Thyroid blood flow and uptake of technetium-99m pertechnetate in Graves' disease

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Abstract

The aim of this study was to assess the relation of early thyroid blood flow (EBF) and technetium-99m pertechnetate ($^{99m}TcO_4^-$) uptake, as an early diagnostic index in patients with Graves' disease (GD) by dynamic thyroid scintigraphy (40 frames, 3 sec/frame). Thirty patients with GD with mean age 50.0 ± 9.0 y, range: 35.0 - 69.0 y, were studied. The results obtained were compared with those of 30 euthyroid individuals (EI) of mean age 46.9 ± 12.5 y, range: 22.0 - 68.0 y. The parameters of $^{99m}TcO_4^-$ EBF and early uptake studied, derived from the background subtracted time activity curves, were as follows: a) The duration of the EBF in sec; b) The perfusion index (PI) - the ratio of counts at the beginning and at the end of the EBF; c) The uptake index 1 (UI1)-the counts ratio between the counts at the end of the EBF and at the 2nd min d) The uptake index 2 (UI2) - the counts ratio between the 1st min and the 2nd min of the uptake curve and e) Delayed $^{99m}TcO_4^-$ thyroid uptake (TcTU) at 20 min was also calculated as a percentage of net counts activity accumulated in the thyroid gland at 20 min. Results were as follows: a) The mean values of the duration of the EBF were shorter in GD patients (9.90 ± 2.94 sec) than in EI (15.70 ± 4.01 sec; P<0.0001); b) PI did not differ significantly (P>0.05); c) The mean UI1 and UI2 values of thyroid uptake of $^{99m}TcO_4^-$ were significantly lower in GD (UI1=0.621, UI2=0.772) as compared to EI (UI1=1.106, UI2=0.947; P<0.0001 for both) and d) TcTU values were significantly higher in GD (13.6%) than in the group of EI (1.29%; P<0.0001). A good correlation was found in patients with GD between early (UI1 and UI2) and delayed TcTU (r = -0.562; P=0.010 and r = -0.459; P=0.042 respectively). Also, in patients with GD the EBF correlated poorly with UI1, UI2 and TcTU (P>0.05 for all these parameters). *In conclusion*, the results of this study indicate that the duration of EBF did not relate significantly to the height of TcTU values in patients with GD. On the contrary, the early uptake, indices UI1 and especially UI2 were shown to be faster in the majority of GD patients and correlated well with the TcTU. These parameters may be used as diagnostic indices for GD. Further investigation is required to support the above findings.

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Introduction

Thyroid blood flow and function can be disrupted in various thyroid disorders and reliable methods are required for their evaluation [1-5]. Under physiological conditions thyroid vascularity and function are mainly dependent on the activation of thyroid stimulating hormone receptor (TSHR) by thyroid stimulating hormone (TSH) thyroid stimulating hormone receptor antibodies (TSHR-Ab) or by gain of function mutation of the TSHR gene. In Graves' disease (GD), TSHR-Ab bind to and activate the TSHR on the thyroidal cells, causing hypersecretion, hypertrophy and hyperplasia of the thyroid follicles [6]. Untreated GD patients have a hypervascular gland inducing thyroid bruit and thrill [7, 8].

Thyroid blood flow can be assessed by various methods, such as angiography, electromagnetic flowmetry, Doppler ultrasonography and radionuclide imaging. The first two methods are not commonly used due to their invasiveness. It seems that color - flow US is the most suitable method for this purpose because of its simplicity and noninvasiveness, and the possibility for a quick differentiation between diffuse [2-4, 9, 10] and nodular thyroid disease [11, 12]. Radionuclide imaging has been used to evaluate the vascularity of "cold" thyroid nodules in order to distinguish neoplastic from non-neoplastic ones [12-18]. Radionuclide "angiography" of the thyroid gland with technetium-99m pertechnetate ($^{99m}TcO_4^-$) can estimate thyroid perfusion in hyperthyroidism [19]. This report is qualitative and performs visual analysis of thyroid blood flow. To our knowledge, there are no reports semi-quantifying thyroid blood flows in GD during radionuclide imaging.

