using ^{99m}Tc pertechnetate.[5] While these issues are not problematic for iodine based evaluation due to delayed measurement times, ^{99m}Tc pertechnetate thyroid function assessment is still the method of choice in Australia and many parts of the world.[4]

Thyroid trapping index (TI) for ^{99m}Tc pertechnetate (neck to thigh ratio) has been used for a number of decades as a simple alternative to thyroid uptake.[2,4,5] Normal ranges for ^{99m}Tc pertechnetate TI have been determined by a number of authors. Hale et al.[2] report a normal range of 2.5 to 6.0 for a trapping index calculated at 20 minutes post injection of ^{99m}Tc pertechnetate and similarly, Selby et al.[5] reported 2.4 to 5.8 at 20 minutes post injection. Schneider[4] used a time 15 minutes post injection to report a tighter normal trapping index of 3.0 to 4.7.

Utilising a normal range for TI of less than six (< 6), it was observed that a number of patients with subjectively diffusely increased thyroid trapping, biochemical hyperthyroidism and chemical features of thyrotoxicosis had been classified as having normal thyroid function. These observations corresponded to the appointment of a new Nuclear Medicine physician and his initial experiences with departmental protocol. The observed phenomena was concerning because the efficacy of ^{131}I therapy dose calculation for hyperthyroidism patients may be jeopardised.

A number of potential causes of the observed phenomena were explored. The aperture to object distance may vary between the neck and thigh images resulting in variable sensitivity. The sensitivity is susceptible to the effects of the inverse square law when using a pinhole collimator.

If there was inclusion of salivary gland activity in neck measurements of the patient database used to determine the normal range, the trapping index normal range may be falsely increased. This may become problematic in patients whose salivary glands were excluded from the neck image. Our protocol was to exclude salivary gland activity from the field of view (FOV) where possible. If this was the cause of the phenomena, the observed phenomena would demonstrate a greater incidence.

As is the case with thyroid uptake, delayed imaging past 20 minutes post IV was thought to allow tracer washout and a decreased target to background ratio (lower TI). Imaging significantly earlier than 20 minutes post IV may also decrease trapping index. Schneider,[4] however, suggests that timing is not critical for trapping index except in a small number of patients with severe hyperthyroidism. In these cases trapping index is markedly elevated and timing errors would not alter diagnostic integrity. Similarly, physiological early washout of tracer from the thyroid gland in hyperthyroidism or delayed tracer accumulation/localisation in the thyroid gland would have minimal impact on diagnostic utility of trapping index.

Decreased accumulation due to medication or interfering material (eg. contrast media, high iodine diet, ^{131}I therapy).[1] It is expected that this would decrease both thyroid uptake and trapping index and, thus, would not cause the observed phenomena. Moreover, ^{131}I therapy and iodine load (medication and diet) are known to have a more profound effect on organification than trapping[4] so the ^{99m}Tc pertechnetate methods are a little more robust.

A partially extravasated dose would decrease the percentage thyroid uptake of tracer with minimal effect on trapping index. This, however, would result in concordance between trapping index and subjective image interpretation. Thyroid uptake calculations would produce a possible false negative finding in hyperthyroid patients which is not consistent with the observed phenomena.

There are external validity concerns with normal ranges reported in the literature. There are a number of extraneous variables impacting on thyroid function determination which may be significantly different across populations. For example, diets have changed between eras or dietary intake of iodine varies geographically.[4] As a consequence of this concern, the normal range we employed was possibly invalid for our patient population.

Aims

The aims of this investigation were to:

- determine the validity of the trapping index for assessment of thyroid function,
- determine the optimal technique (total counts per image or region of interest counts),
- determine the appropriate normal range for trapping index if it was shown to be a valid method.

The research question

Does ^{99m}Tc pertechnetate trapping index provide a valid and precise assessment of thyroid function?

Methodology

A prospective, non randomised observational study was undertaken on 43 patients having routine thyroid studies. Patients were injected intravenously with ^{99m}Tc pertechnetate and imaged at 20 minutes post intravenous injection. Imaging was performed using pinhole collimation. A standard dose of ^{99m}Tc pertechnetate was prepared at the same time as the patient dose and diluted in a 10 ml vial. The mean patient dose was 212.4 MBq with a range of 181.8 to 273.9 MBq and the mean standard dose was 8.9 MBq with a range of 6.2 to 13.2 MBq.

