

Impaired functional and hemodynamic response to graded exercise testing and its recovery in patients with subclinical hyperthyroidism

Capacidade funcional e hemodinâmica em esforço e na recuperação de pacientes com hipertireoidismo subclínico

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ABSTRACT

Objective: To evaluate the functional and hemodynamic responses during exercise and its recovery in patients with subclinical hyperthyroidism (SCH). **Subjects and methods:** A cross-sectional study was carried out with 29 patients on TSH-suppressive therapy with levothyroxine for thyroid carcinoma and 35 euthyroid subjects. All volunteers underwent a cardiopulmonary exercise testing on a treadmill and functional and hemodynamic variables were measured during exercise and its recovery. **Results:** SCH patients showed impaired functional response to exercise, marked by lower values for oxygen consumption and exercise duration in addition to premature achievement of the anaerobic threshold. Heart-rate and blood pressure recovery immediately after exercise were slower among SCH patients when compared to euthyroid subjects. **Conclusion:** SCH is associated with impaired functional and hemodynamic responses during exercise and its recovery. *Arq Bras Endocrinol Metab.* 2011;55(3):203-12

Keywords

Hyperthyroidism; oxygen consumption; heart-rate; blood pressure

RESUMO

Objetivo: Avaliar a capacidade funcional e hemodinâmica em esforço e durante a recuperação em pacientes com hipertireoidismo subclínico (SCH). **Sujeitos e métodos:** Foi realizado um estudo seccional em que participaram 29 pacientes em terapia supressiva de TSH com levotiroxina para carcinoma diferenciado de tireoide e 35 indivíduos sem doença tireoidiana. Todos foram submetidos a um teste cardiopulmonar de esforço em esteira, no qual foram medidas variáveis funcionais e hemodinâmicas durante o exercício e a recuperação. **Resultados:** Os pacientes apresentaram um comprometimento na capacidade funcional, evidenciado por menores valores de consumo de oxigênio e duração de exercício, além do alcance prematuro do limiar anaeróbico. Imediatamente após o exercício, os pacientes apresentaram uma curva mais lenta de recuperação da frequência cardíaca e da pressão arterial. **Conclusão:** O SCH está associado ao comprometimento na capacidade funcional e hemodinâmica em esforço e na recuperação. *Arq Bras Endocrinol Metab.* 2011;55(3):203-12

Descritores

Hipertireoidismo; consumo de oxigênio; frequência cardíaca; pressão arterial

INTRODUCTION

Differentiated thyroid carcinoma is relatively rare in the general population, accounting for 1% of all

cancers. It has an excellent prognosis, with long-term survival rates of 90%-95% (1). As part of the treatment, TSH-suppressive therapy with levothyroxine (LT₄) is

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Received on Oct/19/2010
 Accepted on Feb/18/2011

recommended in order to minimize the risk of disease recurrence (2). This kind of therapy accounts for the majority of subclinical hyperthyroidism (SCH) cases in the general population. SCH is characterized by a serum thyrotropin (TSH) level below the lower limit of the reference range with normal free thyroxine (FT₄) and tri-iodothyronine (T₃) levels (3).

Recent studies have shown that SCH has adverse effects on the cardiovascular system similar to those found in overt hyperthyroidism (4). The most common functional cardiac alterations include decreased diastolic function, enhanced left ventricular mass, elevated heart rate (HR), and decreased exercise performance (5,6). In addition, SCH is related to autonomic imbalance characterized by attenuated vagal activity and increased sympathetic activity (7,8). All those manifestations, however, seem to be less severe in SCH patients when compared to those with overt hyperthyroidism (9).

Cardiopulmonary exercise testing (CPET) is a noninvasive and a cost-effective method that adds gas exchange measurements to an electrocardiogram and blood pressure analysis, conventionally assessed in ergometric tests. It evaluates the interaction between the cardiovascular system (heart and systemic circulation), pulmonary system (lungs and pulmonary circulation), and contractile muscles during exercise (10). Through measurements of expired fractions of oxygen and carbon dioxide, and ventilation flow during exercise, it is possible to evaluate the functional capacity, which is an important predictor of cardiovascular disease (11). The major advantage of the CPET is related to the fact that it is a direct measurement of functional capacity, in contrast to the conventional ergometric test which may overestimate functional capacity in about 20% (12).