Thyroid uptake of ^{99m}Tc (TcTU) may assess thyroid function because $^{99m}TcO_4^-$ has a similar molecular size with iodine ($V=4.05\times10^{-23}$ and $V=4.22\times10^{-23}$ respectively) and is also transported into the thyroid by the Na^+/I symporter. Its maximal thyroid uptake is usually

achieved at 10-20 min after the injection of the radiopharmaceutical. Thus, the 20 min thyroid uptake of $^{99m}TcO_4^-$ may be used to estimate thyroid function [20-23]. In this paper we have studied if patients with GD had increased early blood flow (EBF) in parallel with increased TcTU at 20 min, so that parameters of EBF derived from dynamic thyroid scintigraphy may be used as indicators of hyperthyroid disease. We have also studied the relation between EBF parameters and delayed TcTU in patients with GD.

Patients and methods

Patients

This prospective study was performed between December 2003 and June 2006 in the Department of Nuclear Medicine at the Clinical Center of the University of Niš, Serbia. Thirty patients with GD and 30 EI were included in the study (Table 1). All persons studied were from the city of Nis and regions where iodine deficiency is not present. Diagnosis of the disease was previously established by the Endocrinology Clinic of the University of Niš. Inclusion criteria for GD were: diffusely and symmetrically enlarged thyroid gland as assessed by palpation and ultrasound, and a history of ophthalmopathy or increased TSHR-Ab levels. Patients with GD had at the time of diagnosis symptoms and signs of hyperthyroidism, elevated levels of thyroid hormones and suppressed TSH level. EI had no symptoms and signs of thyroid disease and normal levels of TT3, TT4 and TSH. Our exclusion criteria included absence of illnesses and conditions associated with high level of thyroid hormone binding albumins which may induce increased TT3 and TT4. Exclusion criteria were: the presence of any associated acute medical or psychiatric illness as well as a history of pituitary disease.

All patients with GD had been treated with thyrostatic drugs from 3 to 36 months as shown in Table 1. Twenty of them received propylthiouracil, while the remaining received methimazole (Table 1). Antithyroid treatment was stopped 7-10 days prior to scintigraphy. The study protocol was approved by the medical ethics committee of the Clinical Center of the University of Niš and all patients provided their written informed consent for this study.

Methods

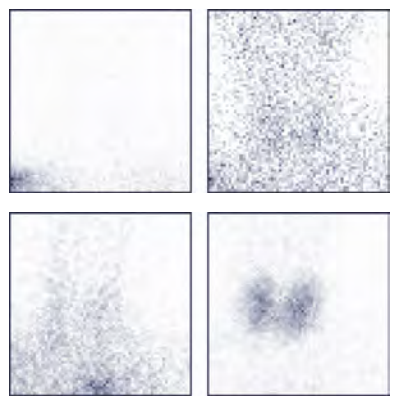
Patients were imaged at the supine position with the neck extended, immediately following the inravenous (iv) injection of 185 MBq of $^{99m}TcO_4^-$ (Laboratory for Radioisotopes, Institute of Nuclear Sciences "Vinca", Serbia) as a bolus into the antecubital vein. Dynamic scintigraphy of the thyroid gland was recorded during the 2 min period (forty images at 3 sec per frame) on a 64×64 computer matrix using 1.5 zoom factor. Gamma camera (type PhO V, Siemens, Germany), equipped with a parallel hole collimator was centered over the thyroid at a distance of 7 cm between the collimator and the thyroid gland. Scintigrams obtained for each patient were analyzed as mentioned below (Fig. 1).

The time activity curves subtracted for the background (bg) were generated, using the irregular regions of interest (ROI) technique. A ROI was drawn around the borders of the thyroid gland and another ROI just below the gland to be used for bg subtraction. For the proper injection of the radiopharmaceutical as a bolus infusion we have first gained considerable experience in order to avoid errors of bolus infusion that could alter the shape of the time-activity EBF and TcTU curves. The following semi-quantitative parameters of the $^{99m}TcO_4^-$ thyroid blood flow and early thyroid uptake were derived from the time activity curves (Fig. 2): a) The duration of the EBF: the time in sec between the start (A) and the end point of the EBF curve (B). b) The perfusion index (PI): the ratio of counts at the beginning (A) and at the end of the EBF (B). c) The uptake index 1 (UI1): the counts ratio be-

