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Scintigraphy for Risk Stratification of Iodine-Induced Thyrotoxicosis in Patients Receiving Contrast Agent for Coronary Angiography: A Prospective Study of Patients with Low Thyrotropin

EVA FRICKE, HARALD FRICKE, ELKE ESDORN, ANNETT KAMMEIER, OLIVER LINDNER, KNUT KLEESIEK, DIETER HORSTKOTTE, AND WOLFGANG BURCHERT

Institute of Molecular Biophysics, Radiopharmacy, and Nuclear Medicine (E.F., H.F., E.E., A.K., O.L., W.B.); Institute for Laboratory and Transfusion Medicine (K.K.); and Department of Cardiology (D.H.), Heart and Diabetes Center North Rhine-Westphalia, D-32545 Bad Oeynhausen, Germany

The risk of iodine-induced thyrotoxicosis in euthyroid patients receiving iodine-containing contrast agents is known to be low, but data on this risk in patients with latent hyperthyroidism are scarce. We investigated the role of thyroid scintigraphy using Tc-99m preceding the application of iodine-containing contrast material to estimate the risk of iodine-induced thyrotoxicosis in patients with low levels of TSH.

In a prospective study on 91 patients, thyroid scintigraphy was performed before coronary angiography (CA). In patients with technetium thyroid uptake (TCTU) less than 1%, CA was done without prophylactic drugs (n = 56). Patients with TCTU greater than 1% were treated either with 900 mg of perchlorate or, depending on the autonomous volume, combined with 20 to 60 mg thiamazole.

In the 56 patients with TCTU less than 1%, no case of iodine-induced hyperthyroidism occurred within 4 wk after CA. In the patients who received prophylactic drugs, two cases of mild thyrotoxicosis were observed.

Our data suggest that in patients with low levels of TSH, the risk of hyperthyroidism after application of iodine-containing contrast media is negligible if TCTU is less than 1%. In these patients, CA can be performed without administration of prophylactic drugs. (*J Clin Endocrinol Metab* 89: 6092–6096, 2004)

THE USE OF iodine-containing contrast media for imaging, *i.e.* for coronary angiography (CA), is widespread. Application of nonionic contrast agents results in considerable iodine load of the thyroid gland, which is mainly caused by *in vivo* deiodination of the contrast medium (1–3). In euthyroid patients, the risk of iodine-induced thyrotoxicosis is low (4–7). The observed frequency of hyperthyroidism ranges from 0 (6) to 2.7% (4), depending on the patient population. To the best of our knowledge, there are no data in the literature on the risk of iodine-induced thyrotoxicosis in patients with preexisting partial or total suppression of the TSH secretion. Because a disturbed control circuit of thyroid function might be an indicator for thyroid autonomy, special attention should be paid to such patients when exposure to high amounts of iodine is unavoidable.

The risk of hyperthyroidism rises with increasing amounts of functionally autonomous tissue (8–11). Quantitative scintigraphy of the thyroid using Tc-99m-pertechnetate has been shown to be a reliable equivalent of the iodine clearance. Therefore, technetium thyroid uptake (TCTU) is a measure of thyroid function and, in the case of TSH suppression, a measure of the function and amount of the autonomous tissue.

The aim of our study was to assess the risk of iodine-induced hyperthyroidism by thyroid scintigraphy. We assumed that, in patients with suppressed TSH value and a TCTU less than 1%, the application of contrast media is safe without application of prophylactic drugs (PDs). Furthermore, we investigated the usefulness of prophylactic medication in patients with proven autonomy of the thyroid gland.

Patients and Methods

Ninety-one consecutive patients admitted for CA to our center were included in this prospective study (69 males and 22 females; mean age, 65 ± 8.7 yr). All patients gave informed consent to study inclusion. Inclusion criteria were a basal TSH level of less than 0.3 mU/l and normal levels of T_3 and free T_4 (fT_4). Patients with immunogenic thyroid diseases, verified by the investigation of thyroid autoantibodies, as well as patients with thyroid-specific medication, were excluded from the study. Moreover, patients with a history of application of contrast agent within the last 3 months, those with amiodarone treatment, and those with renal insufficiency (creatinine >1.5 mg/dl) were excluded.

