



Incidentally recognised thyroid focal uptake of ^{99m}Tc -sestamibi during stress myocardial perfusion scintigraphy

Znaczenie przypadkowo rozpoznanego ogniskowego wychwytu ^{99m}Tc -sestamibi w tarczycy w trakcie scyntygrafii perfuzyjnej mięśnia sercowego

Krzysztof Giejda¹, Stanisław Piszczek², Zofia Stembrowicz-Nowakowska², Marek Saracyn¹, Mirosław Dziuk², Grzegorz Kamiński¹

¹Department of Endocrinology and Isotope Therapy, Military Institute of Medicine, Warsaw, Poland

²Department of Nuclear Medicine, Military Institute of Medicine, Warsaw, Poland

Abstract

Introduction: ^{99m}Tc -sestamibi, a radiopharmaceutical widely used in the assessment of myocardial perfusion, can be used as an indicator of thyroid disease due to its oncophilic character. The aim of this study was to establish the usefulness of performing additional examinations of radiotracer uptake in the thyroid gland during standard stress scintigraphy with sestamibi in order to identify thyroid diseases.

Material and methods: After a retrospective evaluation of 330 consecutive myocardial perfusion scintigraphies performed in our hospital during one year, 41 patients with a focal accumulation of ^{99m}Tc -sestamibi in the thyroid were enrolled in the study. The patients underwent clinical examinations, including thyroid ultrasonography and TSH, fT4, fT3, aTPO, TRAb, calcitonin, and CEA levels. Based on the thyroid ultrasounds, 21 patients were referred for fine-needle aspiration biopsy of the thyroid.

Results: An abnormal accumulation of radiotracer in the thyroid was found in 41 (12.4%) of 330 patients who underwent stress cardiac scintigraphy. Thirteen (31.7%) of those patients had multinodular euthyroid goitres, 12 (29.2%) had a single thyroid nodule (including two autonomous nodules), 11 (26.8%) had autoimmune thyroid disease, and one (2.4%) had papillary thyroid carcinoma. In 12 (29.2%) with thyroid tracer uptake there was no thyroid pathology.

Conclusions:

1. Additional evaluation of radiotracer uptake in the thyroid during standard myocardial perfusion scintigraphy is a valuable tool in the detection of thyroid diseases.

2. The additional or parallel evaluation of radiotracer uptake in the thyroid should be considered during every myocardial scintigraphy. (*Endokrynol Pol* 2015; 66 (6): 521-525)

Key words: thyroid nodules; sestamibi; myocardial scintigraphy; thyroid cancer; thyroid autoimmune disease

Streszczenie

Wstęp: ^{99m}Tc -sestamibi jest radiofarmaceutykiem stosowanym standardowo między innymi w ocenie perfuzji mięśnia sercowego. Ze względu na właściwości onkofilne może być także wykorzystywany w diagnostyce chorób tarczycy. Celem pracy była analiza przydatności dodatkowej oceny gruczołu tarczowego podczas scyntygraficznej próby wysiłkowej z wykorzystaniem sestamibi do wykrywania chorób tarczycy.

Materiał i metody: Po ocenie 330 kolejnych badań scyntygrafii perfuzyjnej serca w Zakładzie Medycyny Nuklearnej WIM wykonanych w okresie od 01.01.2009 do 1.01.2010 do dalszych badań zakwalifikowano 41 chorych, u których rozpoznano ogniskowe gromadzenie ^{99m}Tc -sestamibi w tarczycy. Następnie przeprowadzono badanie kliniczne, wykonano USG tarczycy oraz oznaczono stężenie: TSH, fT4, fT3, aTPO, TRAb, kalcytoniny, CEA. Na podstawie wyniku badania ultrasonograficznego tarczycy 21 osób skierowano na biopsję cienkoigłową tarczycy.

Wyniki: U 41 (12,4%) z 330 chorych poddanych scyntygrafii serca stwierdzono nieprawidłowe gromadzenie radioznacznika w tarczycy. U 13 (31,7%) z nich rozpoznano wole wieloguzkowe, 12 (29,2%) miało pojedynczy guzek tarczycy (w tym dwóch chorych guzek autonomiczny), 11 chorych (26,8%) prezentowało autoimmunizacyjną chorobę tarczycy, u jednej (2,4%) znaleziono raka brodawkowatego tarczycy. W 12 przypadkach (29,2%) nieprawidłowego gromadzenia radioznacznika nie potwierdzono choroby tarczycy.