Heart-rate (HR) response to exercise and its recovery is a complex physiologic process controlled by the autonomic nervous system (ANS). The increase in HR during exercise is due to activation of the sympathetic nervous system and inhibition of vagus nerve activity, while parasympathetic reactivation is related to HR recovery. An attenuated HR response to exercise, also called chronotropic incompetence, and a slow HR recovery after exercise reflect impairment of the ANS (13,14). A study conducted in a large cohort of asymptomatic men revealed that those with a slower decrease in HR had a 2.1 times increased risk of sudden death from myocardial infarction in relation to the reference group. Also, the relative risk of sudden death from

myocardial infarction was 6.18 in subjects with lower increase in HR from rest to peak of exercise (15).

In this scenario, it is evident that poor exercise tolerance (functional capacity), elevated resting heart-rate (HR), and inadequate HR and blood pressure responses to both exercise and its recovery contribute to an increased cardiovascular risk and all-cause mortality (11,13,14).

Although functional and hemodynamic responses to exercise and its recovery have been studied in a variety of diseases, specially the cardiovascular diseases, regarding SCH patients, these two issues have not been evaluated together, so far. Thus, the aim of this study was to evaluate functional capacity and hemodynamic response during and immediately after cardiopulmonary exercise testing in patients with SCH on TSH-suppressive therapy with LT₄ for differentiated thyroid carcinoma.

SUBJECTS AND METHODS

Study and sample

A cross-sectional study was conducted in 29 SCH patients (2 males) on TSH-suppressive therapy with LT₄ for differentiated thyroid carcinoma for at least six months (with stable subclinical hyperthyroidism) prior to the beginning of the study. All volunteers were recruited from the Endocrine Clinic of the Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Brazil. SCH was defined as TSH levels < 0.4 μU/mL and FT₄ between 0.8 and 1.9 ng/dL. The inclusion criteria adopted for SCH patients were the following: age ≥ 18 years, TSH serum levels < 0.4 mU/L (Immulite-DPC, Los Angeles, CA), FT₄ serum levels between 0.8 and 1.9 ng/dL (Immulite-DPC, Los Angeles, CA), T₃ serum levels between 86.0 and 187.0 ng/dL (Immulite-DPC, Los Angeles, CA), absence of functioning thyroid tissue, and sedentary lifestyle for at least six months before the study. Active lifestyle was defined as the practice of aerobic physical activity for at least 30 minutes on five or more days a week or vigorous-intensity aerobic physical activity for at least 20 minutes on three or more days a week (16). The exclusion criteria were: positive whole body radioiodine scan, detectable serum thyroglobulin, overt hyperthyroidism, current smoker, cardiovascular or any chronic disease (even if treated), muscle and joint impairments that could limit the performance of the car-

cardiopulmonary exercise testing, and use of medications that could affect the ANS.

A control group comprised of 35 euthyroid subjects (5 males) > 18 years-old with TSH and FT₄ serum levels within the reference range and no history of thyroid disease was also evaluated for the same parameters considered in the study. The same exclusion and inclusion criteria were adopted for this group, except for thyroid status.

In order to verify the impact of suppressive LT₄ therapy, even in mildly suppressed patients, a subanalysis of SCH patients according to the last serum TSH measurement was performed: group 1 = TSH < 0.1 µUI/mL (n = 17) and group 2 = TSH ≥ 0.1 µUI/mL (n = 12). The local Ethics Committee approved the study and written informed consent was obtained from SCH patients and euthyroid subjects.

