Cardiovascular Effects of Thyroxine in Combination with Methimazole in Premenopausal Female Graves’ Disease Patients: Case-control Study

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Aim. To evaluate cardiovascular consequences of combined treatment in Graves’ disease patients with addition of thyroxine (LT4) to antithyroid drugs in doses sufficient to suppress serum thyrotropin (TSH) levels below normal.

Methods. Eleven premenopausal female patients who reached subnormal TSH levels (<0.3 μU/mL) under the combined therapy were evaluated by equilibrium radionuclide ventriculography at rest, and during the peak stage of fixed moderate exercise workload (75W) initially at diagnosis and after at least 8 months of stable euthyroidism, as judged by peripheral free thyroxine and triiodothyronine. The control group included 12 euthyroid healthy women.

Results. Post-treatment resting systolic and diastolic blood pressure, heart rate, and left ventricular (LV) systolic function were similar to control values. Log-transformed TSH releasing factor-stimulated TSH response correlated with LV resting early diastolic peak filling rate (PFR) (r=0.802, p=0.003) and resting diastolic blood pressure (r=0.795, p=0.003), which, in turn, was a significant predictor of basal renin secretion (r=-0.84, p=0.001). Treated patients had increased peak exercise systolic blood pressure (median 175, interquartile range 25 vs median 156, interquartile range 29 mmHg, p=0.019), delayed recovery of post-exercise heart rate to basal levels, and reduced exercise ejection fraction (median 66, interquartile range 9 vs median 74, interquartile range 13 %, p=0.037) in comparison with controls. Exercise ejection fraction was inversely related to exercise diastolic blood pressure, (r=-0.818, p=0.002); and exercise systolic blood pressure to exercise time to peak filling rate in a heart rate-independent manner, (rpartial=0.89, p<0.001).

Conclusion. Persistent TSH suppression in LT4-treated Graves’ disease patients promotes pressure dependent renin secretion, and modulates resting early LV diastolic relaxation. It is also associated with exaggerated exercise systolic blood pressure response and decreased ejection fraction response to exercise.

Key words: blood pressure; exercise; hyperthyroidism; radionuclide ventriculography; renin

Overt hyperthyroidism results in a hyperdynamic circulatory state that is readily reversible by rapid restoration of biochemical euthyroidism (1-3). Numerous studies have provided evidence that prompt antithyroid medication and normalization of serum thyrotropin (TSH) levels (3) leads to rapid and complete reversion of related cardiovascular alterations, at least in the case of short term, uncomplicated hyperthyroidism in otherwise healthy subjects (3). However, discontinuation of antithyroid medication is often followed by a recurrence of hyperthyroid state. With the combined therapy, patients receive thyroxine (LT4) in addition to antithyroid drugs to maintain an undetectable TSH levels in order to inhibit the release of thyroid antigens, and thereby, to modify the immune response and Graves’ disease evolution (4). Yet, several well-planned studies failed to show any beneficial effect of the proposed combined treatment (5-7). Such therapy resulted in serum free thyroxine (FT4) values in the upper normal range in one trial (7), which, together with the suppressed TSH, were consistent with the definition of subclinical hyperthyroidism. Indeed, side effects compatible with persistent, symptomatic hyperthyroidism were reported in two studies following rigorous attempts to suppress TSH (6,7). Others have reported an increased risk of disease recurrence in patients with undetectable serum TSH at the time of antithyroid drug withdrawal (5). This suggests that either non suppressible thyroid hormone synthesis or paracrine effects of TSH receptor autoantibodies, rather than prolonged hypothalamo-pituitary axis recovery, were responsible for persistent TSH suppression. Therefore, combined treatment with LT4 in TSH-suppressive doses may result in a unique combination of overt hyperthyroidism followed by exogenous, subclinical hyperthyroidism. Mounting evidence indicate that suppressed TSH is functionally relevant (8-10), even in TSH-suppressed Graves’ disease patients maintained on antithyroid drugs (10). Both subclinical endogenous T4 excess and T4 treatment in doses which suppress TSH to below normal have been associated with ei-
other preserved (11,12) or enhanced left ventricular systolic function (13,14), increased left ventricular mass index (11-14) and impaired left ventricular diastolic function (13-15). Nevertheless, we are currently unaware of any study exploring potential effects of persistent TSH suppression on cardiovascular functional recovery after overt hyperthyroidism. The purpose of this study was to investigate whether cardiovascular performance is still altered in LT4-treated TSH-suppressed Graves’ disease patients even after the normalization of FT4 and free triiodothyronine (FT3).

