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ORIGINAL PAPER

# Cardiovascular assessment of hyperthyroid patients with multinodular goiter before and after radioiodine treatment preceded by stimulation with recombinant human TSH

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**Abstract** Treatment of large multinodular goiter (MNG) with radioiodine preceded by recombinant human thyrotropin (0.1 mg rhTSH) has been shown to be a safe alternative for patients with comorbidities that preclude surgery. However, the increase in serum thyroid hormones that follows both treatments may be harmful for some patients, particularly those with underlying cardiovascular disease. In this study, we evaluated cardiac parameters (clinical, ECG, 24-h Holter, Doppler echocardiogram, treadmill stress test) in 27 of 42 patients (ages 42–80 years) with large MNGs who were treated with rhTSH before receiving 30 mCi radioiodine therapy. At baseline, 18 patients had subclinical and six patients had overt iodine-induced hyperthyroidism. All patients had a transient surge in serum levels of free T4 and total T3 into the hyperthyroid range after therapy. However, repeated cardiac evaluation did not show significant changes as compared with baseline evaluation. In conclusion, rhTSH stimulated RAI treatment of MNG did not affect structural and functional parameters of the heart, despite transient high-serum levels of thyroid hormones.

**Keywords** Atrial fibrillation · Diastolic dysfunction · Multinodular goiter · Radioiodine · Recombinant · Human thyrotropin · Hyperthyroidism

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## Introduction

Multinodular goiter (MNG) is a frequent finding in countries with iodine deficiency. Clinical manifestations are related to the degree of goiter size, compressive symptoms to cervical area structures, and functional autonomy of one or more nodules. Iodine fortification of salt for human use may result in excessive nutritional iodine intake that ultimately causes overt and subclinical hyperthyroidism in patients with MNG. This is particularly dangerous in the elderly who may develop atrial fibrillation and other cardiac abnormalities [1–4].

Subclinical hyperthyroidism is characterized by reduced serum thyrotropin (TSH) levels despite free thyroxine (T4) levels within the reference range, in the absence of symptoms of hyperthyroidism. Two distinct entities of subclinical hyperthyroidism exist, endogenous and exogenous. The latter is frequently due to deliberate treatment with TSH-suppressive doses of exogenous levothyroxine (L-T4), typically in patients with previously treated thyroid cancer. Endogenous subclinical hyperthyroidism is typically seen in MNG patients, and the natural history is that of slow progression toward overt hyperthyroidism, with a rate of approximately 4–5% per year [2]. At present, there is no consensus as to when to treat these patients, since in general they feel well.

Treatment of MNG is controversial [5]. Surgery of MNG carries a risk of both surgical and anesthetic complications. In addition, cardiac complications such as arrhythmias are frequently found in these patients, representing an additional surgical risk [4, 5]. Moreover, in a country like Brazil, the number of patients older than 40 years with MNG is relatively large (estimated at 4 million) probably due to a past history of chronic iodine deficiency that affected 190 million inhabitants [6]. This

extremely large number of patients with MNG presents to the National Health System a logistical problem in terms of providing access to thyroid surgery for all.

As a non-invasive alternative, radioiodine therapy results in a significant reduction in thyroid volume and correction of the hyperthyroid state [7–19]. However, radioiodine ($^{131}$I) tracer uptake by the MNG has been found to be relatively low and not uniformly distributed among the various nodules. Therefore, higher amounts of radioiodine are needed for consistent results. The use of recombinant human thyrotropin (rhTSH) has been shown to increase the amount and homogeneity of radioiodine uptake (RAIU) within the MNG [12–19]. Studies on $^{131}$I kinetics during therapy of MNG with radioiodine have previously shown that 0.3 mg rhTSH increases the retained thyroid dose by 75% compared with placebo [14]. A number of trials published on rhTSH use prior to MNG radioiodine therapy have shown promising results. Some groups have used relatively high-doses of rhTSH in single [19] and double rhTSH injections [15], which may transiently exacerbate hyperthyroidism. The transient elevation of serum free T4 and total T3 (transient hyperthyroidism) may affect cardiovascular function inducing arrhythmias (atrial fibrillation, tachycardia) and altering diastolic function. Therefore, cardiovascular assessment of these patients is warranted and should be performed before and after the radioiodine therapeutic dose. In the current study, we evaluated cardiovascular parameters in subjects with MNG and subclinical and overt hyperthyroidism before and after radioiodine treatment preceded by stimulation with rhTSH.