Before study enrollment, patient history was documented and an ultrasound investigation of the thyroid was performed. Scintigraphy of the thyroid was acquired according to the procedure guidelines of the German Society of Nuclear Medicine (12). In all cases, thyroid uptake of technetium-99m-pertechnetate was determined under partial or total endogenous suppression of TSH, and scintigrams were classified as nonautonomic, focal autonomic, and disseminated autonomic (Fig. 1). Levels of thyroid hormones (total T_3 and fT_4, Abbott AxSYM System), basal TSH (AxSYM Ultrasensitive hTSH II assay; functional sensitivity 0.06 μIU/ml), and urinary iodine content were measured before CA, the day after CA, and 2 and 4 wk after CA. Internal quality controls of the laboratory investigations were performed according to the guidelines of the German General Medical Council (13). External quality controls were

Abbreviations: CA, Coronary angiography; fT_4, free T_4; PD, prophylactic drug; TCTU, technetium thyroid uptake; TCTUs, TCTU under suppression.

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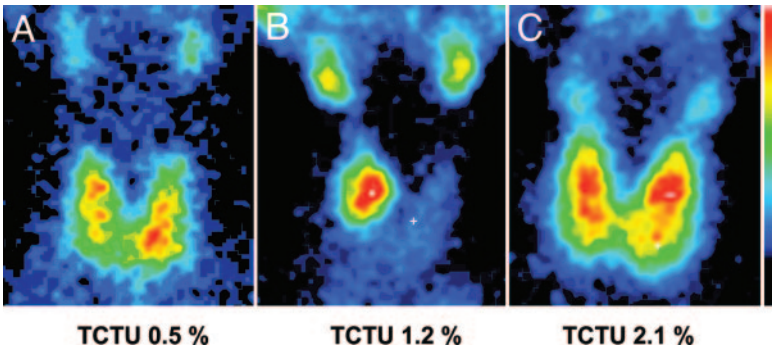

FIG. 1. Typical examples for scintigraphic findings: nonautonomic thyroid gland (A), thyroid gland with autonomous adenoma in the right lobe (B), and disseminated autonomic thyroid gland (C).

implemented by participation in round-robin tests of the German Society of Clinical Chemistry. Because most patients left the hospital within a few days after CA, blood and urine samples for the later controls were collected by the general practitioners and sent to our laboratory. Urinary iodine excretion was measured as described by Wawschinek *et al.* (14) and normalized to renal excretion of creatinine.

Two and 4 wk after CA, patients were asked to fill out questionnaires. These questionnaires were designed to collect and to affirm information about the prescribed drugs (see below); potential side effects of the medication; clinical signs of thyroid disorders; and cardiac complications, *e.g.* arrhythmias.

Prophylactic medication to prevent manifest hyperthyroidism was given depending on the results of the quantitative scintigraphy. In accord with the usual procedures in our center, no medication was given under the following circumstances: 1) homogenous tracer distribution in the thyroid, TCTU less than 1.5%, and basal TSH ranging from 0.05 to less than 0.3; 2) homogenous tracer distribution in the thyroid, TCTU less than 1.0%, and basal TSH less than 0.05; and 3) focal uptake indicating focal autonomy and TCTU less than 1.0%.

All patients not belonging to these categories were treated for 2 wk with 900 mg perchlorate per day, divided into three doses. The drug treatment started at least 3 h before CA to provide sufficient serum levels at the time of contrast agent application. Depending on the autonomous volume, thiamazole was administered additionally. Twenty milligrams were given for 7 d if the autonomous volume was more than 5 ml and less than 10 ml. If the autonomous volume was greater than 10 ml, CA was performed only in patients with an urgent clinical indication. In those patients, 60 mg thiamazole was given for the first and 20 mg thiamazole for the second week. In patients with focal autonomy, autonomous volume was calculated using ultrasound after subtraction of cystic parts within the nodules. In case of disseminated autonomy, autonomous volume was calculated according to Emrich *et al.* (8). In that approach, autonomous volume in milliliters is assumed to be five times the value of TCTU. It has to be considered that this formula should only be used when TSH levels are totally suppressed, which was not always the case in our patient population.

CA was carried out with different amounts of iopromid (157 ± 85 ml), containing 370 mg iodine per milliliter (Ultravist 370, Schering AG, Berlin, Germany).