A one minute standard phantom image was acquired at 20 minutes post IV with the pinhole aperture positioned 9cm from the phantom. On completion of the standard image, a one minute neck image and a one minute thigh image were acquired on the patient with the aperture to object distance being 9cm. A one minute injection site image was also acquired prior to the remainder of the standard thyroid imaging protocol being completed.

Three methods were used to calculate thyroid function in all 43 patients. Method A was a trapping index calculated from total image counts of the neck image and total image counts of the thigh image. Method B was a trapping index calculated from region of interest (ROI) counts drawn around the thyroid and counts from the same ROI superimposed on the thigh. Method C was a standard based percentage thyroid uptake involving counts in a thyroid ROI, a standard activity count measurement and dose, and injected activity.

Method A

$$TI = \frac{\text{total counts in neck image}}{\text{total counts in thigh image}}$$

Method B

$$TI = \frac{\text{counts in ROI around thyroid}}{\text{counts in ROI superimposed on thigh}}$$

Method C

$$\frac{\%\ \text{uptake} = [\text{thyroid cts x std act x 100/std cts}]}{\text{inj act}}$$

where,
thyroid cts = background corrected thyroid counts in ROI
std act = calibrated standard activity in MBq
std cts = total counts in standard ROI
inj act = injection activity corrected for syringe residual

Results

There were 43 patients included in the investigation. The mean age of the patients was 56.5 years with a range of 20 to 90 years. There were 34 (79.1 per cent) females and 9 (20.9 per cent) males. Five (11.6 per cent) patients were shown to be hyperthyroid by thyroid uptake while trapping index was within normal limits. There were no studies demonstrating abnormal trapping index with a normal thyroid uptake. No statistically significant correlation was seen between patient age and thyroid function ($p=0.4309$). No statistically significant correlation was seen between gender and thyroid function ($p=0.4123$).

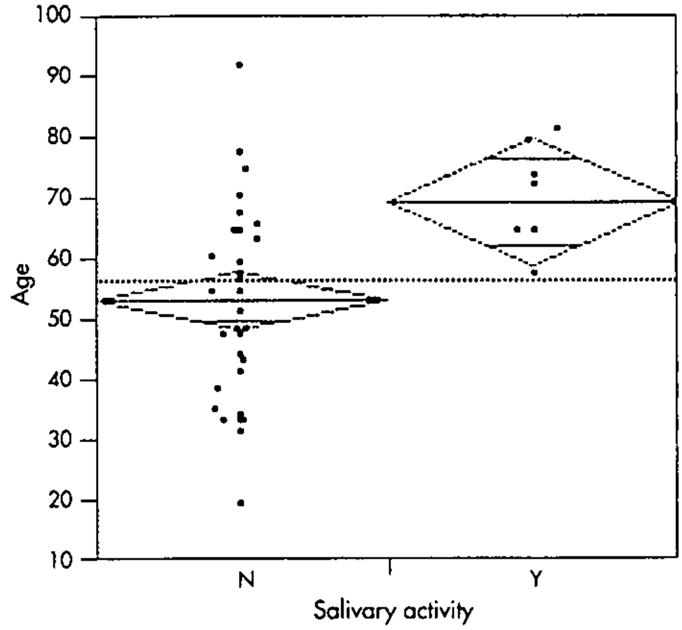
Salivary glands

Nine (20.9 per cent) patients demonstrated salivary gland activity visually on their neck image. Thyroid uptake is independent of salivary gland activity so a trapping index to thyroid uptake ratio was calculated for methods A and B to assess the impact of salivary activity. No statistical difference between the means of patients with and without salivary gland activity was demonstrated for method B ($p=0.2744$). Method A, however, demonstrated a statistically significant difference between the means of patients with and without salivary gland activity ($p=0.0056$). There was also a statistically significant increase in the age of patients with and without visually detectable salivary gland activity ($p=0.0084$). This may be associated with positioning difficulties in older patients (Figure 1). No statistically significant correlation was seen between gender and salivary gland activity ($p=0.3893$).