Wnioski:

1. Dodatkowa ocena wychwytu radioznacznika w tarczycy podczas standardowej scyntygrafii perfuzyjnej serca jest cennym narzędziem w wykrywaniu chorób tarczycy.

2. W opisie wyniku badania scyntygrafii perfuzyjnej serca powinno się także uwzględnić ocenę wychwytu radioznacznika w tarczycy. (*Endokrynol Pol* 2015; 66 (6): 521-525)

Słowa kluczowe: zmiany ogniskowe tarczycy; sestamibi; scyntygrafia serca; rak tarczycy; autoimmunologiczna choroba tarczycy



Krzysztof Giejda M.D., Department of Endocrinology and Isotope Therapy, Military Institute of Medicine Warszawa, Polska, phone/fax: +48 22 68 161 10, e-mail: kgiejda@wim.mil.pl

Introduction

Myocardial perfusion scintigraphy is a valuable tool in the diagnosis of ischaemic heart disease. This test uses sestamibi labelled with ^{99m}Tc (^{99m}Tc-sestamibi), which accumulates in the cells and is characterised by enhanced metabolism, high proliferative activity, and increased number of mitochondria. These features are also typical of tumour cells [1]. For this reason, sestamibi is used in nonspecific cancer diagnostics, including breast, thyroid, and lung cancers [1]. Due to its high positive predictive value, sestamibi imaging is used in thyroidology, to qualify lesions for cytological examination, while negative prediction helps in identifying thyroid nodules, qualified based on a biopsy to Bethesda category III (follicular lesion of undetermined significance) and category IV (suspicious for a follicular neoplasm) [1, 2]. Lack of uptake excludes, while increased uptake indicates, the malignant nature of the lesion [3].

Ultrasonography is more accessible and is used more commonly in the differential diagnosis of thyroid cytopathology. Scintigraphic imaging is associated with exposure to ionising radiation, and therefore, it is rarely used in the diagnosis of thyroid nodules. However, there is a large group of patients in whom sestamibi analysis is performed to assess myocardial perfusion in the diagnosis of coronary artery disease. While raw images (before software processing) obtained during this test comprise a “window” that may include part or all of the thyroid field, nuclear physicians who evaluate myocardial perfusion omit extracardiac image elements from further analysis. Nonetheless, additional evaluation of sestamibi uptake in the thyroid during myocardial perfusion scintigraphy might be a valuable tool in the diagnosis of thyroid disease, and it requires no additional monetary expenditure or exposure to additional ionising radiation. Evaluation of the thyroid during myocardial scintigraphy can also be considered a screening test with high positive prediction of malignancy, reaching more than 20% according to some sources [3, 4].

The aim of this study was to analyse the usefulness of additional assessment of the thyroid gland during stress scintigraphy using sestamibi in order to detect thyroid pathology and evaluate thyroid function.

Material and methods

We retrospectively evaluated 330 consecutive myocardial perfusion images captured in the Department of Nuclear Medicine, Military Institute of Medicine in Warsaw, from 14 January 2009 to 6 December 2009. The tests had been conducted for the diagnosis or control of coronary disease. The radiopharmaceutical sestamibi,

with an activity of 740 MBq, was administered during either a treadmill stress test or a pharmacological test with dipyridamole. An Infinia Hawkeye 4 gamma camera (GE Healthcare, WI, USA) was used for imaging with a low-energy, high-resolution collimator and 64 × 64 camera matrix. Single-photon emission computed tomography (SPECT-CT) imaging was performed 60 minutes after administration of the radiotracer. Image data were processed on a GE Xeleris diagnostic station using software with a *Volumetrix for Hawkeye* option. As the field of view of the gamma camera detector was 54 × 40 cm, the “window” of the test before software processing (for heart examination) covered part or all of the thyroid gland.