The one-sample Kolmogorov-Smirnov test did not reveal normality for all of the outcome parameters. Therefore, the nonparametric two-sided Wilcoxon matched-pair signed-rank test was used to compare parameters before and after CA. Probability values less than 0.05 were considered statistically significant. Statistical analysis was performed using StatView 5.0 (SAS Institute Inc., Cary, NC) and SPSS 11 (SPSS Inc, Chicago, IL).

Results

Of 91 patients, 75 (82%) could be included in further investigation. Fourteen patients were excluded because of the lack of feedback from the general practitioner. In one case, CA was not performed because of high autonomous volume. In another case, contrast agent was given a second time for angioplasty.

In 56 patients, scintigraphy matched the criteria mentioned above, and CA was performed without application of PDs. TCTU in this group was 0.66 ± 0.34%. Seven of these patients exhibited small autonomous adenomas with volumes of less than 5 ml, TCTU being less than 1%. In 19 patients (TCTU 1.64 ± 0.52%), PDs were given according to the autonomous volume, in six patients perchlorate only, and in 13 patients a combined therapy with thiamazole. In 47% of those patients, scintigraphy was interpreted as disseminated, 21% multifocal, and 32% unifocal autonomy. Because of the small patient number for further evaluation, this group was not divided into patients with and without thiamazole medication. Thyroid volume was slightly larger in the group of patients with PDs (35.1 ± 16.2 ml) than in the nontreated group (27.6 ± 15.6 ml). There was no major difference in the frequency of thyroid nodules or changes of echogenity of the thyroid gland within the two groups.

Levels of thyroid hormones were in the normal range in all patients without PDs. The level of T_3 displayed a significant decrease the day after CA (Fig. 2). T_3 levels 14 and 28 d after CA did not differ from levels at the starting point. Initially, fT_4 levels evinced no significant change (day after CA), exhibiting a significant increase within normal range 14 and 28 d after CA. During follow-up, TSH levels revealed significant rises compared with initial values 1 and 14 d after CA.

Within the patient group with PDs, two cases of hyperthyroidism occurred. In one case, the patient suffered from focal autonomy, having an autonomous volume of 11 ml and a TCTU of 1.2% under endogenous suppression. PDs had to be interrupted because of side effects, and subsequently this patient developed hyperthyroidism. In the second case, a patient with multifocal autonomy developed mild hyperthyroidism the day after CA despite continuous medication with perchlorate. After addition of 40 mg of thiamazole, euthyroidism was reestablished within a few days. Scintigraphy had shown multifocal autonomy with a TCTU of 1.2% and an autonomous volume of approximately 5 ml (nodular volume in ultrasound).

In the remaining 17 patients, T_3 levels remained almost unchanged until 14 d after CA (Fig. 3). Twenty-eight days after CA, T_3 levels exhibited a significant decrease. On the other hand, fT_4 levels showed an initial rise the day after CA, followed by a significant descent 28 d after CA. TSH levels did not significantly change before day 28.

At the time of inclusion, the median of the urinary excretion of iodine of all patients was 103.4 μg iodine per gram creatinine (interquartile range 72.6 μg iodine per gram cre-