Extravasated doses

There were 16 (37.2 per cent) patients with activity detected at the injection site. The mean tissued activity was 10.18 MBq with a range of 0.04 to 116.93 MBq. No statistically significant difference was seen between thyroid function for patients with or without extravasated doses ($p=0.1270$). Thyroid uptake was determined with and without correction of the patient dose to account for the tissued activity. Of these 16, 11 were shown to be less than 0.5 MBq which correlated to a less than 0.0063 per cent change in the calculated uptake. With rounding to 1 decimal place, no patient results were altered in these 11 patients and consequently these patients were excluded from the extravasated group.

Figure 1: Patients' age for those with (Y) and without (N) visually detectable salivary gland activity.



The diamonds represent 95% confidence intervals and the horizontal line is the mean age of the population. Note that all patients with salivary gland activity are above the mean age of the total population. There is also no overlap of the 95% confidence intervals, supporting a significant difference between the two groups.

Figure 2: Correlation between detected standard counts and standard activity calibrated.

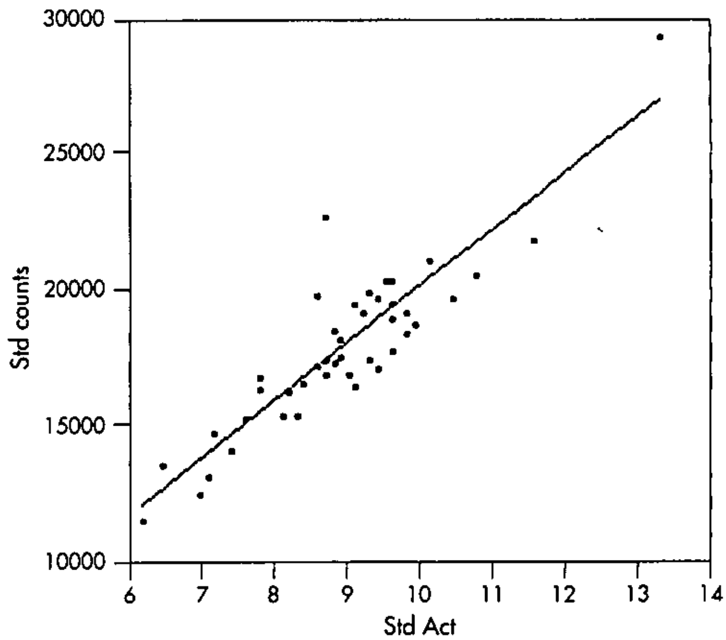


Figure 3: Weak association between thigh counts and injected activity.

