Chronic thyrotropin-suppressive therapy with levothyroxine and short-term overt hypothyroidism after thyroxine withdrawal are associated with undesirable cardiovascular effects in patients with differentiated thyroid carcinoma

José I Botella-Carretero, Manuel Gómez-Bueno1, Vivencio Barrios1, Carmen Caballero2, Rafael García-Robles, José Sancho and Héctor F Escobar-Morreale

Department of Endocrinology, Hospital Ramón y Cajal, Madrid, Spain
1Department of Cardiology, Hospital Ramón y Cajal, Madrid, Spain
2Department of Nuclear Medicine, Hospital Ramón y Cajal, Madrid, Spain

(Requests for offprints should be addressed to H F Escobar-Morreale, Department of Endocrinology, Hospital Ramón y Cajal, Carretera de Colmenar Km. 9.1, 28034 Madrid, Spain; Email: hescobar.hrc@salud.madrid.org)

Abstract

To evaluate cardiovascular functionality in patients with thyroid cancer, we have performed echocardiography and ambulatory blood pressure monitoring in 19 women with differentiated thyroid carcinoma during thyroxine withdrawal, at three time points: the last day on TSH-suppressive thyroxine doses (subclinical or mild hyperthyroidism), 4–7 days after withdrawal (normal free thyroxine (FT4) and free triiodothyronine (FT3) levels), and before 131I whole body scanning (overt hypothyroidism). Twenty-one healthy euthyroid women served as controls.

When compared with the values at visit 2, when patients had normal serum FT4 and FT3 levels, night-time systolic and mean blood pressure were increased when the patients were mildly hyperthyroid, and night-time systolic, diastolic and mean blood pressure were increased during overt hypothyroidism. The proportion of nondippers (absence of nocturnal decline in blood pressure) was markedly increased compared with healthy controls (7%), when patients were hyper- or hypothyroid (58% and 50% respectively), but not when patients had normal FT4 and FT3 levels (12%).

No changes were observed in office blood pressure or in daytime ambulatory blood pressure readings.

Diastolic function worsened during thyroxine withdrawal (E and A waves (early and late mitral flow) decreased, and the E/A ratio and the isovolumic relaxation time increased), and cardiac output decreased in parallel with the decrease in heart rate and systolic blood flow.

In conclusion, the chronic administration of TSH-suppressive doses of thyroxine and the withdrawal of thyroxine frequently used for the management of differentiated thyroid carcinoma, are associated with undesirable cardiovascular effects.

Endocrine-Related Cancer (2004) 11 345–356

Introduction

Papillary and follicular thyroid cancer, together termed differentiated thyroid carcinoma (DTC), are frequent among endocrine disorders. Although mortality rates in DTC patients have fallen in the United States during the last two decades — possibly because of generalized use of initial complete surgical resection and ablation of thyroid remnants using radioactive
iodine (Hundahl et al. 1998) — DTC patients are followed-up for a long time to exclude cancer recurrences (Mazzaferri & Kloos 2001). Supraphysiological doses of oral levothyroxine are usually administered to most of these patients to suppress the endogenous secretion of thyrotropin (TSH), and subsequent follow-up strategies may vary according to the patient’s individual risk (Mazzaferri & Kloos 2001, Mazzaferri et al. 2003). The current availability of recombinant human TSH (rhTSH) for determination of stimulated thyroglobulin and diagnostic 131I whole body scanning have limited the need for thyroxine withdrawal-induced hypothyroidism in many patients (Meier et al. 1994, Haugen et al. 1999, Robbins et al. 2001). However, the latter is still the preferred approach for ablation therapy of thyroid remnants or metastases with radioactive iodine (Mazzaferri & Kloos 2001, Robbins & Robbins 2003).

The cardiovascular system is a major target for thyroid hormone action, and both hyper- and hypothyroidism have been associated with disturbances in cardiac hemodynamics and blood pressure (Klein & Ojamaa 2001). It is well known that hyperthyroidism has overt and striking cardiovascular effects that may lead to arrhythmias, especially atrial fibrillation, cardiomyopathy and hypertension, resulting in increased mortality (Umpierrez et al. 1995, Osman et al. 2002). Subclinical endogenous hyperthyroidism has been reported to induce cardiovascular dysfunction as well (Biondi et al. 2000, Sawin 2002), and treatment with suppressive doses of thyroxine has been associated with atrial premature beats, a hypercontractile state, cardiac hypertrophy and diastolic dysfunction (Banovac et al. 1989, Biondi et al. 1993, 1999, Fazio et al. 1995, Ching et al. 1996). However, there is no overall agreement on the clinical significance of these findings, especially when suppressive doses of thyroxine are individually tailored (Shapiro et al. 1997, Mercuro et al. 2000).