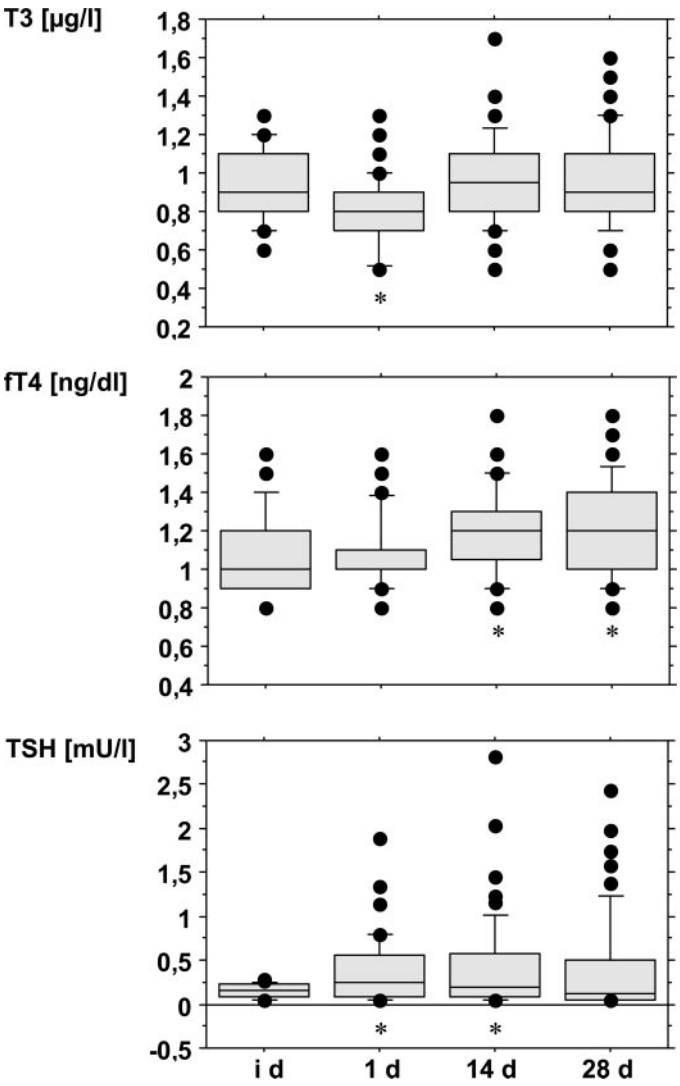

FIG. 2. Course of thyroid hormones and TSH levels in the 56 patients without application of PDs at inclusion (i d) and 1, 14, and 28 d after CA (*box plots*). Median and 10th, 25th, 75th, and 90th percentiles are given. ●, All observations lower than the 10th percentile and higher than the 90th percentile. *, Significant changes compared with hormone levels at the time of inclusion. Levels of thyroid hormones remained within the normal range.

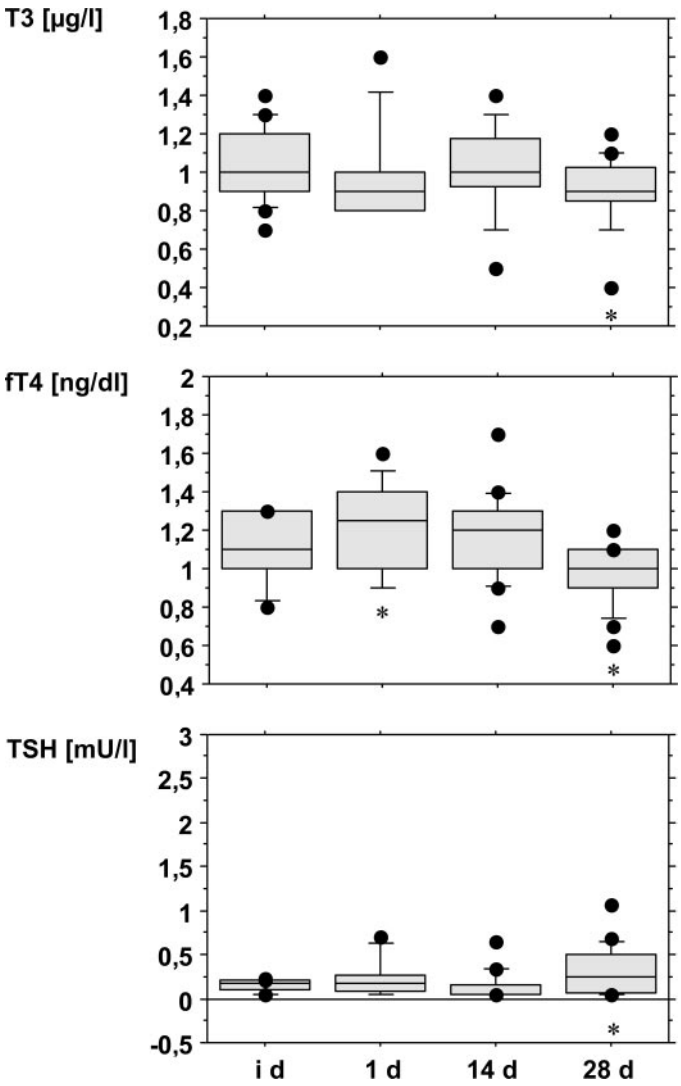

FIG. 3. Course of thyroid hormones and TSH levels in the 17 patients with application of PDs according to the study protocol at inclusion (i d) and 1, 14, and 28 d after CA (*box plots*). Median and 10th, 25th, 75th, and 90th percentiles are given. ●, All observations lower than the 10th percentile and greater than the 90th percentile. *, Significant changes compared with hormone levels at the time of inclusion.