SPECT imaging of the thyroid field was performed in transversal, frontal, and lateral projections. Focal uptake of sestamibi in the thyroid was defined as a thyroid nodule. Forty-one patients were diagnosed with focal radiotracer uptake in the thyroid gland, and they underwent the following laboratory tests: thyroid stimulating hormone (TSH), thyroxine (fT4), triiodothyronine (fT3), thyroid peroxidase antibodies (aTPO) and TSH receptor (TRAB), calcitonin, carcinoembryonic antigen (CEA), calcium and phosphorus, and ultrasound of the thyroid gland. AutoDELFI A packages (PerkinElmer Life and Analytical Sciences, Turku, Finland) were used to determine TSH, fT3, and fT4. Anti-TPO and anti-TRAB antibody levels were determined by quantitative radioimmunoassay (BRAHMS, Hennigsdorf, Germany), and calcitonin and CEA were assayed using CLIA immunochemiluminescence (LIAISON; DiaSorin, Stillwater, MN). Each patient underwent thyroid ultrasonography (USt) (Siemens Acuson x150, CA, USA, linear probe at 10 MHz frequency), and based on the results, 21 patients qualified for fine-needle aspiration according to Polish recommendations [2]. Selected cases were referred for thyroid resection. All of the patients were informed about the purpose and method of the examination, and they gave their written consent. The study protocol was approved by the Bioethics Committee of the Military Institute of Medicine in Warsaw.

Results

We analysed 330 myocardial perfusion images, and focal uptake was observed in 41 cases (12.4%). Among the 41 patients enrolled in the next stage, 16 were men and 25 were women. The mean age was 63.4 years (men, 61.7; women, 64.9). Thyroid disease was confirmed in 29 patients (70.7%) by ultrasound and/or laboratory tests. Eight of the patients were diagnosed with two thyroid pathologies. Each of the pathologies was considered as a separate case; thus, the number of pathologies identified was 37.

Table I. Summary of the results

Tabela I. Podsumowanie wyników

Diagnosis		n	%	
No thyroid pathology		12	29.2%	
Thyroid nodules	Single nodules	Autonomus nodule	2	4.9%
		Other	10	24.4%
	Multinodular goitre	13	31.7%	
	Thyroid cancer	1	2.4%	
Autoimmune thyroid disorders				
	AT	10	24.4%	
	Graves' disease	1	2.4%	

AT — autoimmune thyroiditis (Hashimoto's Thyroiditis)

Thyroid nodules were observed in 25 patients in the study group (n = 41; 60.9%) [Table 1], including 13 cases of multinodular lesions (31.7%), and 12 cases of single nodules (29.2%). Among the single changes, two cases of autonomous nodules in the subclinical hyperthyroidism stage were found. Ten patients were diagnosed with Hashimoto's thyroiditis (AT autoimmune thyroiditis) based on elevated levels of anti-TPO antibodies and the characteristic ultrasound image; two of those patients had elevated TSH levels and clinical hypothyroidism features. These cases represented 24.4% of the study group. One subject was diagnosed with Graves' disease with clinical and hormonal euthyroid. Together, autoimmune diseases were found in 26.8% of the study group. In 12 patients (29.2%) with thyroid radiotracer uptake there was no thyroid pathology. The values of CEA and calcitonin were normal in all patients.

Fine-needle aspiration biopsy of the thyroid, according to the guidelines of the Polish Thyroid Association, was performed in 21 patients [2]. One case of papillary thyroid carcinoma was determined and confirmed by histopathology after thyroidectomy: pT1b(m)N1Mx.

Discussion

The results of autopsies indicated that approximately 50% of the population had thyroid nodules [5] and 36% had thyroid cancer [6]. According to the 2009 data of the Central Statistical Office, 4.6% of the Polish population was diagnosed with thyroid disease [7]. The almost ten-fold disparity in prevalence rate between autopsy results and clinical studies highlights the importance of searching for new thyroid diagnostic methods or modifying the existing ones.

Extensive screening and the subsequent diagnostics of thyroid nodules would result in huge costs from public funds. In addition, such an undertaking would not provide certainty in cancer exclusion, as most cases involve multinodular goitres, and separate diagnos-

tics of each lesion is usually impossible. The situation changes with the application of high positive prediction tests performed for non-thyroidal indications. Such screening tests do not generate additional costs, and the selected cases represent a high-risk group that require further diagnostics. Myocardial perfusion scintigraphy, evaluated in the current study, certainly belongs in that category of procedures.