Hypothyroidism has been associated with significant cardiovascular abnormalities, including diastolic dysfunction, reduced cardiac output, hypertension and an increase in peripheral vascular resistance (Grossman et al. 1994, Bengel et al. 2000, Diekman et al. 2001, Fommei & Iervassi 2002, Obuobe et al. 2002). Of note, even mild states of thyroid failure may disturb cardiac contractility and hemodynamics, changes that can be reversed by thyroxine replacement therapy (Monzani et al. 2001, Faber et al. 2002). Yet these findings may have no clinical relevance in patients without underlying heart disease (Arem et al. 1996).

However, knowledge of the influence of thyroid function on cardiovascular performance in humans has been hampered by the fact that most studies have explored cardiac function or blood pressure monitoring in groups of patients with several degrees and duration of hypo- or hyperthyroidism, and submitted to different therapeutic measures, making difficult the interpretation of the findings because of these confounding variables. To avoid these limitations, we have evaluated cardiac hemodynamics and blood pressure monitoring in a single cohort of patients with DTC, before and after thyroxine withdrawal prior to 131I whole body scanning, and compared them with a healthy euthyroid control group, in order to assess the cardiovascular impact of short time overt hypothyroidism and, more importantly, the cardiovascular effects of chronic administration of thyroxine TSH-suppressive doses to these patients.

Materials and Methods

Subjects

Twenty-one women with differentiated thyroid carcinoma referred for a routine 131I whole body scanning during follow-up after initial surgery and radioactive iodine ablation, were recruited prospectively. Patients were studied during levothyroxine withdrawal at three time points: the last day on levothyroxine at their usual TSH-suppressive doses, 4–7 days after withdrawal (DeGroot et al. 1997), and the day before administering radioactive iodine for the 131I whole body scanning. Thyroid function in these patients was expected to change from subclinical or mild hyperthyroidism at the first visit, to a situation of normal circulating levels of free thyroxine (FT4) and triiodothyronine (FT3) at the second, ending in a state of overt hypothyroidism at the last visit. Two patients presented with normal TSH levels at the first visit and were excluded from the study. Therefore, only 19 patients completed evaluation at the three visits.

The indication for 131I whole body scanning after thyroxine withdrawal (rhTSH was not available in Spain at the time of the study), as well as the degree of suppression of endogenous TSH secretion and the doses of levothyroxine used during follow-up, were decided by the physicians referring these patients, and were not influenced by any of the authors of this study. Before recruitment, none of the patients had any cardiovascular abnormality nor were hypertensive. Patients were not taking any drug known to affect blood pressure levels, cardiac function or thyroid hormone metabolism other than levothyroxine sodium. The age of the patients was 42.6 ± 14.1 years (mean ± S.D.). Patients had been taking TSH-suppressive doses of thyroxine for 47 ± 54 months (range 6–249 months), and were taking a 171 ± 22 µg per day thyroxine dose at recruitment.

Twenty-one normotensive healthy female volunteers, matched for age (42.7 ± 14.5 years) and without cardiovascular disease, served as euthyroid controls. They were not taking any drug known to influence thyroid or cardiac
function. Preliminary data regarding quality of life and psychometric functionality of some of the patients and controls have been published previously (Botella-Carretero et al. 2004).

The ethics committee of the Hospital Ramón y Cajal approved the study, and written informed consent was obtained from all the participants or their legal representatives.

Study protocol

Patients and controls reported early in the morning after a 12 h fast. Patients were advised to take their usual levothyroxine dose just after waking up, before reporting to the hospital on the day of the first visit, and medication was withdrawn thereafter. Evaluation was repeated in the patients after 4 to 7 days (second visit, mean ± S.D.: 5.6 ± 1.1 days after levothyroxine withdrawal), and the day before 131I whole body scanning was performed (third visit, mean ± S.D.: 30.8 ± 4.4 days after levothyroxine withdrawal). Controls were evaluated only at one time point.

An independent evaluator performed M-mode, two dimensional, and Doppler echocardiography on every patient at each visit and in the controls, using a Philips HDI 5000 system (Philips Medical Systems, Eindhoven, The Netherlands) equipped with a 2–4 MHz phased array transducer. The following measurements were recorded on M-mode: left atrial diameter, systolic and diastolic left ventricular diameter, posterior wall and septum thickness, and shortening fraction. Two dimensional left ventricular ejection fraction was also acquired by the summation method. The left ventricular myocardial mass was calculated using Devereux’s formula and left ventricular mass index obtained (ventricular mass per body surface). Doppler studies provided indexes of ventricular filling derived from the mitral valve flow velocity curves at both the early phase (E wave) and the maximal late flow (A wave), as well as the E/A ratio. The isovolumic relaxation time (IVRT) also served as an index of ventricular filling, and the deceleration time was also measured. The aortic velocity time integral was calculated, and used as a measure of systolic blood flow out of the left ventricle. Finally, cardiac output was also calculated as the stroke volume by heart rate.