atinine). In the subgroup with PDs, iodine excretion was lower compared with the subgroup without PDs (Fig. 4). Reliable measurement of iodine excretion the day after CA was not possible because the main part of the contrast agent is renally excreted within the first 24 h, and the assay is not able to differ between bound and free inorganic iodine. Fourteen days after CA, iodine excretion exceeded baseline levels more than three times. Twenty-eight days after CA, iodine excretion was still significantly higher than baseline levels. In the group with PDs, iodine excretion was slightly lower than in that without PDs at this time.

Side effects of PDs leading to discontinuation of the therapy were only present in one patient (see above). No cardiac complications related to the thyroid metabolism, *i.e.* occurrence of arrhythmia, were observed.

Discussion

Within the patient collective not treated with PDs, there was no case of iodine-induced hyperthyroidism. These data suggest that in patients with suppressed TSH value and TCTU less than 1%, high amounts of iodine may be applied with low risk. The observed changes in the hormone levels were slight and therefore not expected to be clinically relevant.

The TCTU less than 1% chosen as cutoff in this study is arbitrary, and it has to be discussed whether the same results might have been reached with a higher threshold. According to Emrich *et al.* (8), patients with an autonomous volume above 10 ml are at risk of becoming hyperthyroid. According to their considerations, an autonomous volume of 10 ml corresponds to a TCTU under suppression (TCTUs) of 2%. It is thus unlikely that patients with TCTUs values less than 2%

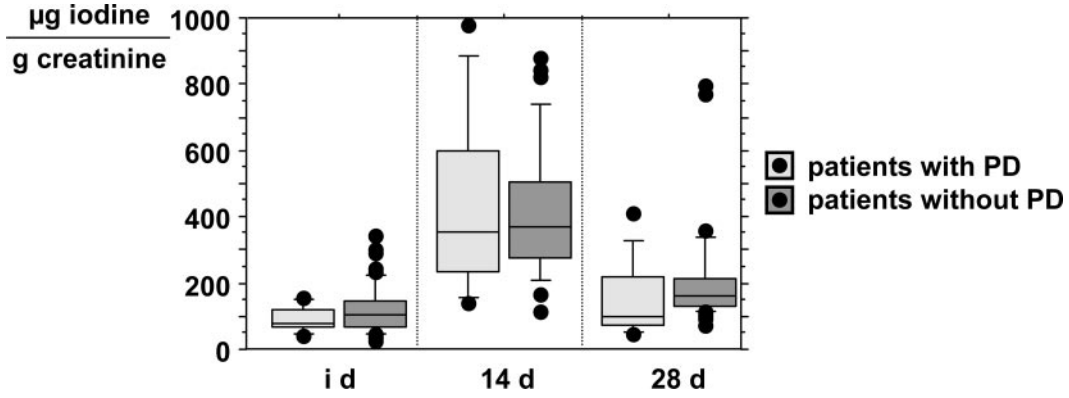

FIG. 4. Urinary excretion of iodine before and after CA in the patient groups with and without application of PDs (*box plots*). Median and 10th, 25th, 75th, and 90th percentiles are given. ●, All observations lower than the 10th percentile and greater than the 90th percentile.

will develop hyperthyroidism if they are exposed to usual amounts of iodine (15, 16). In our study, as shown by the measurement of urinary excretion of iodine, iodine exposure was immense compared with normal values. Because the incidence of hyperthyroidism depends not only on the autonomous tissue but also on the amount of the iodine supply, the observations of Emrich *et al.* (8) do not exactly apply to our study conditions. In a study of Kreisig *et al.* (9) on 19 euthyroid patients, six patients developed subclinical hyperthyroidism after administration of 500 μg iodine per day for 3 to 14 months. All of these patients presented with a TCTUs of greater than 1%, suggesting this value as a cutoff in case of unusually high iodine exposure. Furthermore, thyrotoxicosis can aggravate preexisting heart disease and can also lead to atrial fibrillation, congestive heart failure, or worsening of angina pectoris (17, 18). Because our patient group was composed of patients with known or suspected coronary artery disease, our aim was to keep the risk of iodine-induced thyrotoxicosis as low as possible.