**Patients and Methods**

**Patients**

The study included 15 previously untreated premenopausal female outpatients with overt hyperthyroidism due to Graves’ disease, selected from the Department of Nuclear Medicine and Radiation Protection, Osijek University Hospital, Croatia within one year. None of the patients had a previous history of arrhythmia, conduction disturbances, hypertension, coronary or valvular heart disease, pulmonary, neuromuscular, or endocrine disorders. Graves’ disease was defined by biochemical hyperthyroidism, diffuse goiter, homogenous Tc-99m pertechnetate scan distribution, elevated 24 h radioiodine uptake, signs of ophthalmopathy, and the presence of either positive thyroid peroxidase autoantibodies or TSH receptor autoantibodies in serum. None of the patients used any cardiovascular medication.

The control group consisted of 12 healthy euthyroid female age-matched volunteers comparable in body habitus and habitual physical activity. All subjects in both groups had sedentary lifestyle. Written informed consent was obtained from all participants prior to the study. The investigation was approved by the hospital’s ethical committee.

**Therapy**

Initially, all patients were treated with 60 mg of methimazole (Favistan, Asta Medica AG, Frankfurt/Main, Germany) and 120 mg of propranolol (Propranolol, Lek, Ljubljana, Slovenia) daily for 1 month. After 1 month, thyroid function was controlled to adjust antithyroid medication. Thereafter, patients were seen at intervals of 4-6 weeks throughout the study. After the restoration of biochemical euthyroidism, as judged by circulating FT4 and FT3 concentrations, L-thyroxine (Euthyrox, Merck KGaA, Darmstadt, Germany) was added at an initial dose of 100 μg daily which methimazole dose was gradually reduced and adjusted to maintenance levels (5-10 μg). The dose of LT4 was adjusted after 1 month to doses ranging from 100-125 mg daily to achieve serum TSH concentrations below 0.3 μIU/mL. Propranolol dose was tapered off within the first 6 months of treatment. Both patients and controls underwent an exercise test and a radionuclide ventriculography study. The patients with serum TSH levels below normal (n = 11) were reassessed after at least 8 (median 10, interquartile range 7) months of stable euthyroidism.

Exclusion criteria were as follows: failure to comply with the regimen (1 patient), inability to achieve target FT4, FT3, and TSH levels (2 patients), and toxic reactions to methimazole (1 patient). The scheme of the study is given in Figure 1.

**Cardiological Data**

Left ventricular studies were performed at rest and during exercise using electrocardiographically (ECG)-gated equilibrium radionuclide ventriculography with the large field-of-view gamma camera (Siemens ZLC 37, Siemens, Erlangen, Germany) interfaced to ADAC 3300 computer system (ADAC Laboratories, Milpitas, CA, USA) equipped with a parallel-hole low-energy all-purpose collimator in the modified best septal left anterior oblique (30°-45°) view with 10° caudal tilt.

Data were acquired in 64×64×8 pixel format with 32 frames per heart cycle for 8-10 min at rest and for 3 min during peak stage of moderate exercise workload. Cardiac cycles that fell outside a 10% range of the average RR interval were rejected.

**Figure 1.** Scheme of the study.

by the computer program. This resulted in adequate quality scintigrams.

All patients received 1 g of Na-perchlorate (Irenat, Dr Kolassa + Merz GmbH, Wien, Austria) perorally 30 minutes before the injection of radioactive tracer. The blood pool was rendered radioactive after IV injection of 740 MBq of Tc-99m human serum albumin obtained after the reconstitution of commercially available kit (Technescan, HSA, Mallinckrodt Med., Petten, Holland) according to the manufacturer’s instructions. Labeling efficiency was determined by thin-layer chromatography (Whatman 1 chromatographic paper, methanol/water 80/20 as mobile phase) and exceeded 95% in all preparations.