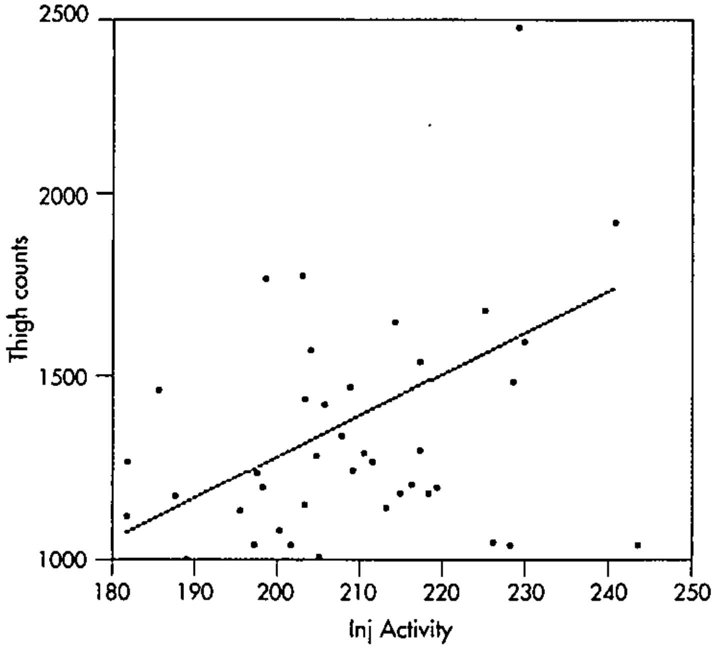
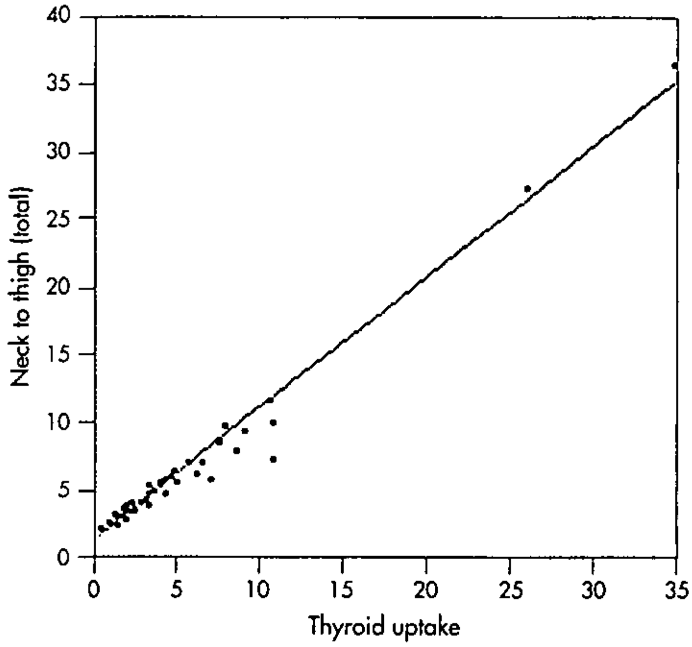


Figure 4: Method A versus method C showing excellent correlation.



Only 5 (11.6 per cent) patients were categorised as having extravasated injections. The mean injection site activity for these 5 patients was 32.2 MBq with a range of 3.1 to 116.9 MBq. Correction of thyroid uptake resulted in increases in thyroid uptake between 0.174 per cent and 5.765 per cent with a mean increase of 1.494 per cent. These corrections did not change trapping index efficacy (ie. there are still the same 5 patients with normal TI and hyperthyroid uptake). No statistically significant difference was noted in the method A to C ratio (P=0.4119) or the method B to C ratio (p=0.8675) for thyroid function when viewed in terms of tissued doses or not tissued doses. As a result of this, having an extravasated dose did not impact on the overall outcome of this research.

The standard

The thyroid uptake calculation requires that the standard counts be proportional to standard activity. There was a good correlation demonstrated between the standard counts detected and the standard activity calibrated with a correlation coefficient of 0.8946 (Figure 2). While not conclusive evidence, this data supports the proposition that gamma camera efficiency and aperture to object distance were uniform throughout the investigation. A control chart of the standard counts to standard activity ratio for sequential patients indicated that the process was in statistical control.

Thigh counts

Thyroid function calculations utilise thigh counts as either a background correction (uptake) or as a comparison (TI). Thigh counts to injected activity ratios, therefore, also needs to be free from non random error. A control chart demonstrated that the process was in statistical control. There was no correlation demonstrated between thigh activity and patient age with a correlation coefficient of 0.0199. A weak association between thigh counts and injected activity was demonstrated (Figure 3) with a correlation coefficient of 0.5138 and RSquare of 0.2640. I suspect a closer correlation would be demonstrated if multivariate analysis was to be performed to include patient surface area, however, height and weight data were not available.