Another important argument against a threshold of more than 1% TCTUs are the cases of the patients who developed thyrotoxicosis either after cessation of PDs as a result of side effects or despite ongoing therapy with perchlorate. In those patients, TCTUs levels were 1.2%, both patients presenting with focal autonomy. This raises the question of how to prevent thyrotoxicosis in case of proven autonomy. Results of animal experiments in nude mice transplanted with autonomous adenoma tissue suggest the effectiveness of a prophylactic thyrostatic treatment, if a combination of perchlorate and thiamazole is given (19). Only a few prospective studies on the virtue of prophylactic treatment exist. In a randomized study on 60 patients undergoing CA, Fritzsche *et al.* (20, 21) demonstrated the effectiveness of short-term therapy with 60 mg methimazol and 1 g perchlorate, leading to a reduced iodine load of the thyroid in comparison with the control group when monitored by scintigraphy 4 and 12 wk after CA. Nolte *et al.* (22) demonstrated the protective effect of a monotherapy with either 20 mg thiamazole per day or 900 mg perchlorate per day in 51 euthyroid patients with thyroid autonomy undergoing CA. Because in both treated groups (17 patients each) a manifest hyperthyroidism occurred, it has been speculated that a combination therapy may be more effective. We pursued this approach, trying to adjust treatment to the individual risk for developing thyrotoxicosis. Overall, treatment has been effective, with a decrease in hormone levels and an increase in TSH in the treated group. However, in the group treated only with perchlorate, one case of mild hyperthyroidism occurred, consolidating the hypothesis that a monotherapy with perchlorate is less effective (22). On the other hand, the risk of side effects increases in cases of combination therapy. Both drugs have a nonnegligible rate of side effects (23, 24). As in the second case of thyrotoxicosis in our collective, cessation of therapy due to side effects bears the risk of manifestation of hyperthyroidism. It is still an unanswered question whether smaller doses of the antithyroid drugs will be effective as well, despite the reduced efficacy of both drugs when in competition with high amounts of iodine. The measurement of the iodine excretion, displaying raised iodine exposition as late as 4 wk after CA, raises the question of the duration of treatment necessary. Further prospective studies may contribute to an evidence-based procedure guideline.

Conclusion

Scintigraphy of the thyroid gland is suitable for risk stratification of iodine-induced hyperthyroidism in patients with low TSH undergoing CA. Up to a thyroid uptake (TCTU) of 1%, the risk of iodine-induced hyperthyroidism is negligible, and CA can be performed without administration of PDs. The kind, dosage, and duration of prophylactic therapy in case of the TCTU being higher is still a matter calling for further investigation.

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Address all correspondence and requests for reprints to: Dr. Eva Fricke, Institute of Molecular Biophysics, Radiopharmacy and Nuclear Medicine, Heart and Diabetes Centre North Rhine-Westphalia, Georgstrasse 11, D-32545 Bad Oeynhausen, Germany. E-mail: efricke@hdz-nrw.de.

References

1. **Rendl J, Saller B** 2001 Schilddruese und Roentgenkontrastmittel. Deutsches Aerzteblatt 7:402–406
2. **Sergeev PV, Belykh AG** 1982 [Effect of contrast agents on the iodine-absorbing function of the thyroid gland]. Farmakol Toksikol 45:96–100 (Russian)
3. **Talner LB, Coel MN, Lang JH** 1973 Salivary secretion of iodine after urog-