Subjects were placed in supine position after cubital vein was cannulated and allowed to rest for at least 30 minutes or until no further change of resting blood pressure and heart rate was observed in two subsequent readings.

Immediately after resting study, continuous, graded, mild to moderate physical exercise was performed using a bicycle ergometer with the initial workload of 50 W for the first 3 minutes, and increasing to 75 W for the next 6 minutes. Data acquisition was done during the last 3 minutes of the peak stage. ECG was continuously monitored and blood pressure was measured every 3 minutes at rest, during and after the exercise in standardized fashion by specifically trained personnel until both systolic blood pressure and heart rate reached basal values. All patients and controls successfully completed the protocol. Neither adverse cardiovascular reactions nor ischemic response to the exercise were observed in any patient or control subject.

The data were processed by a single, experienced observer according to the previously published methods (16). Briefly, the indexes of left ventricular systolic function-peak ejection rate, time-to peak ejection rate, left ventricular diastolic function-early peak filling rate, and time-to-peak filling rate were derived by semiautomatic computer analysis of background-corrected time activity curves at rest and during the exercise allowing the operator to intervene if necessary. Peak ejection and peak filling rates were normalized to end-diastolic volume. Ejection fraction (EF) determinations were performed according to the standard count-based method of analysis.

Mean arterial pressure (MAP) was determined using the formula: MAP = (2xdiastolic blood pressure + systolic blood pressure)/3.

ΔEF was calculated as ΔEF = exercise EF – resting EF. ΔEF > 5% was considered normal (17).
Hormonal Data

Food and salt intake were generally not restricted, but eating and drinking was prohibited on the day of the examination until testing was complete. The examinations started between 7:30-8:00 am after overnight fasting.

Blood samples were taken from the cubital vein immediately before the injection of the radioactive tracer, placed on ice, and followed by an immediate centrifugation. Aliquots of plasma samples were stored at -70°C and assayed for plasma aldosterone and plasma renin activity.

Plasma FT4, FT3, TSH, aldosterone, and plasma renin activity were determined by commercial radioimmunoassay kits (Amerlite FT4 Assay, Amersham Int plc., Amersham, UK; FT3- and TSH-Serozyme, both from Serono Diagnostic SA, Cointrins, Switzerland; ALDOCTK-2, and RENCTK, both from Sorin Biomedica, Saluggia, Italy, respectively) according to the manufacturer’s instructions. The normal range was 10-25 pmol/L for FT4; 0.3-4.5 pmol/L for FT3; 0.2-2.8 ng angiotensin 1 (AI)/mL/h for plasma renin activity (supine); and 42-416 nmol/mL for aldosterone (supine).

TSH receptor autoantibodies were determined by radioimmunoassay (Thybia Assay, Byk Gulden, Milan, Italy); values >15% were considered positive.

Thyrotropin-releasing hormone (TRH) test was performed by IV injection of 200 µg of TSH-releasing hormone (Relefact TRH, Aventis Pharma, Frankfurt/Main, Germany) between 8 and 12:00 am. Basal and 20 minutes post-TRH serum samples were obtained for TSH measurements; FT4 and FT3 were determined from basal sera. In order to avoid the influence of TRH-related hemodynamic alterations (18) on data acquisition and interpretation, radionuclide ventriculography was performed between 24-48 hours after TRH test.

The assay sensitivities were 0.5 pmol/L for FT4, 0.03 pmol/L for FT3, 0.03 µU/mL for TSH, 0.13 ng/mL for renin, and 42 nmol/mL for aldosterone.

The interassay coefficients of variations were 5.9-6.4% for FT4; 4.2-7.5% for FT3; 4.2-8.6% for TSH; 6.6-17.7% for aldosterone, and 7.7-11.5% for plasma renin activity across the ranges measured.

Statistical Analysis

Data are expressed as medians and interquartile ranges if not stated otherwise. The unpaired data were analyzed with the Mann-Whitney U-test. Patients’ data obtained before and after the treatment were compared by the Wilcoxon signed-rank test. All tests were two-tailed. Significance was accepted at p<0.05.