Table 1. *Patients' data*

Groups	N	Female/Male	Age (years) mean±SD (range)	Duration of treatment (months) mean±SD (range)
EI	30	29/1	46.9±12.5 (22.0-68.0)	–
GD	30	20/10	50.0±9.0 (35.0-69.0)	17.0± 9.2 (3.0-36.0)

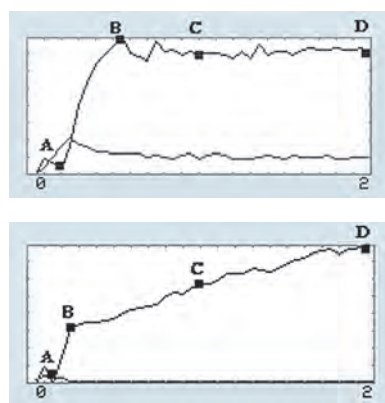
EI: euthyroid individuals, GD: Graves' disease patients



(A)

(B)

Figure 1. Early uptake phase at 60 sec and scintigrams of an euthyroid subject (A) and a patient with Graves' disease (B).



(A)

EBF: t=18 sec,
PI=0.084,
UI1=1.114,
UI2=0.928

(B)

EBF: t=6 sec,
PI=0.274,
UI1=0.466
UI2=0.744

A=the beginning of the EBF phase, B=the end point of the EBF phase, C=the 1st min of the curve, D= the 2nd min of the curve.

Figure 2. Typical time activity curves subtracted for bg of an euthyroid individual (A), and Graves' disease patient (B).

tween the end point of the EBF (B) and the counts at the 2nd min (D) and d) The uptake index 2 (UI2): the counts ratio between the 1st (C) and the 2nd min of the uptake curve (D) and e) The delayed TcTU, calculated at 20 min following the injection of $^{99m}TcO_4^-$ as a percentage of net applied activity accumulated in the thyroid gland from the dose injected. Thyroid and syringe counts before and after injection of the radiopharmaceutical were measured under the same conditions, with a parallel hole collimator, 60 sec acquisition, 128×128 matrix and 1.5 zoom factor. These counts were then corrected for bg and radioactive decay [22].

Statistical analysis

Data were expressed as mean ± SD, and as minimal and maximal values. Parameters measured were considered increased or decreased if they varied more than ±2 SD from the corresponding mean of the euthyroid group. Parameters among the GD and the euthyroid group were compared by the Student's t test. Pearson's coefficient (r) was calculated to evaluate the correlation between different parameters in the same Group. The results were considered statistically significant when the P value was below 0.05. Computations were carried out with the SPSS statistical package version 9.0 (Chicago, Illinois, USA).

Results

Typical scintiscans of an EI showing homogeneous distribution of radioactivity in the EBF phase, as well as a relatively slow rise of activity until the end of the study, are shown in Fig. 1A. Corresponding time activity subtracted curve shows a steady activity level throughout the study (Fig. 2A). Figure 1B shows in a patient with GD, elevated EBF through the entire gland with progressively increased activity of UI1 and UI2, till the end of the study. The time activity curve of this patient shows shorter EBF when compared with the EBF of the EI followed by a rapid and gradual rise of the uptake with maximal counts at the end of the 2 min study (Fig. 2B).

Semiquantitative parameters of the EBF, UI1 and 2 are shown in Tables 2 and 3. The group value of the time of EBF was significantly shorter in GD than in EI , while PI did not differ significantly. In 11 (36.7%) out of the 30 patients with GD, the duration of EBF was less than ±2 SD of the mean of the EI group. Individual values of PI were elevated in only two (6.67%) patients with GD.

UI1 and UI2 were significantly faster in GD as compared with EI. Analysis of individual values of the UI2 showed faster uptake in 70.0% of the patients with GD, while no patient had UI1 below the established normal limit. Also these parameters were considered increased or decreased if they varied ±2 SD from the corresponding mean of the euthyroid group.