raphy. Further evidence for in vivo deiodination and salivary secretion of contrast media. Radiology 106:263–268
4. **Conn JJ, Sebastian MJ, Deam D, Tam M, Martin FI** 1996 A prospective study of the effect of nonionic contrast media on thyroid function. Thyroid 6:107–110
5. **de Bruin TW** 1994 Iodide-induced hyperthyroidism with computed tomography contrast fluids. Lancet 343:1160–1161
6. **Fassbender WJ, Schlueter S, Stracke H, Bretzel RG, Waas W, Tillmanns H** 2001 [Thyroid function after iodine-containing contrast agent administration in coronary angiography: a prospective study of euthyroid patients]. Z Kardiol 90:751–759 (German)
7. **Hintze G, Blombach O, Fink H, Burkhardt U, Kobberling J** 1999 Risk of iodine-induced thyrotoxicosis after coronary angiography: an investigation in 788 unselected subjects. Eur J Endocrinol 140:264–267
8. **Emrich D, Erlenmaier U, Pohl M, Luig H** 1993 Determination of the autonomously functioning volume of the thyroid. Eur J Nucl Med 20:410–414
9. **Kreisig T, Pickardt CR, Horn K, Stalla G, Willemsen F, Knesewitsch P** 1992 TcTUs zur Abschätzung des Hyperthyreoserisikos nach Jodkontamination von euthyreoten Strumapatienten mit kompensierter Autonomie. In: Roeher H-D, Weinheimer B, eds. Schilddruese 1991. Berlin, New York: de Gruyter; 393–399
10. **Meller J, Becker W** 1998 Scintigraphic evaluation of functional thyroidal autonomy. Exp Clin Endocrinol Diabetes 106:S45–S51
11. **Meller J, Becker W** 1999 Scintigraphy with 99mTc-pertechnetate in the evaluation of functional thyroidal autonomy. Q J Nucl Med 43:179–187
12. **Dietlein M, Dressler J, Eschner W, Leisner B, Reiners C, Schicha H** 2003 [Procedure guideline for thyroid scintigraphy (version 2)]. Nuklearmedizin 42:120–122 (German)
13. **Bundesaerztekammer** 2003 Richtlinie der Bundesaertzekammer zur Qualitaetssicherung laboratoriumsmedizinischer Untersuchungen. Deutsches Aerzteblatt 50:A3335–A3338
14. **Wawschinek O, Eber O, Petek W, Wakonig P, Gürakar A** 1985 Bestimmung der Harnjodausscheidung mittels einer modifizierten Cer-Arsenitmethode. Ber OGKC Jahrgang 8:13–15
15. **Joseph K** 1994 Estimation of the volume of autonomously functioning thyroid tissue. Exp Clin Endocrinol 102:12–19
16. **Schneider D, Joseph K, Hoeffken H, Kuemmel H, Nebe R, Skamel H-J, Stapp J, Welke U** 1992 Werden Patienten mit funktioneller thyreoidaler Autonomie durch Optimierung der taeglichen Jodzufuhr gefaehrdet? In: Roeher H-D, Weinheimer B, eds. Schilddruese 1991. Berlin, New York: de Gruyter; 400–404
17. **Gessl A, Raber W** 2002 Schilddruese und Herz. Z Kardiol 91:125–128
18. **Kahaly GJ, Nieswandt J, Mohr-Kahaly S** 1998 Cardiac risks of hyperthyroidism in the elderly. Thyroid 8:1165–1169
19. **Schumm-Draeger P-M, Usadel K, Senekowitsch R** 1989 Effekt einer thyreostatischen Therapie bei iodinduzierter Hyperthyreose—Untersuchungen an xenotransplantierten Geweben immunogener sowie nicht immunogener Hyperthyreoseformen. In: Pickardt CR PP, Weinheimer B, eds. Schilddruese 1987. Stuttgart, New York: Thieme-Verlag; 253–258
20. **Fritzsche H, Benzer W, Furlan W** 1992 Praevention jodinduzierter Hyperthyreosen bei Koronarangiographie. In: Roeher H-D, Weinheimer B, eds. Schilddruese 1991. Berlin, New York: de Gruyter; 406–413
21. **Fritzsche H, Benzer W, Furlan W, Hammerle D, Langsteger W, Weiss P** 1993 Prevention of iodine-induced hyperthyroidism after coronary angiography. Acta Med Austriaca 20:13–17 (German)
22. **Nolte W, Muller R, Siggelkow H, Emrich D, Hufner M** 1996 Prophylactic application of thyrostatic drugs during excessive iodine exposure in euthyroid patients with thyroid autonomy: a randomized study. Eur J Endocrinol 134: 337–341
23. **Wolf J** 1998 Perchlorate and the thyroid gland. Pharmacol Rev 50:89–105
24. **Molnar I** 2000 Systemic adverse effect of antithyroid drugs. Clin Rheumatol 19:78

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