## Results

Clinical and laboratory evaluation of the patients are shown in Table 1.

Eighteen patients (43%) at baseline had elevated urinary iodine content (308 ± 130 μg/l). After 90 days on a low-iodine diet, iodine concentration in the urine was 165 ± 98 μg/l ($P < 0.01$). Only two patients had persistently elevated urinary iodine excretion after low-iodine diet.

### Baseline

#### *Thyroid volume*

On baseline CT scan, mean goiter volume was 184.0 ± 168.2 ml (range 31.1 ml to 871.6 ml). Thyroid radioiodine uptake at 24 hr was 26.9 ± 14.4% and increased to 44.8 ± 14.0% after the low-iodine diet and stimulation by 0.1 mg of rhTSH.

#### *Thyroid function tests*

At baseline, serum TSH was 0.71 ± 0.80 mIU/l. Twenty-four patients had suppressed serum TSH values (<0.5 mU/l) with normal serum free T4 ($n = 18$, subclinical hyperthyroidism) or elevated serum free T4 ($n = 6$, overt hyperthyroidism). Eighteen patients had normal serum TSH concentrations. Thirty-six patients presented normal values for both serum free T4 and total T3. The six subjects with overt hyperthyroidism received methimazole 10 mg q.d. for 90 days. As it is expected for large goiters, serum thyroglobulin (TG) concentrations were elevated at baseline (428.0 ± 426.5 μg/l). There was a positive and significant correlation between serum TG and goiter volume ($r = 0.568$, $P < 0.01$). TSH-receptor antibody (TRAb) was negative in all patients and only two patients had a low-positive value for both anti-TPO and anti-TG autoantibodies.

#### *Cardiovascular evaluation*

A past history of hypertension was present in 21 patients and 8 had concomitant diabetes. One patient had a history of coronary bypass surgery performed 3 years before. Eleven patients were on beta-blocker medication. No abnormal cardiac signs or symptoms were clinically found in 38 patients, further confirmed by electrocardiogram (ECG). Doppler echocardiographic evaluation was performed in 39 patients (Table 2). Mean left ventricular diastolic diameter (LVD), left ventricular ejection fraction (LVEF), left atrial diameter (LA), and aortic diameter (Ao) were all normal at baseline. Mild aortic, mitral, and tricuspid regurgitation were observed in eight patients. The treadmill stress test was performed in 27 patients. In 23 subjects (85%), submaximal and maximal target heart rate was achieved. Atrial fibrillation was observed in four patients during the test. No ischemic ST-T wave abnormalities were detected. Holter monitoring was also performed in 27 patients. Sinus rhythm was present in 25 and atrial fibrillation detected in two patients. Maximum, minimum, mean heart rate in 24 h, number of premature ventricular beats, episodes of bigeminy, and ventricular tachycardia, are shown in Table 3.

### Post-treatment

#### *Goiter volume*

There was a significant reduction in goiter mass on repeat CT scans. Goiter volume was reduced to 49.4 ± 56.6 ml at 36 months, corresponding to a 75.2% reduction compared with baseline ($P < 0.001$).