Office blood pressure was determined at every patient’s visit and in controls as the mean of two manual sphygmomanometer readings in the sitting position, immediately after performing echocardiography. Mean arterial blood pressure was calculated as \([\text{systolic} - (2 \times \text{diastolic})]/3\). Heart rate was recorded, and systemic vascular resistance was calculated as the mean arterial blood pressure/cardiac output.

In a subgroup of 12 patients and 16 controls, 24 h ambulatory blood pressure monitoring was performed using an A&D TM2430EX oscillometric device (A&D Company, Ltd, Tokyo, Japan) which passed evaluation by the protocol of the Association for the Advancement of Medical Instrumentation, and has been graded A for systolic and diastolic blood pressure measurements using the protocol of the British Society of Hypertension (O’Brien et al. 2000). These patients and controls were not different when compared with the whole cohort in terms of age (patients 44.1 ± 16.7 years and controls 39.4 ± 16.2 years), or levothyroxine dose before withdrawal in patients (166 ± 24 µg per day). The period from 0800 h to 2300 h was considered daytime, and from 2300 until 0800 h next day was considered night-time, reflecting the usual sleeping habits of Spaniards (Ocon & Ibeas 2002). The nocturnal decreases in systolic and diastolic blood pressure were calculated using the equation (mean of diurnal blood pressure–mean of nocturnal blood pressure)/mean of diurnal blood pressure) × 100. Nondippers were defined as those subjects who did not show a reduction in mean systolic and diastolic blood pressures by ≥10% from day to night, and the remaining subjects were considered as dippers (Verdecchia et al. 1990, Khattar et al. 1999).

Serum samples were obtained for determination of TSH, FT4 and FT3 using commercial immunochemiluminescent assays (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA). The mean coefficients of variation were below 10% for all these assays. The normal ranges were 0.4–4.0 µU/ml for serum TSH, 0.8–1.9 ng/dl for FT4, and 1.8–4.2 pg/ml for FT3 as reported by the Central Laboratory of the Hospital Ramón y Cajal.

In the subgroup of 12 patients and 16 controls submitted to ambulatory blood pressure monitoring, plasma renin activity and creatinine clearance were determined. Plasma renin activity was assessed by measuring by radioimmunounassay the amount of angiotensin I generated in plasma samples after a 90 min incubation at 37°C, under conditions which prevent degradation of angiotensin I (Rencitk P2721, DiaSorin s.r.l., Saluggia, Italy). Mean intra- and interassay coefficients of variation were 7.6% and 9.1% respectively. Blood and 24h urine samples were assayed for creatinine by the alkaline sodium picrate method using an Abbott Aeroset Automated Instrument Analyzer (Abbott Laboratories, Abbot Park, IL, USA) with mean intra- and interassay coefficients of variation below 2%. Creatinine clearance (CrCl) was calculated from serum and urine creatinine concentrations using the equation CrCl (ml/min) = (urinary creatinine (mg/dl) × urine volume (ml)/(serum creatinine (mg/dl) × time (min))).
Statistical analysis

Data are expressed as means ± S.D. unless otherwise stated. The normal distribution of the variables was analyzed using the Kolmogorov–Smirnov test. Logarithm or square root transformations were applied to ensure normal distribution whenever possible. The values of the patients at the three visits were compared by repeated measures analysis of variance, or Friedman two-way analysis of variance by ranks, as appropriate. After Friedman analysis, comparisons between visits 1, 2 and 3 were performed using repeated Wilcoxon signed rank tests applying the Bonferroni correction to the level of significance.

The comparisons of the values of the patients at each visit with the controls were performed by one-way analysis of variance followed by Dunnet’s test, or by Kruskall–Wallis one-way analysis of variance by ranks followed by Mann–Whitney tests, depending on the distribution of the variables. After a significant Kruskall–Wallis test was obtained, the identification of the particular visit, or visits, which were different compared with the controls, was made using separate Mann–Whitney tests. Because no comparisons were made between visits, no correction was applied to the level of significance. The comparison of the proportion of dippers and nondippers between visits and with the controls was analyzed by the χ² test. An α value of 0.05 was chosen as the level of statistical significance with the exceptions described above. Statistical analyses were performed using SPSS for Macintosh, version 10 (SPSS Inc., Chicago, IL, USA).

Results

Serum thyroid hormone concentrations during levothyroxine withdrawal (Fig. 1)

As expected from chronic treatment with supraphysiological doses of levothyroxine, the mean serum thyroid hormone levels were in the mild hyperthyroid range at visit 1 (16 of 19 patients had increased FT4 levels, whereas all the patients had suppressed TSH levels, and only two had increased FT3 concentrations).