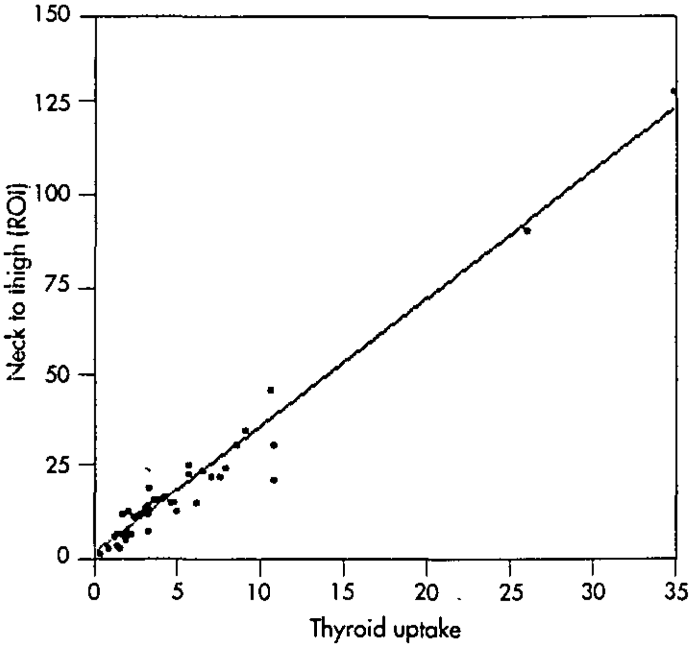
Correlation of methods

Excellent correlation was demonstrated between the three methods of thyroid function determination. The comparison of method A with method C demonstrated excellent correlation with a correlation coefficient of 0.9859 (RSquare = 0.972). Figure 4 illustrates this correlation which is particularly strong for values within the normal range for thyroid uptake. It is clear from figure 5 that the correlation with the line of best fit diverges a little with thyroid uptake values above the normal range. In particular, the trapping index values seem to scatter below the line of best fit which may offer some explanation of the observed phenomena.

Figure 5 demonstrates the relationship between methods B and C which has a correlation coefficient of 0.9804 (RSquare = 0.961). Generally.the correlation with the line of best fit is 'looser' when compared to that of methods A and C, however, this impression is gained by examination of the correlation within the normal range for thyroid uptake. For results above the normal limits of thyroid uptake, correlation appears to be more reliable for method B than for method A.

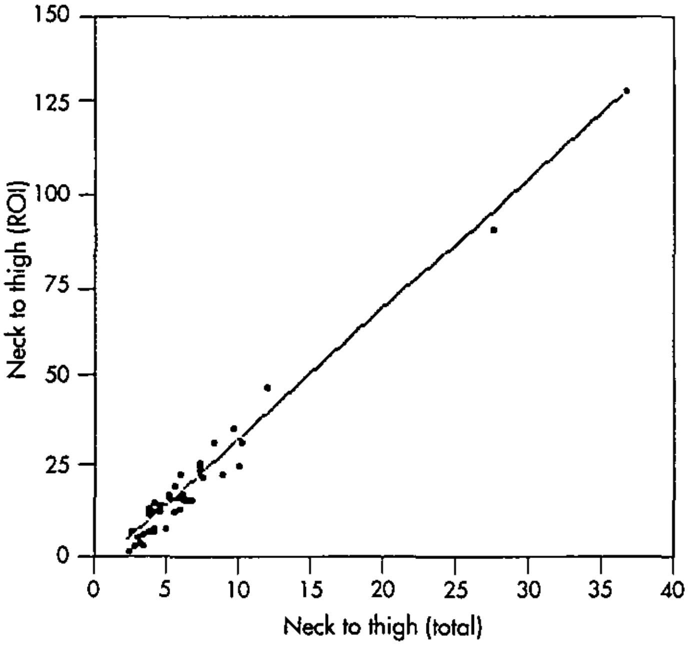
As expected, the correlation between the neck to thigh total and the neck to thigh ROI are quite consistent with a correlation coefficient of 0.9870 (RSquare = 0.974) (figure 6). A stronger relationship may have been demonstrated if neck images excluded salivary glands in all patients and if non anatomical background areas were controlled.

Figure 5: Method B versus method C showing excellent correlation.



Neck to thigh (ROI) = 1.98418 + 3.50301 Thyroid uptake

Figure 6: Method A versus method B showing excellent correlation.



Neck to thigh (ROI) = -3.0794 + 3.59412 Neck to thigh (total)

Discussion

The normal range for percentage thyroid uptake has been established to be 0.5 to 3.75 per cent.[3] Using this normal range and the equations for the lines of best fit established in the results section (figures 4,5 and 6), the corresponding normal ranges were established for the two trapping index methods.