**Table 1** Clinical and laboratory data for the included patients, before radioiodine treatment

| Patients | Gender | Age (years) | Thyroid vol. | Thyroid function | | | | Diagnosis |
|---|---|---|---|---|---|---|---|---|
| | | | CT scan (ml) | TSH (mUI/l) | FT4 (pmol/l) | TT3 (nmol/l) | TG (μg/l) | N |
| 1 CRN | F | 45 | 299.6 | 0.80 | 19.3 | 2.8 | 158.5 | N |
| 2 MAS | F | 74 | 170.8 | 1.00 | 15.4 | 2.0 | 174.6 | N |
| 3 EC | F | 51 | 318.1 | 2.20 | 9.0 | 3.5 | 492.1 | N |
| 4 IDCF | F | 49 | 145.0 | 1.60 | 14.1 | 3.1 | 399.0 | N |
| 5 ICR | F | 72 | 162.9 | 2.14 | 12.9 | 3.0 | 1100.0 | N |
| 6 GSS | F | 44 | 107.9 | 0.50 | 18.1 | 2.4 | 255.0 | N |
| 7 ESL | F | 52 | 50.3 | 2.20 | 15.4 | 1.9 | 259.0 | N |
| 8 DRS | F | 57 | 54.6 | 2.00 | 12.9 | 2.4 | 731.0 | N |
| 9 ARL | M | 59 | 81.8 | 2.00 | 14.1 | 1.7 | 167.0 | N |
| 10 MLSS | F | 54 | 35.6 | 2.70 | 12.9 | 2.1 | 59.0 | N |
| 11 HM | F | 80 | 81.6 | 0.70 | 12.9 | 1.5 | 46.0 | N |
| 12 MLC | F | 57 | 68.0 | 2.30 | 12.9 | 2.1 | 324.0 | N |
| 13 RCF | F | 79 | 480.0 | 0.80 | 16.7 | 2.3 | 1030.0 | N |
| 14 IMG | F | 76 | 114.0 | 0.91 | 12.9 | 2.2 | 74.0 | N |
| 15 VPMS | F | 62 | 49.8 | 1.00 | 18.1 | 1.9 | 60.0 | N |
| 16 PRB | F | 60 | 51.4 | 1.30 | 12.9 | 2.1 | 30.0 | N |
| 17 ALAB | F | 64 | 359.2 | 0.88 | 14.1 | 2.0 | 49.4 | N |
| 18 AMN | F | 42 | 129.6 | 1.40 | 11.6 | 2.0 | 809.0 | N |
| 19 ORL | F | 77 | 165.7 | 0.03 | 28.3 | 3.1 | 54.0 | C |
| 20 ICJ | F | 69 | 371.1 | 0.01 | 20.6 | 3.3 | 838.0 | C |
| 21 JCT | F | 70 | 231.4 | 0.05 | 50.2 | 3.9 | 285.0 | C |
| 22 JSS | F | 61 | 320.4 | 0.05 | 28.3 | 2.7 | 899.0 | C |
| 23 AMC | F | 51 | 31.1 | 0.01 | 23.2 | 2.9 | 263.0 | C |
| 24 MBJ | F | 76 | 192.0 | 0.03 | 28.3 | 2.2 | 378.0 | C |
| 25 RC | F | 71 | 76.5 | 0.13 | 11.6 | 2.7 | 259.4 | SC |
| 26 SLF | F | 72 | 217.9 | 0.01 | 20.6 | 2.8 | 462.4 | SC |
| 27 LRC | F | 79 | 110.6 | 0.30 | 1.93 | 2.0 | 401.5 | SC |
| 28 LAP | F | 55 | 197.4 | 0.40 | 15.4 | 2.7 | 1110.0 | SC |
| 29 LS | F | 72 | 107.8 | 0.30 | 18.1 | 1.5 | 97.8 | SC |
| 30 HPG | F | 46 | 137.5 | 0.03 | 19.3 | 2.2 | 87.0 | SC |
| 31 APP | F | 69 | 85.1 | 0.07 | 18.1 | 2.3 | 41.0 | SC |
| 32 IPDS | F | 63 | 31.2 | 0.30 | 15.4 | 2.5 | 61.0 | SC |
| 33 GLS | F | 45 | 80.6 | 0.30 | 15.4 | 2.0 | 49.0 | SC |
| 34 RSF | F | 75 | 120.0 | 0.20 | 15.4 | 1.9 | 965.0 | SC |
| 35 MGE | F | 55 | 628.0 | 0.01 | 1.54 | 3.0 | 1200.0 | SC |
| 36 RSF | F | 75 | 280.0 | 0.20 | 15.4 | 2.0 | 965.0 | SC |
| 37 MRLR | F | 48 | 154.0 | 0.03 | 14.1 | 2.1 | 363.0 | SC |
| 38 MMR | F | 59 | 871.6 | 0.03 | 11.6 | 2.1 | 1600.0 | SC |
| 39 MGRD | F | 52 | 307.0 | 0.24 | 16.7 | 1.6 | 1200.0 | SC |
| 40 MLCA | F | 57 | 85.8 | 0.40 | 15.4 | 2.4 | 32.0 | SC |
| 41 DPC | F | 49 | 91.0 | 0.20 | 11.6 | 1.9 | 73.5 | SC |
| 42 KA | F | 67 | 85.3 | 0.19 | 14.1 | 1.9 | 75.0 | SC |
| Mean | | 61.6 | 184.0 | 0.71 | 17.1 | 2.4 | 428.0 | |
| SD | | 11.4 | 168.2 | 0.80 | 6.9 | 0.5 | 426.5 | |