At visit 2, mean TSH levels were below the normal range, whereas mean serum FT4 and FT3 were within the normal range. Sixteen of nineteen patients still had decreased TSH levels, but their FT4 and FT3 levels were within the normal range except in one patient who still had minimally increased FT4 levels. When considering patients as a group, at visit 2 patients presented with lower mean TSH and FT3 levels compared with euthyroid controls.

At visit 3, all the patients presented with increased serum TSH and low serum FT4 and FT3 levels, with the exception of two patients who had FT3 levels in the lower limit of the normal range. When considering patients as a group, mean serum TSH was increased, and mean FT4 and FT3 levels were decreased, compared with controls and with respect to the normal range established in the Laboratory.

Office blood pressure and heart rate, and systemic vascular resistance (Table 1)

No differences were observed in office systolic, diastolic and mean blood pressure during thyroxine withdrawal in patients, or when comparing patients and euthyroid controls. Heart rate decreased during thyroxine withdrawal in patients with differentiated thyroid carcinoma, and was lower compared with controls at visit 3, when patients were overtly hypothyroid.

Systemic vascular resistance increased in patients during thyroxine withdrawal. Systemic vascular resistance was lower at visit 1 when patients received TSH-suppressive thyroxine doses, and was higher at visit 2 when the patients had normal circulating levels of FT4 and FT3. When compared with euthyroid individuals, systemic vascular resistance was higher in patients at visit 3 when in overt hypothyroidism.

Echocardiographic findings (Table 2)

Doppler echocardiography showed worsening of diastolic function in patients with differentiated thyroid carcinoma during thyroxine withdrawal, because the magnitude of the E and A waves decreased, and the E/A ratio and the IVRT increased. Also, the E wave was significantly smaller when compared with controls at visit 3 when patients were in a state of overt hypothyroidism.

Cardiac output also showed a significant decrease in the group of patients with differentiated thyroid carcinoma during thyroxine withdrawal, parallel to the decreases in heart rate and systolic blood flow (as measured by the velocity time integral). When in overt hypothyroidism at visit 3, patients presented with lower cardiac output and heart rate compared with controls.

In contrast, no changes were observed in M-mode measurements (left atrial diameter, systolic and diastolic left ventricular diameter, posterior wall and septum thickness, and the percentage of shortening fraction) and in the two-dimensional study (left ventricular mass and mass index, and ejection fraction), either in differentiated thyroid carcinoma patients during thyroxine withdrawal, or when compared with healthy controls.
Figure 1 Clinical and biochemical indexes of thyroid hormone function during levothyroxine withdrawal in patients with differentiated thyroid carcinoma compared with euthyroid controls. Data are represented as means ± S.E.M., and the dot scattergram shows the individual data. The shaded areas represent the normal ranges for serum thyroid hormone levels as reported by the Central Laboratory of the Hospital Ramón y Cajal. Statistically significant differences between visits 1, 2 and 3 were observed in serum TSH, FT4 and FT3 levels, with \( P < 0.05 \) or less for all the comparisons. \(*P < 0.05\) or less compared with the values from the euthyroid control group, which were TSH = 1.87 ± 0.88 µU/ml, FT4 = 1.29 ± 0.13 ng/dl and FT3 = 3.38 ± 0.77 pg/ml (means ± S.D.).
Table 1 Office blood pressure and heart rate, and systemic vascular resistance, in patients with differentiated thyroid carcinoma during thyroxine withdrawal, and in euthyroid controls. Data are means ± S.D.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=19)</th>
<th>Controls (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>116 ± 9</td>
<td>118 ± 10</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td>70 ± 5</td>
<td>72 ± 5</td>
</tr>
<tr>
<td><strong>Mean BP (mmHg)</strong></td>
<td>84 ± 6</td>
<td>85 ± 6</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td>79 ± 9</td>
<td>76 ± 7</td>
</tr>
<tr>
<td><strong>SVR (dyn/s/cm⁻²)</strong></td>
<td>1801 ± 308‡*</td>
<td>1999 ± 402</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| BP, blood pressure; SVR, systemic vascular resistance
*P < 0.05 or less compared with euthyroid controls; †P < 0.05 or less compared with visit 1; ‡P < 0.05 or less compared with visit 2.

Ambulatory monitoring of blood pressure (Table 3)

In the subgroup of 12 patients and 16 controls submitted to 24 h monitoring of blood pressure, serum thyroid hormone and TSH levels, and their changes during thyroxine withdrawal were similar to those found in the whole cohort of patients and controls described above.

All the subjects presented with mean systolic blood pressure values below 140 mmHg during the 24 h recordings, and also during daytime and night-time separately.