Study protocol

SCH patients and euthyroid subjects underwent clinical evaluation with an endocrinologist. A structured review was conducted to gather data on thyroid disease history, symptoms, medication, coronary risk factors, health-related behaviors, and other clinical diagnoses. Serum TSH and FT₄ were measured by immunometric assay (Immulite-DPC, Los Angeles, CA), with respective reference ranges of 0.4 – 4.0 µUI/mL (sensitivity of 0.002 µUI/mL) and 0.8-1.9 ng/dL (sensitivity of 0.15 ng/dL). In addition to the last serum TSH and FT₄ measurements, which were considered in most statistical analysis, we also evaluated serum TSH over the last six months. After the written informed consent was obtained, SCH patients and euthyroid subjects were submitted to cardiopulmonary exercise testing at the Physical Education School of the same University.

Cardiopulmonary exercise testing

SCH patients and euthyroid subjects were submitted to cardiopulmonary exercise testing on a treadmill (constant velocity of 4.8 km/h at a 3% grade increment during every 2 minutes) (17).

Electrocardiograms were continuously monitored at rest, during exercise, and during the first five minutes of exercise recovery. Blood pressure was checked at rest, every three minutes during the test, and in the first, third and fifth minutes of exercise recovery (mercury sphygmomanometer; Narcosul 1400-C). The following hemodynamic parameters were analyzed: a) *At*

rest: heart-rate (HR_{rest} ; bpm), systolic blood pressure (SBP_{rest} ; mmHg), and diastolic blood pressure (DBP_{rest} ; mmHg); b) *During exercise*: peak heart-rate (HR_{peak} ; bpm); peak systolic blood pressure (SBP_{peak} ; mmHg); peak diastolic blood pressure (DBP_{peak} ; mmHg); rate-pressure product ($RPP = HR \times SBP$; bpm.mmHg), and median difference from exercise peak to resting for HR, SPB and DBP ($\Delta HR_{peak-rest}$; $\Delta SBP_{peak-rest}$, and $\Delta DBP_{peak-rest}$, respectively). Chronotropic incompetence was assessed in two ways: failure to achieve 85% of the target HR ($220 - age$) and failure to achieve ≥ 80% of the HR reserve ($CI = (HR_{peak} - HR_{rest}) / ((220 - age) - HR_{rest}) \times 100$). These last data were also called chronotropic index (18); c) *Recovery immediately after exercise*: HR in the first five minutes, median difference from HR_{peak} for every minute of recovery (a first-minute HR recovery < 12 bpm was considered abnormal) (19), SBP and DBP in the first, third and fifth minutes, and the median difference from SBP_{peak} and DBP_{peak} to the first, third and fifth minutes of recovery. SCH patients and euthyroid subjects performed an active recovery (velocity = 3.0 km/h at a 0% grade).

Respiratory gas exchange was sampled from a mouthpiece connected to a medium flow meter and a gas analyzer (Medical Graphics; VO2000). Ventilation flow, oxygen, and carbon dioxide expired fractions were measured breath-by-breath and recorded as the mean of three incursions. Before each test, the system was calibrated using a known fixed concentration of standard gases. The following parameters were considered at exercise peak: relative oxygen consumption ($\dot{V}O_{2peak}$; defined as the highest value of $\dot{V}O_2$ achieved at the end of exercise; mL/kg.min; STPD); relative carbon dioxide production ($\dot{V}CO_{2peak}$; mL/kg.min; STPD); minute ventilation ($\dot{V}E_{peak}$; L/min; STPD); expired fraction of O₂ and CO₂ (Fe_{O_2peak} and Fe_{CO_2peak} ; %, respectively); oxygen pulse ($\dot{V}O_2 / HR$; mL/bpm), and gas exchange ratio ($R = \dot{V}CO_2 / \dot{V}O_2$). Exercise workload was analyzed considering total exercise duration in minutes (min:s) and the stage of the protocol (km/h and %). Anaerobic threshold (AT) was determined by analyzing the graph of ventilation equivalent for oxygen ($\dot{V}E_{O_2} = \dot{V}E / \dot{V}O_2$) vs. carbon dioxide ($\dot{V}E_{CO_2} = \dot{V}E / \dot{V}CO_2$) plotted during the exercise testing (20). AT is the point in which the $\dot{V}E / \dot{V}O_2$ graphic curve increases without a concomitant increase in $\dot{V}E / \dot{V}CO_2$ (21).