Ever since ^{99m}Tc -sestamibi was synthesised for the first time (1982), many studies have been carried out to assess the usefulness of the radiopharmaceutical in cancer diagnostics. Benign lesions are characterised by the lack of accumulation of the radiopharmaceutical. Hurtado-Lopez et al. [4] evaluated nine studies involving 448 patients with hypofunctional thyroid nodules, who underwent sestamibi imaging. Uptake of the radiopharmaceutical was detected in all 127 cases of differentiated and four medullary thyroid carcinomas and in one of three anaplastic carcinoma cases. Based on this analysis, it was concluded that a lack of uptake of sestamibi in thyroid nodules precludes the existence of differentiated thyroid cancer. Approximately two-thirds (i.e. 212 patients) of the benign thyroid nodule cases were characterised by an accumulation of sestamibi. Therefore, the positive prediction rate of malignancy in the study group was 38.2%. We did not expect such results, for several reasons. First, the qualification for inclusion in the group was based on abnormal sestamibi uptake in the thyroid, and not thyroid nodules detected by ultrasound. As such, there was a group with no thyroid pathology (12 patients), and thyroid nodules confirmed by USt occurred in 25 patients (61%). In addition, by treating myocardial perfusion scintigraphy as a screening test, we had no previous data on thyroid diseases in these patients. It should be noted that the cited work qualified patients diagnosed with thyroid nodules, while "warm" and "hot" changes in the iodine or technetium scintigraphy were excluded. Thus, in the study group, one case of differentiated

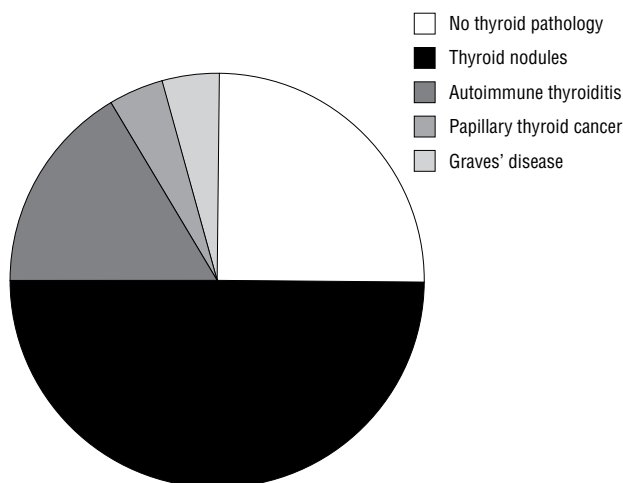


Figure 1. Patients with focal uptake in the thyroid qualified to the group ($n = 41$)

Rycina 1. Pacjenci z ogniskowym wychwytem sestamibi w tarczycy ($n = 41$)

thyroid cancer was found out of 41 patients showing sestamibi uptake (2.4%).

Not without significance is the method of the study. Sestamibi imaging has previously been performed in many ways. Kresnik et al. [8] evaluated the washout of the radiopharmaceutical by two-phase scanning performed 30 and 120 minutes after injection. The result was an 84% negative prediction, not 100%. Hurtado-Lopez et al. [3] used a combination of pertechnetate and sestamibi scans. The technetium test allowed them to separate patients with hypofunctional nodules, who subsequently underwent sestamibi imaging. Nodules that did not uptake any of the tracers (so-called matches) were always benign. In contrast, nodules "cold" in technetium scintigraphy and "hot" using sestamibi (so-called mismatches) were characterised by a positive malignancy prediction of 60.9%. The setup of our study was different; the tracer was injected during the stress test or after the administration of dipyridamole, and imaging was performed once after 60 minutes. We did not find any studies in the literature similar to our method. Provided that our study was a screening examination to assess the thyroid function of patients undergoing myocardial perfusion imaging, adjusting the diagnostic scheme would change the aim of the study. Thyroid nodules were found to be present in 61% of our study group, which is higher than the incidence rate in the general population, estimated at 50% based on autopsies [5].

Many studies have been performed to demonstrate the usefulness of further diagnostics of thyroid incidentalomas. Czepczyński et al. [9], who analysed thyroid nodules found accidentally during positron emission

tomography CT (PET-CT) with 18F-FDG, adopted assumptions similar to ours. The authors evaluated 1925 PET-CT scans performed to diagnose and determine the severity of cancers with extrathyroidal starting points. They found thyroid incidentalomas in 71 cases (3.7%), of which six were papillary carcinomas, one was a medullary carcinoma, and one was a case of lung cancer metastasis to thyroid. The positive prediction rate of malignant incidentalomas in their study was high at 40%. The incidence rate of thyroid incidentaloma found during myocardial perfusion imaging in our study was 18.4%, but the specificity in malignant tumour diagnostics was significantly lower. One of the reasons might be the lack of determination of cutoff points characteristic of malignancy in clinical SPECT-CT, which increases the frequency of lesion detection and decreases specificity, largely dependent on the experience of the diagnostician. PET studies use standardised uptake values, which allow a high certainty of determination of malignancy risk.