Table 1. Hormonal tests and anthropometric data (median, interquartile range) in control subjects and patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hyperthyroid patients (n = 11)</th>
<th>Controls (n = 12)</th>
<th>p1</th>
<th>p2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35 (6)</td>
<td>34 (8)</td>
<td>ND</td>
<td>0.235</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58 (11)</td>
<td>65 (14)</td>
<td>65 (16)</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 (10)</td>
<td>163 (9)</td>
<td>ND</td>
<td>0.733</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>78.1 (21.2)</td>
<td>21.5 (6.9)</td>
<td>18.1 (3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT3 (pmol/L)</td>
<td>26.1 (14.9)</td>
<td>5.54 (1.14)</td>
<td>6.2 (1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRA (ng/mL/h)</td>
<td>2.17 (2.69)</td>
<td>0.89 (0.82)</td>
<td>0.79 (0.93)</td>
<td>0.002</td>
</tr>
<tr>
<td>Aldosterone (pmol/L)</td>
<td>377 (364.4)</td>
<td>244.5 (324.7)</td>
<td>224.1 (75)</td>
<td>0.116</td>
</tr>
<tr>
<td>TSH (µU/mL)</td>
<td>&lt;0.03</td>
<td>0.03 (0.15)</td>
<td>1.45 (1.06)</td>
<td>0.068</td>
</tr>
</tbody>
</table>

*Abbreviations: FT4 – free thyroxine; FT3 – free triiodothyronine; PRA – resting supine plasma renin activity; TSH – thyrotropin; ND – not done.

†Hyperthyroid patients before vs after treatment, Wilcoxon signed-rank test.

‡Hyperthyroid patients after treatment vs controls, Mann-Whitney U-test.

Results

Thyroid Function Tests and Hormonal Data

Serum TSH concentrations were undetectable in all patients before treatment. FT4 values after treatment were within the normal range, but higher in the TSH-suppressed group than in controls. Serum FT3 concentrations, resting plasma renin activity, and aldosterone did not differ from controls following the treatment. Body weight increased significantly in treated patients. Detailed anthropometric and hormonal data are given in Table 1.

Serum TSH values were below the limit of assay sensitivity (<0.03 µU/mL) in 7 patients receiving LT4, while the remainder of the group had detectable serum TSH concentrations below the normal range (in two patients <0.1 µU/mL, and in another two patients 0.1-0.3 µU/mL).

Consistent with the previous report, most (6/7) LT4-treated patients with undetectable basal TSH levels had detectable TRH responses. In addition, absolute TRH response (median 0.33, interquartile range 1.5 µU/mL) agreed well with the previously published results (19). Absolute TRH response correlated significantly with basal TSH (r=0.921, p<0.001) and FT4 (r=-0.645, p=0.032). Resting plasma renin activity correlated strongly to resting plasma aldosterone (r=0.809, p=0.003). Neither serum TSH response, FT4, nor FT3 correlated with TSH receptor autoantibodies (p=0.78, p=0.27, p=0.21, respectively).

Cardiological Data

Standard ECG was considered normal in all patients and controls except for sinus tachycardia in overtly hyperthyroid patients.

In untreated patients, both resting heart rate and heart rate during the peak stage of exercise workload were significantly higher than in controls or euthyroid patients. Systolic blood pressure at rest and during exercise was markedly increased in overt hyperthyroidism, whereas diastolic blood pressure at rest was comparable among groups.

Treatment of hyperthyroidism resulted in decrease in resting systolic blood pressure, resting left ventricular ejection fraction, resting and exercise peak ejection rates, and peak filling rates to values comparable to controls (Table 2). No segmental wall motion abnormalities were observed in any ventriculographic study.

Post-treatment peak exercise systolic blood pressure remained similar to pretreatment values and was significantly higher when compared to controls (Table 3). Three minutes post-exercise heart rate was markedly higher in treated patients and significantly more time was required for recovery of heart rate to basal values (Table 4). Significant correlations were found between the time to heart rate recovery and duration of treatment (r=-0.766, p=0.006) and between resting diastolic blood pressure and resting plasma
renin activity \((r=0.84, p<0.001, \text{Figure 2})\). Logarithmically transformed TRH-stimulated TSH response correlated with resting diastolic blood pressure \((r=0.795, p<0.003)\) and resting peak filling rate \((r=0.802, p<0.003, \text{Fig. 3})\).