Twenty-four-hour, daytime and night-time mean diastolic blood pressure measurements were below 90 mmHg in all the subjects with the exception of one patient, who presented a mean diastolic blood pressure of 100 mmHg at night-time at visit 1.

Night-time ambulatory blood pressure monitoring showed a biphasic pattern of changes during thyroxine withdrawal, because systolic and mean blood pressure were higher at visit 1 (when patients were in mild or subclinical hyperthyroidism) and systolic, diastolic and mean blood pressure were higher at visit 3 (during overt

Table 2 Echocardiographic findings in patients with differential thyroid carcinoma during thyroxine withdrawal, and in euthyroid controls. Data are means ± S.D.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=19)</th>
<th>Controls (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
</tr>
<tr>
<td><strong>Doppler echocardiography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E wave (cm/s)</td>
<td>80.8 ± 17.9</td>
<td>75.8 ± 15.2†</td>
</tr>
<tr>
<td>A wave (cm/s)</td>
<td>69.4 ± 23.6</td>
<td>62.6 ± 22.1†</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.3 ± 0.5</td>
<td>1.4 ± 0.6</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>87.6 ± 18.1</td>
<td>94.5 ± 17.5†</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>159.2 ± 32.8</td>
<td>158.4 ± 32.4</td>
</tr>
<tr>
<td>Velocity time integral (cm)</td>
<td>23.1 ± 3.7</td>
<td>22.6 ± 3.4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73.9 ± 8.1</td>
<td>67.5 ± 6.0†‡</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>4.8 ± 1.0</td>
<td>4.4 ± 0.9†‡</td>
</tr>
<tr>
<td>M-mode measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter (cm)</td>
<td>3.1 ± 0.5</td>
<td>3.1 ± 0.5</td>
</tr>
<tr>
<td>Diastolic LV diameter (cm)</td>
<td>4.4 ± 0.4</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>Systolic LV diameter (cm)</td>
<td>2.7 ± 0.3</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>Septum thickness (cm)</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>Shortening fraction (%)</td>
<td>38.7 ± 3.8</td>
<td>38.9 ± 3.5</td>
</tr>
<tr>
<td>Two dimensional study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>124.1 ± 33.5</td>
<td>122.4 ± 31.9</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>72.1 ± 16.7</td>
<td>71.5 ± 17.1</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>69.2 ± 4.8</td>
<td>69.4 ± 4.3</td>
</tr>
</tbody>
</table>

LV, left ventricle; IVRT, isovolumic relaxation time.
*P < 0.05 or less compared with euthyroid controls; †P < 0.05 or less compared with visit 1; ‡P < 0.05 or less compared with visit 2.

www.endocrinology.org
hypothyroidism) compared with visit 2 when patients had normal FT4 and FT3 levels. However, these increased values at visits 1 and 3 did not reach statistical significance when compared with euthyroid controls, possibly because of the small sample size being compared.

Of note, the proportion of nondippers was markedly increased in patients with differentiated thyroid carcinoma compared with euthyroid patients both at visit 1 (58%, when in mild or subclinical hyperthyroidism) and at visit 3 (50%, when in overt hypothyroidism), whereas this proportion was similar to that in controls at visit 2 (17%, when FT4 and FT3 levels were within the normal range). Only one of the patients was a nondipper throughout the study.

On the contrary, daytime ambulatory blood pressure monitoring did not disclose any change during thyroxine withdrawal, and the mean values were comparable to those of the controls.

As occurred with office heart rate, the ambulatory blood pressure recorder also demonstrated a progressive decrease in heart rate during thyroxine withdrawal, both during daytime and night-time.

Plasma renin activity and creatinine clearance decreased, and serum creatinine levels increased, during thyroxine withdrawal in patients. Compared with controls, only the increase in serum creatinine concentrations during overt hypothyroidism reached statistical significance.

### Discussion

In the present study, we have evaluated cardiac hemodynamics and blood pressure monitoring in a single cohort of patients with DTC, before and after thyroxine withdrawal prior to 131I whole body scanning, and compared them with a healthy euthyroid control group.

The most relevant cardiovascular abnormalities occurred when our patients were in overt hypothyroidism just before 131I whole body scanning. In our study, short-term hypothyroidism resulted in an increase in night-time systolic, mean and diastolic blood pressure, and was accompanied by an increase in the proportion of nondippers. Thyroid hormone deficiency results in increased systemic vascular resistance (Klein & Ojamaa

Table 3 Hormonal and biochemical variables, and blood pressure, in the subgroup of patients and controls submitted to ambulatory blood pressure monitoring. Data are means ± S.D. except for the nocturnal decrease in blood pressure in which data are absolute counts.