Assessment of the usefulness of sestamibi scintigraphy for the detection of autoimmune thyroid diseases is a separate issue. Santos et al. [10] attempted to determine the optimal time interval between administration of the radiotracer and maximum uptake in the organ to obtain the best quality in the diagnostics of autoimmune thyroid diseases. They studied healthy patients with atrophic and hypertrophic Hashimoto's thyroiditis and Graves' disease and found that a five-minute interval between administration of the tracer and the measurement was optimal. Using that interval, they were able to distinguish healthy patients from subjects with autoimmune thyroid disease, with the exception of an atrophic form in which sestamibi accumulation was lower than in healthy subjects. Although imaging was performed 60 minutes after administration of the radiotracer in our study, we found ten cases of chronic autoimmune thyroiditis and one case of Graves' disease, for a total of 26.8%. The ratio of male to female was five to six, and the estimated incidence rate of autoimmune thyroid disease in the population was 4–10% [11].

In 12 patients (29.2%) with focal uptake of sestamibi we did not find any thyroid pathology. We suppose that this finding is due to the contamination of sestamibi with free technetium during production of radiotracer.

We do not find any studies in the medical literature pertaining to the issue discussed in our work. The results of this study indicate the need for a broader perspective on myocardial perfusion scintigraphy. Most thyroid diseases that can be diagnosed during the test are in the presymptomatic phase. Early diagnosis and

treatment improves the prognosis of thyroid cancers, while in benign diseases, early treatment can prevent extrathyroidal complications (heart, bones).

By detecting additional autonomous nodule or presymptomatic forms of Graves' disease, we can prevent symptomatic hyperthyroidism after iodine load during the next diagnostic stage of coronary heart disease, which is coronary angiography.

An important conclusion of this study is to consider sestamibi imaging in the detection of other cancers, such as lymphoma, breast, lung, and liver cancers. This costless, low-burden study should provide significant benefits in those cases as well.

Conclusions

1. Additional evaluation of radiotracer uptake in the thyroid during standard myocardial perfusion scintigraphy is a valuable tool in the detection of thyroid diseases.
2. The additional or parallel evaluation of radiotracer uptake in the thyroid should be considered during every myocardial scintigraphy.

References

1. Bucerius J, Ahmadzadehfar H, Biersack H. ^{99m}Tc-Sestamibi. Clinical Applications. Wyd. Springer-Verlag Berlin Heidelberg 2012.
2. Jarząb B, Sporny S, Lange D et al. Diagnostyka i leczenie raka tarczycy – rekomendacje polskie. *Endokrynol Pol* 2010; 61: 518–568.
3. Hurtado-López LM, Arellano-Montano S, Torres-Acosta EM et al. Combined use of fine-needle aspiration biopsy, MIBI scans and frozen section biopsy offers the best diagnostic accuracy in the assessment of the hypofunctioning solitary thyroid nodule. *Eur J Nucl Med* 2004; 31: 1776–1780.
4. Hurtado-López LM, Martínez-Duncker C. Negative MIBI thyroid scans exclude differentiated and medullary thyroid cancer in 100% of patients with hypofunctioning thyroid nodules. *Eur J Nucl Med Mol Imaging* 2007; 34: 1701–1703.
5. Mortensen JD, Woolner LB, Bennett WA et al. Gross and microscopic findings in clinically normal thyroid glands. *J Clin Endocrinol Metab* 1955; 15: 1270–1280.
6. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer* 1985; 56: 531–538.
7. GUS. Stan zdrowia ludności Polski w 2009 roku. GUS, Warszawa 2011: 128–143.
8. Kresnik E, Gallowitsch H, Mikosch P et al. Technetium-99m-MIBI Scintigraphy of Thyroid Nodules in an Endemic Goiter Area. *J Nucl Med* 1997; 38: 62–65.
9. Czepczyński R, Stangierski A, Oleksa R et al. Incidental ¹⁸F-FDG uptake in the thyroid in patients diagnosed with PET/CT for other malignancies. *Nuclear Medicine Review* 2011; 14: 68–72.
10. Santos AO, Zantut-Wittmann DE, Nogueira RO et al. ^{99m}Tc-sestamibi thyroid uptake in euthyroid individual and in patients with autoimmune thyroid disease. *Eur J Nucl Med Mol Imaging* 2005; 32: 702–707.
11. Van den Driessche A, Eenkhoorn V, Van Gaal L et al. Type 1 diabetes and autoimmune polyglandular syndrome: a clinical review. *Neth J Med* 2009; 67: 376–387.