An adequate increase in exercise EF was observed in the three groups. However, exercise ejection fraction and \(\Delta\text{EF}\) were significantly higher in the control group than in the post-treatment patient group.

Exercise ejection fraction was inversely related to exercise diastolic blood pressure \((r=0.818, p<0.002)\) and exercise MAP \((r=0.788, p<0.007)\). Exercise systolic blood pressure correlated with exercise time to peak filling rate \((r=0.74, p<0.009)\) in a heart rate-independent manner \((r _{\text{partial}}=0.89, p<0.001)\).

### Discussion

The principal findings of the present study are that TSH suppression in LT4-treated Graves’ disease patients elicits an exaggerated systolic blood pressure response to exercise, adversely attenuates left ventricular exercise ejection performance, modifies resting left ventricular early diastolic filling rates and leads to blood pressure-dependent stimulation of renin secretion.

In conceptual agreement with our present results, several previous studies have reported a strong correlation between TSH levels and diastolic blood pressure \((20)\) or systemic vascular resistance, \((8)\) both in endogenous subclinical hyperthyroidism and during thyroxine replacement therapy. Indeed, the expression of thyroid hormone receptors and pituitary-type 5'-deiodinase II \((21)\), which plays a crucial role in the regulation of TSH secretion \((22)\) and converts T4 to local T3, was recently reported in human vascular muscle cells. This supports the hypothesis that locally generated, i.e., ambient T3, rather than circulating FT3 levels, might considerably affect vascular resistance in conditions of mild T4 excess. Thus, it appears that vascular reactivity is at least comparable to hypothalamo-pituitary axis sensitivity to changes in TSH and TSH-related feedback mechanisms.

### Table 2. Blood pressure indices and radionuclide ventriculography data (median, interquartile range) at rest

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Hyperthyroid patients ((n=11))</th>
<th>Controls ((n=12))</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>143 (14)</td>
<td>128 (15)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80 (15)</td>
<td>80 (11)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>100.3 (10.4)</td>
<td>95.6 (8.4)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>115 (25)</td>
<td>71 (13)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>6.7 (10)</td>
<td>60 (9)</td>
</tr>
<tr>
<td>PER (EDV/s)</td>
<td>-4.20 (1.16)</td>
<td>-3.18 (0.99)</td>
</tr>
<tr>
<td>TPER (s)</td>
<td>0.08 (0.03)</td>
<td>0.12 (0.18)</td>
</tr>
<tr>
<td>PFR (EDV/s)</td>
<td>3.74 (1.84)</td>
<td>2.76 (0.80)</td>
</tr>
</tbody>
</table>

*Abbreviations: SBP – systolic blood pressure; DBP – diastolic blood pressure; MAP – mean arterial pressure; HR – heart rate; EF – left ventricular ejection fraction; PER – left ventricular peak ejection rate; EDV – end-diastolic volume; TPER – time to PER; PFR – left ventricular early diastolic peak filling rate; TPER – time to PFR.

### Table 3. Comparison of exercise blood pressures and left ventricular hemodynamic data (median, interquartile range) at peak stage

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Hyperthyroid patients ((n=11))</th>
<th>Controls ((n=12))</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>188 (34)</td>
<td>175 (25)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>82 (21)</td>
<td>97 (17)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>111.3 (28)</td>
<td>126.2 (22.3)</td>
</tr>
<tr>
<td>HRmax (beats/min)</td>
<td>164 (24)</td>
<td>147 (22)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>74 (13)</td>
<td>66 (9)</td>
</tr>
<tr>
<td>(\Delta\text{EF}) (%)</td>
<td>7 (5)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>PER (EDV/s)</td>
<td>-5.55 (1.94)</td>
<td>-4.23 (3.22)</td>
</tr>
<tr>
<td>TPER (s)</td>
<td>0.08 (0.03)</td>
<td>0.09 (0.02)</td>
</tr>
<tr>
<td>PFR (EDV/s)</td>
<td>6.23 (2.44)</td>
<td>4.1 (1.21)</td>
</tr>
<tr>
<td>TPER (s)</td>
<td>0.09 (0.03)</td>
<td>0.11 (0.06)</td>
</tr>
</tbody>
</table>