<table>
<thead>
<tr>
<th>Patients (n=12)</th>
<th>Controls (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal and biochemical variables</td>
<td></td>
</tr>
<tr>
<td>TSH (μU/ml)</td>
<td>0.03 ± 0.03*†</td>
</tr>
<tr>
<td>FT4 (ng/dl)</td>
<td>1.98 ± 0.26**†</td>
</tr>
<tr>
<td>FT3 (pg/ml)</td>
<td>3.31 ± 0.84</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>2.15 ± 1.52</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>0.80 ± 0.12</td>
</tr>
<tr>
<td>CrCl (ml/min)</td>
<td>114 ± 29</td>
</tr>
<tr>
<td>Daytime blood pressure monitoring</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>120 ± 11</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>73 ± 6</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>89 ± 7</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>84 ± 9</td>
</tr>
<tr>
<td>Night-time blood pressure monitoring</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>112 ± 12†</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>67 ± 12</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>80 ± 7†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>66 ± 10</td>
</tr>
<tr>
<td>Nocturnal decrease in blood pressure</td>
<td></td>
</tr>
<tr>
<td>Dippers/Nondippers</td>
<td>5/7*</td>
</tr>
</tbody>
</table>

Nondippers were defined as those subjects who did not show a reduction in mean systolic and diastolic blood pressures by ≥10% from day to night, and the remaining subjects were considered as dippers. FT4, free serum thyroxine; FT3, free serum triiodothyronine; PRA, plasma renin activity; Cr, serum creatinine; CrCl, creatinine clearance; BP, blood pressure.

*P < 0.05 or less compared with euthyroid controls; †P < 0.05 or less compared with visit 1; ††P < 0.05 or less compared with visit 2.
2001) and decreased creatinine clearance (Sahün et al. 2001), findings that were all present in our patients when overtly hypothyroid. Aside from these, other factors such as increased central arterial stiffness (Obuobie et al. 2002), sympato-adrenal stimulation resulting in increased catecholamine concentrations (Foley et al. 2001, Faber et al. 2002, Fommei & Iervassi 2002), and increased vasopressin secretion (Skowsky & Kikuchi 1978) may also have contributed to the increase in blood pressure found in our patients during hypothyroidism, despite the low plasma renin activity found (Marchant et al. 1993, Asmah et al. 1997).

In conceptual agreement with our present results, short term hypothyroidism has recently been shown to produce systolic and diastolic hypertension when evaluated by ambulatory blood pressure monitoring (Fommei & Iervassi 2002). In this study, a group of 12 normotensive patients in whom total thyroidectomy and radioactive iodine ablation were used for thyroid carcinoma, were studied. The authors found an increase in daytime systolic and diastolic blood pressure in these patients when hypothyroid before $^{131}$I whole body scanning, compared with the same patients on thyroxine treatment two months later, when they had normal TSH levels (Fommei & Iervassi 2002). No changes in blood pressure were observed at night-time, and no mention was made to the dipper or nondipper status of the patients (Fommei & Iervassi 2002). Moreover, these patients were not studied when in chronic TSH-suppressive therapy (Fommei & Iervassi 2002).

In addition to the finding of increased night-time blood pressure and increased prevalence of nondippers after short-term hypothyroidism, our present results are in agreement with previous studies showing diastolic dysfunction, decreased heart rate and decreased cardiac output after thyroxine withdrawal (Grossman et al. 1994), and a reversal of these changes with thyroxine administration (Bengel et al. 2000).

More importantly, we have shown for the first time that TSH-suppressive thyroxine treatment results in an increase in night-time systolic and mean blood pressure, and that more than half of the patients in our series were nondippers because of the supraphysiological thyroxine doses used to suppress endogenous TSH secretion. Although in all the patients the increase in night-time systolic blood pressure was within the normal range, the relationship between systolic ambulatory blood pressure and the incidence of cardiovascular events is linear (Khattar et al. 1999), and organ damage progression and the incidence of cardiovascular disease are considerably increased in nondippers (Verdecchia et al. 1990, even in normotensive subjects (Ohkubo et al. 2002, Hoshide et al. 2003). Given that patients with differentiated thyroid carcinoma may suffer these undesirable cardiovascular effects for long periods of time, even for a lifetime, future studies should seek to find out if the long-term use of thyroxine at TSH-suppressive doses is associated with a significant cardiovascular risk.

The increase in systolic and mean blood pressure when our patients were mildly hyperthyroid occurred during night-time. However, most studies have failed to demonstrate hypertension as a result of chronic TSH-suppressive doses of thyroxine (Biondi et al. 1993, Fazio et al. 1995, Ching et al. 1996, Mercuro et al. 2000). We hypothesize that the use of ambulatory blood pressure monitoring has allowed us to detect the increase in night-time blood pressure, whereas it is also possible that physical activity may have blunted similar differences during daytime.