The level of physical exertion during exercise was assessed using the Borg Exertion Perceived Scale, ran-

ging from 6 (very easy) to 20 (maximum effort). SCH patients and euthyroid subjects were encouraged to reach symptom-limited maximal exercise.

The test was considered as maximal when one or more of the following parameters were obtained: Borg Exertion Perceived Scale ≥ 18 , a plateau of oxygen ($\dot{V}O_{2\max}$), $R \geq 1.1$ and/ or maximum heart-rate. It is important to give evidence that the attainment of one or more of these parameters was not a criteria for test interruption. Test interruption criteria were: pectoris angina, SBP > 220 mmHg, DBP > 115 mmHg, dizziness, electrocardiogram signal alterations or physical manifestations of extreme fatigue.

All cardiopulmonary exercise testing measures were made by the same skilled professional, in a non-blinded manner in relation to thyroid status, but blinded concerning to TSH suppression level.

Statistical analysis

Continuous variables are presented as median and 25th and 75th percentiles, while categorical variables are presented as relative frequency, for descriptive analysis.

Distribution of the variables was assessed by the Kolmogorov-Smirnov test. As most of them presented nonparametric distribution and considering sample size, the comparison of continuous variables between SCH patients and euthyroid subjects was made by applying the Mann-Whitney U-test while categorical variables were compared by using Fisher's Exact test. The comparison of continuous variables among SCH patients with TSH < 0.1 $\mu\text{UI/mL}$, SCH patients with TSH ≥ 0.1 $\mu\text{UI/mL}$, and euthyroid subjects was made with the Kruskal-Wallis test and differences between two different subgroups were identified by applying the Mann-Whitney U-test.

Differences were statistically significant at $p < 0.05$ and all analyses were performed using the software SPSS 13.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

General characteristics of SCH patients and euthyroid subjects are shown in table 1. SCH patients and euthyroid subjects were well-matched in respect to age, BMI, gender, and menopause status, which are potential confounding variables and thus, could interfere with the results. Median serum levels of the last TSH and FT₄ measurements were significantly lower and higher, respectively, in SCH patients ($p < 0.05$). The

median disease duration was of 6.0 (4.0 – 10.3) years. Evaluation of the two subgroups of SCH patients according to the grade of serum TSH suppression allows us to confirm that stable SCH occurred in the last six months, because mean serum TSH in that period was of 0.005 (0.009 – 0.08) $\mu\text{UI/mL}$ in the group of patients with last serum TSH measurement < 0.1 $\mu\text{UI/mL}$ and 0.16 (0.12 – 0.40) $\mu\text{UI/mL}$ in the group of patients with last serum TSH measurement ≥ 0.1 $\mu\text{UI/mL}$. Minimum and maximum serum levels of the last FT₄ measurements were, respectively, 1.52 and 1.84 ng/dL in the group of patients with last serum TSH < 0.1 $\mu\text{UI/mL}$ and 1.19 and 1.81 ng/dL in the group of patients with last serum TSH ≥ 0.1 $\mu\text{UI/mL}$.

Cardiopulmonary parameters

SCH patients presented impaired functional capacity characterized by significantly reduced duration of exercise ($p < 0.01$), exercise intensity ($p < 0.01$) and median peak values of $\dot{V}E$ ($p < 0.01$), relative $\dot{V}O_2$ ($p < 0.01$), relative $\dot{V}CO_2$ ($p < 0.01$), and $\dot{V}O_2/HR$ ($p = 0.03$) (Table 2). No differences were found in R , $Fe_{O_2\text{peak}}$ and $Fe_{CO_2\text{peak}}$ between the groups, which means that SCH patients and euthyroid subjects achieved the same level of metabolic stress at the end of exercise. However, as SCH patients presented shorter duration of exercise, the end moment was achieved prematurely in this group.