N = normal thyroid function; C = clinical hyperthyroidism; SC = subclinical hyperthyroidism

**Table 2** Doppler echocardiographic measurements at baseline and after treatment ($n = 39$)

| | LVD | LVEF | LA | Ao |
|---|---|---|---|---|
| Baseline | | | | |
| Mean ± SD (mm) | 48.2 ± 5.2 | 0.72 ± 0.05 | 36.1 ± 5.7 | 28.6 ± 5.6 |
| Range (mm) | 39–65 | 0.65–0.87 | 29–53 | 22–36 |
| Post-treatment | | | | |
| Mean ± SD (mm) | 47.5 ± 4.2 | 0.72 ± 0.04 | 37.6 ± 4.9 | 28.6 ± 6.9 |
| Range (mm) | 39–54 | 0.65–0.80 | 28–45 | 26–35 |
| P | 0.63 | 0.73 | 0.35 | 0.98 |

LVD = left ventricular diastolic diameter (normal <50 mm); LVEF = left ventricular ejection fraction (normal >0.55 mm); LA = left atrial diameter (normal <4.0 mm); Ao = aortic diameter (normal <4.0 mm)

There was a positive and significant correlation between baseline goiter volume and percentage of goiter reduction at 36 months ($r = 0.48$, $P = 0.004$). Patients with goiter volume up to 200 ml had a significantly higher volume reduction than those with larger goiters ($P < 0.037$).

*Thyroid function tests*

Serum TSH elevation was observed 24 h after administration of rhTSH, reaching 12.4 ± 5.85 mU/l. There was a progressive return to normal values 30 days after the RAI therapy. In the few months which followed, a rise in mean serum TSH was observed, with the presence of clinical and biochemical hypothyroidism in 16 patients (38%). Most of these patients ($n = 12$) were hypothyroid within the first 6 months of the study and were medicated with L-T4.

There was a marked increase (transient hyperthyroidism) in both serum free T4 to 31.2 ± 15.2 pmol/l and total T3 to 4.98 ± 1.79 nmol/l at 48 h. Seven days after therapeutic RAI, these values slowly declined, normalizing within 30 days. Throughout the follow-up period of 36 months, both variables remained within the normal range for the majority of patients except for those who progressively developed hypothyroidism.

*Cardiovascular evaluation*

Cardiologic evaluation in the post-treatment period was performed between 7 and 12 days after the RAI dose (Tables 2 and 3). Only one patient complained of chest pain but ECG was normal as was laboratory evaluation for cardiac ischemia. Doppler echocardiography was repeated in 36 patients and Holter monitoring was obtained for 23 patients. No major abnormalities were detected compared to baseline examination. Maximum, minimum, and mean heart rate did not differ from baseline to post-treatment period. Two patients developed ventricular tachycardia. The number of ventricular premature beats and bigeminy episodes were similar between baseline and post-treatment periods. However, there was a threefold increase in mild left ventricular diastolic dysfunction in the post-treatment period, probably related to the transient hyperthyroid state.