*Abbreviations: SBP – systolic blood pressure; DBP – diastolic blood pressure; MAP – mean arterial pressure; HRmax – maximal heart rate; EF – left ventricular ejection fraction; PER – left ventricular peak ejection rate; EDV – end-diastolic volume; TPER – time to PER; PFR – left ventricular early diastolic peak filling rate; TPER – time to PFR.

### Table 4. Three-minute post-exercise recovery data (median, interquartile range): comparison of blood pressures and heart rates in control subjects and patients before and during the treatment

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Hyperthyroid patients ((n=11))</th>
<th>Controls ((n=12))</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>136 (15)</td>
<td>136 (14)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75 (13)</td>
<td>75 (20)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>130 (21)</td>
<td>107 (26)</td>
</tr>
<tr>
<td>Time to HR recovery (min)</td>
<td>12 (7)</td>
<td>18 (9)</td>
</tr>
</tbody>
</table>

*Abbreviations: SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate.

1[^1]: Hyperthyroid patients before vs after treatment, Wilcoxon signed rank test.
2[^2]: Hyperthyroid patients before vs after treatment, Mann-Whitney U-test.
3[^3]: Hyperthyroid patients after treatment vs controls, Mann-Whitney U-test.
local T4/T3 ratios. Alternatively, TSH receptor auto-
antibodies, previously shown to directly suppress
TSH independently of thyroid hormone levels via
binding to pituitary TSH receptors (23), might also tar-
get cardiac (24) and vascular cells (25), as previously
argued for osteoblasts (10). Nevertheless, when thy-
roid status is stable, the pituitary is most sensitive to
ambient FT4 (26). Indeed, stimulated TSH levels in
our patients were concordant with the peripheral FT4,
but not TSH receptor autoantibodies levels, indicat-
ing that TSH suppression, and particularly blunted
TRH test response, reflected stable pituitary ambient
T4 excess rather than paracrine TSH receptor auto-
antibodies effects or delayed hypothalamo-pituitary
axis recovery. However, simultaneously, TSH recep-
tor autoantibody-mediated vascular alterations mask-
ed by prevailing effects of T4 excess could not be
ruled out.

Consistently with the predicted existence of re-
nal baroreceptor mechanism (27), an increase in
renin release secondary to hormone-dependent de-
crease in arterial pressure, together with permissive
effects of local T3 excess generated by trapping of circu-
laratory FT3 (28) and local conversion of T4 to T3 by
renal parenchymal type I 5'-deiodinase (29) on renin
synthesis (30), may stimulate renin-angiotensin sys-
tem (RAS). This is not a minor issue since RAS can
promote cardiac growth in both load-dependent (31)
and independent manner (32), alter pressure-natriu-
resis response (33), and play a role in the develop-
ment of hypertension (34) even in hyperthyroidism
(34,35). Nevertheless, the exact pathogenetic role of
RAS in subclinical hyperthyroidism remains poorly
defined.

Both exogenous and endogenous subclinical
hyperthyroidism may induce cardiac dysfunction
(36). In particular, diastolic dysfunction associated
with increased left ventricular mass index received
most attention (11-13,15). Notably, at variance with
our model, most of the studies focused on patients
with undetectable basal TSH levels. Here, post-treat-
ment systolic and diastolic performances were appar-
ently not different from controls at rest. Even so, left
ventricular early diastolic peak filling rates in treated
patients correlated with TRH-stimulated TSH levels.
Taken together with the previous findings, such rela-
tion indicates that there might be a continuum in the
progressive appearance of diastolic abnormalities re-
sulting in larger clinical impact with greater magni-
tude and longer duration of T4 excess. Accordingly,
decreased diastolic peak filling rates were reported by
Biondi et al (37) using a similar approach in a study
restricted exclusively to patients with undetectable
TSH levels.