Euthyroid subjects presented later AT achievement ($p < 0.01$) (Table 2), with higher $\dot{V}O_2$ [EU = 19.4 (16.0 – 24.3) *vs.* SCH = 16.1 (14.6 – 17.6) mL/kg.min; $p < 0.01$], and $\dot{V}CO_2$ [EU = 17.2 (13.8 – 22.4) *vs.* SCH = 14.3 (13.2 – 17.1) mL/kg.min; $p < 0.01$]. The groups achieved AT with the same HR percentage in relation to HR_{peak} [SCH = 88.6 (79.6 – 94.2) *vs.* EU = 85.5 (75.4 – 93.0) %; $p = 0.34$], as well as the same $\dot{V}O_2$ percentage in relation to $\dot{V}O_{2\text{peak}}$ [SCH = 78.3 (71.2 – 88.9) *vs.* EU = 77.7 (70.2 – 88.7) %; $p = 0.71$]. The groups showed similar median values of R when the AT was achieved [SCH = 0.89 (0.82 – 1.00) *vs.* EU = 0.90 (0.84 – 0.99) mL/kg.min; $p = 0.98$].

At peak of exercise, SCH patients and euthyroid subjects both presented the same median score on the Borg Scale (Table 2), indicating decreased exercise tolerance, i.e., premature fatigue in comparison to euthyroid subjects (considering that SCH patients achieved lower exercise intensity and duration).

Table 1. Clinical and hormonal characteristics of SCH patients and euthyroid subjects

Parameter	SCH Patients (n = 29)	SCH Patients TSH < 0.1 (n = 17)	SCH Patients TSH ≥ 0.1 (n = 12)	Euthyroid subjects (n = 35)	p-value [†]	p-value*
Age (years)	48.0 (41.5 – 50.5)	48.0 (46.0 – 52.0)	44.5 (38.0 – 50.8)	47.0 (38.0 – 53.0)	0.95	0.05
BMI (kg/m ²)	26.4 (22.0 – 30.6)	23.0 (22.1 – 29.1)	27.1 (22.2 – 33.2)	26.9 (23.3 – 29.8)	0.57	0.69
Gender (male; %)	6.9	5.9	8.3	14.3	0.44	0.28
Menopause (yes; %)	29.6	35.3	16.6	37.1	0.60	0.68
Disease duration (years)	6.0 (4.0 – 10.3)	6.0 (4.0 – 14.0)	6.5 (3.8 – 9.5)	–	–	0.77
TSH (last) (μUI/mL)	0.09 (0.02 – 0.3)	0.03 (0.02 – 0.08)	0.19 (0.11 – 0.26)	2.1 (1.48 – 2.9)	0.04	< 0.01 [‡]
FT ₄ (ng/dL)	1.7 (1.5 – 1.8)	1.7 (1.7 – 1.8)	1.6 (1.4 – 1.8)	1.2 (1.1 – 1.2)	0.04	< 0.01 [‡]

Results are presented as median (25th and 75th percentiles) for continuous variables and as relative frequency for categorical variables.

[†] Mann-Whitney U-test for numeric variables and Fisher's Exact test for categorical variables; SCH patients vs. euthyroid subjects; statistical significance set at p < 0.05.

* Kruskal-Wallis test for numeric variables and Fisher's Exact test for categorical variables; SCH patients TSH < 0.1 vs. SCH patients TSH ≥ 0.1 vs. euthyroid subjects; statistical significance set at p < 0.05. The differences were identified by the Mann-Whitney U-test.

[‡] Mann-Whitney U-test; SCH patients TSH < 0.1 ≠ SCH patients TSH ≥ 0.1; SCH patients TSH < 0.1 ≠ euthyroid subjects and SCH patients TSH ≥ 0.1 ≠ euthyroid subjects; statistical significance set at p < 0.05.