## Discussion

A large segment of the Brazilian population that previously inhabited rural areas with chronic iodine deficiency, and over the years developed large MNGs, are at risk of subclinical or overt hyperthyroidism as well as of possible cardiac arrhythmias. These events may be linked to the sharp increase in iodine intake due to relatively high-iodine concentration in salt for human use [2, 20]. Thus, the combination of MNG plus elevated nutritional iodine intake was the major reason for proposing a combined therapeutic approach for these patients (radioiodine preceded by low-iodine diet and rhTSH).

**Table 3** Holter monitoring measurements at baseline and after treatment ($n = 27$)

| | Min HR (bpm) | Mean HR (bpm) | Max HR (bpm) | VPB (*n*/24 h) | Bigem (*n*/24 h) | Pair (*n*/24 h) | VT (*n*/24 h) | APB (*n*/24 h) | AT (*n*/24 h) |
|---|---|---|---|---|---|---|---|---|---|
| Baseline | | | | | | | | | |
| Mean ± SD | 54.3 ± 10 | 79.4 ± 11 | 121.6 ± 17 | 181 ± 667 | 16.9 ± 74 | 3.1 ± 15 | 0.4 ± 1.4 | 797.7 ± 2844 | 3.5 ± 10.4 |
| Range | 40–86 | 62–106 | 96–158 | 0–3535 | 0–385 | 0–79 | 0–7 | 0–14.861 | 0–53 |
| Post-treatment | | | | | | | | | |
| Mean ± SD | 52.7 ± 8 | 80.1 ± 10 | 126.8 ± 19 | 388 ± 1653 | 7.5 ± 33 | 25.1 ± 143 | 2.4 ± 13 | 557.6 ± 1518 | 3.1 ± 8.5 |
| Range | 37–72 | 55–100 | 85–171 | 0–9742 | 0–190 | 0–847 | 0–77 | 0–7364 | 0–37 |
| P | 0.77 | 0.44 | 0.39 | 0.5 | 0.53 | 0.37 | 0.37 | 0.69 | 0.86 |

Min HR = minimum heart rate in 24 h; Mean HR = mean heart rate in 24 h; Max HR = maximum heart rate in 24 h; VPB = number of ventricular premature beats in 24 h; Bigem = number of episodes of bigeminy in 24 h; Pair = number of paired VPB in 24 h, VT = number of ventricular tachycardia in 24 h; APB = number of premature atrial beats in 24 h; AT = number of atrial tachycardia in 24 h

Most patients with large goiters coming to our University Hospital for treatment had a relatively low-radioiodine uptake and thus needed an increased amount of radioiodine to effectively reduce the volume of the goiter. Since rhTSH approximately doubles thyroid $^{131}$I uptake in patients with MNG, as well as homogeneously distributes the tracer throughout the various nodular compartments, several reports have evaluated the efficacy of rhTSH stimulated $^{131}$I therapy on goiter reduction [12–19]. In our previous report [19], we analyzed the effect of a relatively high-rhTSH dose (0.45 mg) and high-$^{131}$I variable dosage 1.85–5.55 GBq (50–150 mCi) in a group of patients with MNG. These patients had to be hospitalized and had a number of side effects within the first few weeks that followed the radioiodine dose (hyperthyroidism, radiation thyroiditis, esophagitis, and enlargement of the goiter). At a later stage, hypothyroidism was a common adverse effect presenting in 64% of patients. Aiming to lower short-term and long-term side effects of RAI preceded by rhTSH, we have used a lower dose of rhTSH (0.1 mg) 24 h before a fixed radioiodine dose of 1.11 GBq (30 mCi) that was administered on an outpatient basis, as legally permitted in Brazil. Consequently, we have considerably reduced the total cost per patient of this outpatient modality of MNG treatment.