The increase in night-time blood pressure observed in our patients when in mild or subclinical hyperthyroidism might be related to direct stimulation of the renin—angiotensin—aldosterone system by thyroid hormones. Thyroid hormones stimulate angiotensinogen synthesis in several tissues (Ruiz et al. 1987, Sernia et al. 1989, Chan et al. 1992, Hong-Brown & Deschepper 1992). Interestingly, the production of angiotensinogen by the liver in response to thyroid hormones appears to require local conversion of thyroxine into triiodothyronine (Ruiz et al. 1987), in agreement with the concordance of the changes in blood pressure with the changes in serum FT3 levels, and not with FT3 concentrations, observed in our patients.

Moreover, thyroid hormones stimulate renin synthesis (Marchant et al. 1993, Asmah et al. 1997, Ichihara et al. 1998, Basset et al. 2001, Kobori et al. 2001), independently of the sympathetic nervous system (Kobori et al. 1997). Infusion of supraphysiological doses of thyroxine in the rat results in an increase in thyroxine and triiodothyronine concentrations in the kidney (Escobar-Morreale et al. 1995), and the kidney-to-plasma ratio of triiodothyronine levels of 10.7 to 1 suggests trapping of circulating triiodothyronine (Oppenheimer & Schwartz 1985) or local conversion of thyroxine into triiodothyronine mediated by type I iodothyronine-deiodinase (Berry et al. 1991) in renal parenchyma. This, in turn, may explain the activation of the renin–angiotensin system during prolonged thyroxine suppressive treatment and the consequent sodium reabsorption and increase in blood pressure, even though circulating levels of FT3 were similar to those observed in controls. However, the activation of the renin–angiotensin–aldosterone system may also be secondary to the thyroid hormone-induced decrease in systemic vascular resistance (Klein & Ojamaa 2001), which was also observed in our patients when on TSH-suppressive thyroxine treatment. Because other studies have shown that hyperthyroidism increases atrial
natriuretic peptide levels (Diekman et al. 2001) and nitric oxide synthase activity (Quesada et al. 2002), these factors may protect mainly against the increase in diastolic blood pressure, but not against the development of the systolic hypertension characteristic of hyperthyroidism (Saito & Saruta 1994).

The cellular action of thyroid hormones on the heart is believed to be mediated mainly by circulating triiodothyronine (Dillmann 2002), because local conversion of thyroxine into triiodothyronine does not appear to occur in any measurable degree in cardiac myocytes (Everts et al. 1996). In addition to an increase in the expression of myosin heavy chain-2 through genomic actions (Morkin 1993, Danzi & Klein 2002), triiodothyronine exerts non-genomic actions that include the activation of calcium, potassium and sodium channels (Carr & Kranias 2002, Davis & Davis 2002) as well as promotes the expression of mitochondrial genes that also influence cardiac contractility (Schneider & Hood 2000). Also, triiodothyronine increases electrical activity of the heart independently of the adrenergic nervous system (Klein & Ojamaa 2001, Dillmann 2002), given that circulating catecholamines are reduced in hyperthyroidism (Levey & Klein 1990, Mercuro et al. 2000). This effect presumably results from an up-regulation of β-adrenergic receptors, without affecting adrenergic sensitivity (Dillmann 2002). This predominant role of triiodothyronine on cardiac muscle and electrical activity might explain why our patients had cardiac function and heart rate comparable to that of controls when on suppressive doses of thyroxine, given that FT3 levels were similar in both groups.

Previous studies have shown that chronic TSH-suppressive thyroxine therapy can induce cardiac structural abnormalities such as increased septum thickness, posterior wall thickness, and left ventricular mass index (Biondi et al. 1993, Ching et al. 1996). Cardiac hypertropy could be improved by beta-adrenergic blockade or by individual tailoring of thyroxine doses in these patients (Fazio et al. 1995, Mercuro et al. 2000). The absence of significant cardiac structural changes in our patients before thyroxine withdrawal might be related to the shorter duration of TSH-suppressive therapy in our patients (a mean of approximately 4 years) compared with those of previous studies (up to 9 years) (Biondi et al. 1993, Ching et al. 1996). Also, the small sample size in our study might have masked a tendency towards increased left-ventricular mass in our patients when compared with euthyroid controls.