The newly established normal range for trapping index using total counts in neck and thigh images (method A) was 1.93 to 5.08. Using this normal range, there were no false negative studies for hyperthyroidism, however, there are 2 false positive studies for hyperthyroidism and 1 false negative study for hypothyroidism (Table 1). Closer inspection of the studies shows that both of the false positive studies were patients demonstrating salivary glands in the field of view which again extends back to age and positioning issues. Similarly, the false negative study for hypothyroidism included both salivary gland activity and significant thoracic background. As expected, these patients were within the normal range for the ROI TI (method B).

The normal range for trapping index using ROI counts (method B) was established at 3.74 to 15.12. Using this normal range, there is one false negative study for hyperthyroidism and no false negative studies for hypothyroidism, however, there were 2 false positive studies for hyperthyroidism (Table 1). None of these studies corresponds to a false positive or false negative studies using method A. Closer inspection of the studies shows that both of the false positive studies are patients with small amounts of extravasated dose (< 0.5 MBq), although this observation is not thought to be significant. The false negative study has no obvious complicating variables.

All three methods of calculating thyroid function scintigraphically demonstrated excellent correlation. Using the valid normal ranges, all three methods also provided accurate and reliable evaluation of thyroid function. Method A, trapping index using total image counts, has the advantage of being simple and automated. The

Table 1: False positive and false negative findings for the three methods of calculating thyroid function scintigraphically.

	TI total counts < 6	TI total counts 1.93-5.08	TI ROI 3.74-15.12	Total
False +ve hyperthyroid	0	2 (10%)	2 (10%)	20
False -ve hyperthyroid	5 (23.8%)	0	1 (4.8%)	21
False +ve hypothyroid	-	0	0	40
False -ve hypothyroid	-	1 (100%)	0	1
Total	5 (12.2%)	3 (7.3%)	3 (7.3%)	41

trapping index can be programmed to be displayed automatically when images are displayed on most commercially available computer systems. This method is also historically consistent with probe methods that were once used. The major disadvantage of method A is the variable impact of salivary gland activity. While exclusion of salivary gland activity is achieved with minimal technical expertise, this study has shown that there is a relationship between salivary gland activity and age. We suspect that this is related to increased positioning difficulties associated with older patients due to difficulty in excluding salivary glands rather than increased presence of salivary activity.

The trapping index using regions of interests (method B) overcomes this problem by excluding non thyroid activity in the neck image. Similarly, a more consistent thigh count would be achieved. Using total counts, thin patients may leave some 'white space' occupying the image where there are no anatomical counts. The ROI trapping index methods allows placement of the ROI to include 'target background' only. Method B appears to be more reliable for evaluation of hypothyroidism, although there is limited data to draw this conclusion with any statistical certainty. Perhaps the main disadvantage of this technique is inter-operator variations in ROI generation. If the ROI is drawn with an inappropriate threshold, the pyramidal lobe or suppressed thyroid with residual function may be excluded from the ROI. Obviously there is an increase in processing time for method B, however, 2 simple regions of interest do not constitute a significant burden on resources.

The advantage of trapping index over percentage thyroid uptake is the simplicity of preparation and processing (no standard/phantom). Trapping index is also more robust than thyroid uptake in the presence of a number of extraneous variables, including; extravasated injection and time post injection that imaging is commenced. It is clear, however, that normal ranges are population specific with questionable external validity across eras and geographic locations. Consequently, the established normal range used in our Nuclear Medicine department appears to be invalid for the patient population. Scrutiny of the documented normal range supports a causal relationship for the observed phenomena. Determining the valid normal range has provided a more accurate and reliable measure of thyroid function.

Conclusion

Thyroid trapping index (TI) using either total counts in the neck and thigh images or region of interest counts over the thyroid and thigh provide reliable, convenient, rapid and cost effective methods for determining thyroid function scintigraphically. Neither technique was demonstrated to be more reliable than the other, however, the use of regions of interest may provide more reliable assessment in a poorly functioning thyroid gland. While robust to a number of extraneous variables, trapping index is susceptible to the effects of the inverse square law if there is variation in aperture to object distance between images on an individual patient and to the validity of the normal range.

The valid normal range for our patient population was determined to be 1.9 to 5.1 for a trapping index using total counts and 3.7 to 15.1 for a trapping index using region of interest counts.

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