Moreover, we took special care in trying to avoid the risk of iodine-induced hyperthyroidism instituting a low-iodine diet at least 90 days before the therapeutic use of radioiodine. Indeed, the relatively high-urinary iodine excretion (reflecting the high-dietary iodine intake) was significantly reduced after 3 months of low-iodine diet. Furthermore, all patients were tested for RAI uptake (RAIU) with a tracer dose of $^{131}$I before and after 0.1 mg rhTSH. There was a significant increase in the tracer uptake by the goiter after stimulation by rhTSH compared with baseline RAIU. Approximately 57% of our patients had suppressed serum TSH at baseline with subclinical and overt hyperthyroidism. Some of these patients were started on beta-blockers and six others were also treated with methimazole. Electrocardiogram, Doppler echocardiography and Holter monitoring identified four patients with atrial fibrillation, a relatively frequent cardiac sign in overt and subclinical hyperthyroidism [3, 4].

Patients with large goiters who are elderly and may have underlying cardiovascular disease could be at risk of cardiac complications after rhTSH and radioiodine administration. Thyroid hormone in excess causes palpitation, some degree of exercise impairment and a widened pulse pressure. Changes in heart rate result from both an increase in sympathetic tone and a decrease in parasympathetic tone [1]. Tachycardia (heart rate >90 beats/min) is common at rest and during sleep. Atrial fibrillation occurs in 5–15% of patients with elevated serum thyroid hormones [1, 3]. Patients with hyperthyroidism have increased left ventricular systolic and diastolic contractile function. The rate of increase in intra-ventricular pressure during systole, the left ventricular ejection fraction, and the rate of blood flow across the aortic valve are all increased [21]. All these effects may be present during a transient period of excessive serum thyroid hormone surge.

After radioiodine therapy, all patients presented an increase in serum free T4 and total T3. Both variables significantly rose above baseline levels over the 7-day period that followed the $^{131}$I dose, persisting in the abnormal high-range for a further period of 3 weeks. Remarkably, this period of biochemical excess of serum thyroid hormones induced few cardiovascular signs or symptoms according to post-treatment cardiologic evaluation. However, a threefold increase in left ventricular diastolic dysfunction was detected in the $^{131}$I treated patients, with laboratorial evidence of clinical hyperthyroidism. Holter monitoring for 24 h indicated that maximum, minimum and mean heart rate did not differ from baseline to values observed in the early phase of RAI treatment. The number of ventricular beats was indeed greater in the baseline period compared to the post-treatment phase. We may assume that the transient hyperthyroidism did not affect structural and functional parameters of the heart. This conclusion should be accepted with reservations due to medication (beta-blockers) and individual variation in thyroid function parameters such as variable serum elevation of free T4 and total T3.

In conclusion, our results indicate that a lower dose of rhTSH along with a fixed 1.11 GBq (30 mCI) dose of RAI on an outpatient basis is highly effective in MNG with a considerable reduction in costs, fewer adverse effects and a relatively lower prevalence of permanent hypothyroidism. Careful monitoring of cardiac function did not detect major cardiovascular complications due to the transient period of hyperthyroidism. This RAI treatment of MNG preceded by rhTSH may be considered as an alternative to thyroid surgery, especially for the elderly.

## Patients and methods

In the period spanning January 2002 to March 2003, 66 patients (59 women, 7 men) with MNG were recruited from the outpatient clinics of the University Hospital. All subjects had a long-standing history of goiter and were resident in previously recognized areas of chronic iodine deficiency. Twenty-four patients were excluded from the study for several reasons, including rejection to any form of treatment, previous radioiodine therapy, inability to complete a prolonged follow-up, and serious cardiovascular disorders. Thus, the present study involved 42 patients (41 women and 1 man) with a mean age ± SD of