Table 2. Cardiopulmonary parameters of SCH patients and euthyroid subjects

Parameter	SCH Patients (n = 29)	SCH Patients TSH < 0.1 (n = 17)	SCH Patients TSH ≥ 0.1 (n = 12)	Euthyroid Subjects (n = 35)	p-value [†]	p-value*
$\dot{V}E_{peak}$ (L/min)	33.4 (28.1 – 41.2)	31.8 (25.0 – 40.7)	34.5 (30.3 – 43.6)	46.0 (37.2 – 54.2)	< 0.01	< 0.01 [‡]
$\dot{V}O_{2peak}$ (mL/kg.min)	20.4 (17.6 – 23.9)	19.6 (17.6 – 23.8)	21.0 (16.8 – 24.8)	25.0 (21.2 – 27.7)	< 0.01	< 0.01 [‡]
$\dot{V}CO_{2peak}$ (mL/kg.min)	19.4 (17.2 – 22.9)	18.7 (16.5 – 22.5)	19.3 (17.9 – 22.7)	25.5 (19.4 – 28.7)	< 0.01	< 0.01 [‡]
$\dot{V}O_2/HR_{peak}$ (l.bpm ⁻¹)	8.6 (7.7 – 10.2)	8.0 (6.2 – 9.8)	9.6 (8.3 – 10.4)	9.9 (8.4 – 12.5)	0.03	0.02 [§]
Fe _{O₂peak} (%)	16.5 (16.2 – 17.2)	16.5 (16.3 – 17.2)	16.5 (16.0 – 17.3)	16.8 (16.5 – 17.4)	0.13	0.32
Fe _{CO₂peak} (%)	4.0 (3.4 – 4.2)	4.0 (3.3 – 4.2)	4.0 (3.4 – 4.4)	3.8 (3.3 – 4.0)	0.25	0.48
R _{peak}	0.97 (0.88 – 1.00)	0.95 (0.87 – 1.00)	1.00 (0.89 – 1.00)	0.98 (0.90 – 1.10)	0.30	0.48
AT workload (min:s)	5:46 (3:44 – 7:33)	5:14 (3:57 – 7:18)	5:19 (3:24 – 7:26)	9:11 (7:58 – 10:27)	< 0.01	< 0.01 [‡]
AT exercise intensity (inclination; %)	7.5 (3.0 – 9.0)	6.0 (3.8 – 9.0)	7.5 (3.0 – 9.0)	12.0 (11.3 – 15.0)	< 0.01	< 0.01 [‡]
Total workload (min:s)	11:32 (8:34 – 13:04)	11:32 (9:03 – 13:25)	10:30 (8:00 – 12:36)	14:45 (10:44 – 16:17)	< 0.01	< 0.01 [‡]
Total exercise intensity (inclination; %)	15.0 (12.0 – 18.0)	15.0 (12.0 – 18.0)	15.0 (12.0 – 18.0)	21.0 (15.0 – 24.0)	< 0.01	< 0.01 [‡]
Borg Scale	19.0 (16.0 – 19.0)	19.0 (15.0 – 19.0)	19.0 (17.5 – 19.8)	19.0 (17.0 – 19.0)	0.70	0.25

Results are presented as median (25th and 75th percentiles).

[†] Mann-Whitney U-test; SCH patients vs. euthyroid subjects; statistical significance set at p < 0.05.

* Kruskal-Wallis test; SCH patients TSH < 0.1 vs. SCH patients TSH ≥ 0.1 vs. euthyroid subjects; statistical significance for p < 0.05. The differences were identified by the Mann-Whitney U-test.

[‡] Mann-Whitney U-test; SCH patients TSH < 0.1 ≠ euthyroid subjects and SCH patients TSH ≥ 0.1 ≠ euthyroid subjects; statistical significance set at p < 0.05.

[§] Mann-Whitney U-test; SCH patients TSH < 0.1 ≠ SCH patients TSH ≥ 0.1 and SCH patients TSH < 0.1 ≠ euthyroid subjects; statistical significance set at p < 0.05.