Patients with GD had highly increased TcTU as compared with the EI (Table 4). Twenty seven out of 30 (90.0%) persons with GD had increased TcTU. The relation between early and delayed uptake in GD was quite satisfactory (UI1 and TcTU: r=-0.562, P=0.010; UI2 and TcTU: r =-0.459, P=0.042) and in EI (UI2 and TcTU: r=–0.745, P=0.0001). In addition,

Table 2. *Duration of the thyroid early blood flow (EBF in sec) and the perfusion index (PI) in euthyroids (EI) and in Graves' disease GD patients*

	EI		GD	
	EBF	PI	EBF	PI
Mean	15.7	0.143	9.90*	0.176
SD	4.01	0.067	2.94	0.069
Minimum	6.00	0.045	6.00	0.102
Maximum	18.0	0.298	12.0	0.340

EBF in GD vs EI: P < 0.0001

Table 3. *Values of the UI1 and UI2 indices in euthyroids and GD patients*

	EI		GD	
	UI1	UI2	UI1	UI2
Mean	1.106	0.947	0.621*	0.772*
SD	0.410	0.074	0.169	0.073
Minimum	0.359	0.799	0.307	0.643
Maximum	2.481	1.053	0.987	0.955

GD patients vs EUI: *P < 0.0001

Table 4. *The $^{99m}TcO_4^-$ uptake (%) in 20 min in euthyroids and GD patients*

	EI	GD
Mean	1.29	13.6*
SD	0.688	9.51
Minimum	0.320	1.54
Maximum	2.82	37.1

GD patients vs EI: *P < 0.0001

in patients with GD, EBF correlated poorly with UI1, UI2 and TcTU (P>0.05). On the contrary, EBF correlated well with UI1 in the EI group (r = -0.645, P=0.002).

Discussion

In previous studies, in untreated GD using US, intrathyroidal blood flow was found to be diffusely and markedly increased throughout the gland, but mildly to moderately increased in other diffuse thyroid diseases associated with hyperthyroidism [4]. It was found by color US that thyroid blood flow in GD patients and thyroid vascularity are increased while in thyrotoxicosis (i.e. a serum increase of thyroid hormone levels) we do not have increased vascularity [7]. Recent reports have shown that TSH can drive the increased expression of growth factors in the thyroid follicular cells, which stimulates synthesis and release of endothelin (ET). ET exerts a paracrine effect on the surrounding cells and has mitogenic effects in vascular smooth muscle, fibroblasts and vascular endothelial cells causing blood capillary enlargement observed during thyroid hyperplasia. It is conceivable that similar effects might be exerted by TSHR-Ab in GD [24].

Radionuclide "angiography" of the thyroid gland with $^{99m}TcO_4^-$ was mainly used for the evaluation of vascularity of scintigraphic "cold" nodules [12-18]. Only one published report refers to visual analysis of thyroid radionuclide angiograms in GD, without semi-quantification [19]. Lee et al. (1982) have presented markedly increased radioactivity in 24/25 patients with GD after visual analysis of thyroid blood flow. They did not indicate if those hyperthyroid patients had been treated with antithyroid drugs [19].

In our study, 7-10 days before performing scintigraphy, all GD patients had been treated with thyrostatic drugs and were at varying functional stages as assessed by thyroid hormone levels. We have demonstrated significantly shorter time of the EBF duration, faster UI1 and UI2 and highly increased TcTU in the GD patients than in EI. In spite of these findings which were related to the increased vascularity and hyperfunction of the thyroid gland, the EBF values in the majority of GD patients were normal, probably because of the thyroid function suppression due to previous antithyroid treatment. This was supported by others who in GD patients treated by antithyroid drugs found decreased thyroid blood flow (113.6 ± 35.1 ml/min before and 74.0 ±12.7 ml/min during antithyroid treatment) [9]. According to our knowledge there are no reports co-relating thyroid blood flow and the duration of thyrostatic drugs treatment [4].

In the TcTU at 20 min is an well established parameter of thyroid function that allows reliable evaluation of thyroid uptake and avidity for iodine [20-23]. The good correlation between the TcTU and the UI1 and UI2 in GD found in our study may point out that early uptake may be also a reliable parameter of thyroid gland function. Thus, UI1 and UI2 may be used as fast indicators of the degree of hyperthyroidism and for adjusting the proper therapeutic dose of ^{131}I.

In conclusion, concerning the results of this study, the duration of EBF does not significantly relate to the increased TcTU in patients with GD and may not be used as an indicator of hyperthyroidism. On the contrary, the early uptake indices, UI1 and especially UI2 were faster in the majority of GD patients correlated well with the TcTU and may be used diagnostically. However, further investigation is required to support such an assumption.

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