61.4 ± 11.2 years (range 42–80 years). Diagnosis of MNG was carried out clinically. Thyroid volume was estimated by CT without contrast. All patients collected a sample of urine for iodine concentration. Venous blood was drawn for thyroid function tests (TSH, free T4, total T3, serum TG, anti-TPO, and anti-TG). A baseline RAIU was determined 24 h after oral administration of 0.5 MBq (14.0 μCi) of $^{131}$I. All patients were instructed to follow a low-iodine diet for 3 months (iodized salt was substituted by non-iodized sodium chloride). As mentioned below RAIU was repeated after the low-iodine diet. Fine-needle aspiration biopsy was performed in echographically dominant and suspicious nodules to exclude malignancy. The study was approved by the Standing Committee for Ethics in Research Projects of the Hospital das Clinicas, University of Sao Paulo Medical School and this study complies with the Declaration of Helsinki. All patients signed an informed consent form. Treatment indications were symptoms of cervical compression, airway compromise, cosmetic discomfort and the presence of subclinical or overt hyperthyroidism. Recombinant human thyrotropin in flasks containing 0.9 mg rhTSH, (Thyrogen®, Genzyme Transgenics Co., Cambridge, MA, USA) was diluted with 9 ml of isotonic sodium chloride solution and 1 ml of this dilution (0.1 mg of rhTSH) was injected intramuscularly. Another tracer dose of 0.5 MBq (14.0 μCi) was administered 15 days before the therapeutic dose of RAI and 0.1 mg rhTSH stimulated radioiodine uptake was carried out. A second spot urine sample for urinary iodine measurement was also collected after 90 days of a low-iodine diet.

## Treatment protocol

Twenty-four hours after intramuscular injection of 0.1 mg rhTSH, administered as described above, patients were treated with a fixed radioiodine dose of 1.11 GBq (30 mCi) $^{131}$I, given as a single oral dose. This fixed dose was chosen because it is the maximum dose allowed to be given as an outpatient in Brazil.

## Thyroid function tests

Following RAI therapy, blood samples were collected during the acute phase (24 h, 48 h, 72 h, 168 h, and 1 month) and also during the prolonged follow-up period (36 months) for functional thyroid studies (serum TSH, free T4, total T3, TG), as well as to test for the presence of anti-TPO, anti-TG, and TRAb. Serum TSH (0.4–4.0 mU/l), free T4 (11.6–20.1 pmol/l), total T3 (1.38–2.77 nmol/l), serum TG (0.1–15 μg/l) were assayed by chemiluminescence (ECLIA, Roche Diagnostics, Manhein, Germany) as were anti-TPO and anti-TG (normal reference up to 60 U/ml). TRAb (normal value: up to 15%) was assayed by Kronus TRAb coated tube kit (Kronus, Boise, ID, USA), while urinary iodine excretion was assayed using a modified Sandell–Kolthoff method with normal values between 100 and 299 μg/l of urine [19].

## Thyroid volume

Thyroid volume evaluation was performed employing helical computed tomography (GE Medical Systems, Milwaukee, WI, USA) by using 130 mA, 120 Kvp and 5 mm collimation with a pitch of 1 from the mandible to the end of the enlarged thyroid gland without contrast media. Axial images were reconstructed with a standard algorithm and post-processing was performed on a commercially available workstation, as previously described [19].

## Cardiovascular evaluation

Patients underwent cardiovascular evaluation by two cardiologists (M.T.O., C.G.) before and after radioiodine treatment. Standard 12-lead ECGs were recorded in all subjects. Two-dimensional Doppler echocardiography was performed with a 3.5 MHz transducer with analysis of systolic function (fractional shortening and ejection fraction) and diastolic function (isovolumetric relaxation time and ratio) as well as left ventricular mass. A 24-h Holter ECG monitoring study to detect rhythm disturbance was also performed in 23 patients. Treadmill stress test was conducted in 27 patients. The cardiovascular assessment was repeated by the same examiners, using the same tests, 7–15 days after the patients had received the $^{131}$I therapeutic dose. At this early phase all patients had an elevated serum free T4 and total T3 values (transient hyperthyroidism).

## Statistical analysis

The R Statistical software program, version 2.5.0 was used (http://www.r-project.org, accessed on April.23.2007). Data are presented as mean ± SD. Non-parametric (Mann–Whitney *U*-test) and parametric tests (Student's *t*-test) were used, depending on the normality of the data. Linear regression analysis was used to test for the relationship between relevant variables. The level of statistical significance was chosen as $P < 0.05$.

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