Although the precise mechanisms explaining the
association of decline in left ventricular peak filling
rates with the suppression of TRH response remain to
be established, structural (11) and hemodynamic fac-
tors (37) are known to affect diastolic function in
subclinical hyperthyroidism under resting conditions.
Left ventricular hypertrophy is associated with T4 ex-
cess as well as with diastolic dysfunction (11-13,15).
Even more, a linear correlation between FT3 and left
ventricular mass over the wide range of normal and
increased FT3 values has been described (38). Never-
theless, despite its proven usefulness and reproduc-
ibility (39,40) in studying thyroid dysfunction-related
cardiovascular alterations (37,39), radionuclide ven-
triculography permits only an indirect estimate of the
diastolic function. Therefore, caution should be taken
when the pathophysiological origins of our results are
interpreted in the absence of echocardiographic data,
which could provide additional important informa-
tion, particularly concerning the changes in cardiac
mass and geometry reported with antithyroid drugs
(11). Prior reports have shown that β-adrenergic re-
cptor blocking agents used here improved diastolic
function in subclinical hyperthyroidism (37,41). This,
together with relatively brief-time TSH suppression

![Figure 2. Influence of resting supine diastolic blood pressure (BP) on resting supine plasma renin activity (PRA) in treated patients (n=11, Spearmann’s rank correlation test).](image)

![Figure 3. Correlation between log-transformed TRH-stimulated TSH response and resting left ventricular early diastolic peak filling rate in treated patients (n=11, Spearmann’s rank correlation test).](image)
might help to explain an overall normal diastolic performance in our patients (41).

An increase in cardiac mass, often associated with subclinical hyperthyroidism is principally the consequence of the chronic increase in cardiac workload (15). However, many, but not all (42) previous studies failed to detect any difference in resting blood pressure irrespectively of the method used (36). More importantly, at comparable workload, patients with exogenous subclinical hyperthyroidism had higher exercise systolic blood pressure (37) and exercise heart rate (12,37) than controls. In accordance with that, our present results demonstrate an exaggerated systolic blood pressure response to heart rate during exercise (43) and delayed post-exercise heart rate recovery in treated patients. Surprisingly, although the pathogenetic and prognostic significance of an excess elevation in blood pressure during exercise is recognized by several authors (43-46), comparable findings in subclinical hyperthyroidism received only limited attention so far. Nevertheless, it should be stressed that these changes, despite persistent TSH suppression, may not be sustained in the long term, (47) as indicated by time-dependent disappearance of positive post-exercise chronotropic effects observed in our study.

In a normal heart, elevating systolic blood pressure may induce afterload mismatch, thus slowing left ventricular relaxation and reducing the extent of ejection independently of intrinsic changes in contractility (48,49). Furthermore, the amount of slowing appears to be related to systolic cardiac function (48-50). Consistently, we found that exercise blood pressure indices inversely correlated with left ventricular systolic performance. In addition, exaggerated systolic blood pressure response and post-treatment left ventricular time to peak filling rate were strongly correlated in a heart rate-independent manner. Thus, the degree to which the amount of ejection was reduced was related to exercise MAP, compatibly with the concept of exercise-induced afterload mismatch or alternatively, developing hypertrophy in which load exceeds output (51). Consequently, TSH-suppressed patients, as previously reported (37), exhibited persistently limited ejection fraction response to exercise, comparably to older and severely hypertrophic subjects (3). Nevertheless, it should be emphasized that our data, due to the complexity of systolic-diastolic interactions, and steady-state neurohumoral adaptive mechanisms cannot specifically distinguish afterload excess with normal left ventricular contractility versus an impaired afterload reserve (48,49).

In conclusion, within the limitations of a small study sample, our preliminary results suggest that TSH suppression in LT4-treated Graves’ disease patients may cause modifications in cardiovascular performance, primarily during physical activity, as well as RAS stimulation. The data may provide important information about a risk factor profile in this particular group of patients. Additional, well planned studies are necessary to better define potential physiologic and clinical relevance of our results.

Acknowledgements

We thank Dr L. Zábar for critical reading of the article and Prof B. Krestošoč for valuable technical assistance during the preparation of the manuscript.

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Received: August 6, 2004
Accepted: November 3, 2004

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