As stated above, our results suggest that some of these cardiovascular effects are more dependent on serum FT4 concentrations, whereas others are more dependent on serum FT3 levels. On the one hand, when patients were receiving TSH-suppressive doses of levothyroxine, their overall cardiac performance was similar to that of euthyroid controls, despite the fact that most patients had increased serum FT4 levels. But, given their normal FT3 levels at visit 1, and that cardiac output, heart rate and diastolic function changed shortly after thyroxine withdrawal at visit 2, when the FT3 levels of the patients were lower compared with controls, our present results suggest that the changes observed in cardiac performance are preferentially dependent on serum FT3 concentrations. On the other hand, systolic and mean blood pressure at night-time were higher at visit 1 when patients had increased serum FT4 concentrations and normal serum FT3 levels, compared with visit 2 when patients had normal serum FT4 and decreased serum FT3 levels. Moreover, the proportion of nondippers was also clearly increased compared with controls at visit 1, and returned to normal at visit 2. Therefore, the influence of thyroid hormones on night-time blood pressure appears to be related mainly to serum FT4 levels, and not to serum FT3 concentrations. These findings are in conceptual agreement with previous results in thyroidectomized rats indicating that the mechanisms regulating thyroid hormone concentrations are tissue-specific, and that the relative importance of plasma thyroid hormones or of local conversion of T4 into T3, as the source of tissue T3 concentrations, is highly variable depending on the tissue studied (Escobar-Morreale et al. 1995).

In conclusion, we here demonstrate that both short-term overt hypothyroidism and chronic thyroxine suppressive treatment induce undesirable cardiovascular effects in patients with DTC. Our present results should stimulate further research in this area to determine the clinical relevance and the possible long-term consequences of the impact of chronic TSH-suppressive therapy and of thyroxine withdrawal on the cardiovascular system of patients suffering this prevalent type of cancer.

Acknowledgements

We thank Mrs Genoveva González, Laboratorio de Endocrinología, Hospital Ramón y Cajal, for excellent technical help. José I Botella-Carretero received fellowships from the Consejería de Educación, Comunidad de Madrid (01/0430/01), and from the Fondo de Investigación Sanitaria (01/F072), Instituto de Salud Carlos III, Spain. Financial aid came from Merck Darmstadt KgaA, Germany. This article was presented at the 6th European Congress of Endocrinology, Lyon, France, 26–30 April 2003, and at the 85th Endocrine Society’s Annual Meeting, Philadelphia, PA, 19–22 June 2003.
References


Botella-Carretero JI, Galán JM, Caballero C, Sancho J & Escobar-Morreale HF 2003 Quality of life and psychometric functionality in patients with differentiated thyroid carcinoma is impaired both by chronic therapy with suppressive doses of levothyroxine, and by levothyroxine withdrawal before whole body scanning with radioactive iodine. Endocrine-Related Cancer 10 601–611.

Carr AN & Kranias EG 2002 Thyroid hormone regulation of calcium cycling proteins. Thyroid 12 453–457.


Ching GW, Franklyn JA, Stallard TJ, Daykin J, Sheppard MC & Gammage MD 1996 Cardiac hypertrophy as a result of long-term thyroxine therapy and thyreotoxicosis. Heart 75 363–368.

Danzi S & Klein I 2002 Thyroid hormone-regulated cardiac gene expression and cardiovascular disease. Thyroid 12 467–472.

Davis PJ & Davis FB 2002 Nongenomic actions of thyroid hormone on the heart. Thyroid 12 459–466.

DeGroot L, Manowitz N, Chait L & Mayor G 1997 Differential end organ responsiveness to suboptimal thyroid hormone concentrations as assessed by short-term withdrawal of levothyroxine sodium in athyreotic patients. 70th Annual Meeting of the American Thyroid Association, Colorado Springs, CO, USA.


Dillmann WH 2002 Cellular action of thyroid hormone on the heart. Thyroid 12 447–452.


Foley CM, McAllister RM & Hassar EM 2001 Thyroid status influences baroreflex function and autonomic contributions to arterial pressure and heart rate. American Journal of Physiology 280 H2061–H2068.


Hoshide S, Kario K, Hoshide Y, Umeda Y, Hashimoto T, www.endocrinology.org 355
Hundahl SA, Fleming ID, Fremgen AM & Menck HR 1998
Ichihara A, Kobori H, Miyashita Y, Hayashi M & Saruta T 1998
Kobori H, Ichihara A, Suzuki H, Miyashita Y, Hayashi M & Klein I & Ojamaa K 2001 Thyroid hormone and the
Khattar RS, Swales JD, Banfield A, Dore C, Senior R & Lahiri A
Levey GS & Klein I 1990 Catecholamine–thyroid hormone
Marchant C, Brown L & Sernia C 1993 Renin–angiotensin
Mokin E 1993 Regulation of myosin heavy chain genes in the heart. Circulation 87 1451–1460.
Oppenheimer JH & Schwartz HL 1985 Stereospecific transport of triiodothyronine from plasma to cytosol and from cytosol to nucleus in the rat liver, kidney, brain and heart. Journal of Clinical Investigation 75 147–154.