All cardiopulmonary differences between SCH patients and euthyroid subjects were maintained when the groups were compared considering TSH suppression levels (i.e., TSH < 0.1 μUI/mL and TSH ≥ 0.1 μUI/mL), except for $\dot{V}O_2/HR$ [SCH TSH ≥ 0.1 = 9.6 (8.2 – 10.4) vs. EU = 9.9 (8.4 – 12.5) l.min⁻¹; p = 0.34].

Hemodynamic parameters

SCH patients and euthyroid subjects differed in all parameters related to HR (Table 3). The increase in HR from rest to peak of exercise ($DHR_{peak-rest}$) was lower among SCH patients, since they presented higher HR_{rest} (p = 0.04) and lower HR_{peak} (p = 0.01). A total of

31.0% of SCH patients did not reach 85% of the age-predicted maximum HR, 66.7% of which presented with TSH < 0.1 μUI/mL. In euthyroid subjects, the ratio was of 5.7% (p = 0.02). Median chronotropic index in the SCH group was significantly lower [SCH = 0.79 (0.65 – 0.95) vs. ES = 0.92 (0.79 – 1.01); p = 0.03] and under the predicted value (i. e., 0.80), which reflects an attenuated HR response to exercise.

The HR recovery response was slower among SCH patients during the first five minutes immediately after the peak of exercise (Table 3). However, considering TSH suppression levels, no statistical differences were found between SCH patients with TSH ≥ 0.1 μUI/mL and euthyroid subjects in the first three minutes.

At the first minute of recovery, the HR_{peak} of all euthyroid subjects had decreased more than 12 bpm, while 17.2% of SCH patients (four patients of which showed TSH < 0.1 µUI/mL) presented an abnormal HR_{peak} recovery, i.e., less than 12 bpm in the same period.

Concerning blood pressure, no differences were found for both SBP and DBP at rest and at the peak of exercise between the two study groups (Table 4). The increase in SBP and DBP from rest to peak of exercise (SBP_{peak - rest} and DBP_{peak - rest}) was also similar between SCH patients and euthyroid subjects. During the

first, third and fifth minutes of recovery, however, SCH patients presented a slower decrease of both SBP and DBP. Considering TSH suppression levels, no statistical differences were found between SCH patients with TSH ≥ 0.1 µUI/mL, patients with TSH < 0.1 µUI/mL and euthyroid subjects in the first, third and fifth minutes of SBP recovery and in the first and third minutes of DBP recovery (Table 4).

Rate-pressure product (RPP = HR x SBP), which reflects cardiac work was similar between the groups even when considering TSH suppression levels.

Table 3. Heart rate parameters at rest, during exercise and recovery

Parameter	SCH Patients (n = 29)	SCH Patients TSH < 0.1 (n = 17)	SCH Patients TSH ≥ 0.1 (n = 12)	Euthyroid Subjects (n = 35)	p-value†	p-value*
HR _{rest} (bpm)	88.0 (76.0 – 96.0)	86.0 (75.0 – 98.0)	89.0 (76.5 – 94.8)	79.0 (60.0 – 90.0)	0.04	0.03 [‡]
HR _{peak} (bpm)	159.0 (143.5 – 167.0)	159.0 (139.5 – 167.0)	157.3 (144.6 – 166.6)	167.0 (154.5 – 179.0)	0.01	0.03 [‡]
Δ HR _{peak - rest} (bpm)	70.0 (55.3 – 81.5)	69.5 (54.5 – 81.0)	71.3 (53.8 – 81.1)	83.5 (76.0 – 93.0)	< 0.01	< 0.01 [‡]
Δ HR _{peak - 1st min rec} (bpm)	20.0 (14.3 – 25.6)	18.0 (12.0 – 25.5)	23.2 (14.2 – 28.0)	23.5 (19.5 – 33.0)	0.03	0.04 [§]
Δ HR _{peak - 2nd min rec} (bpm)	35.3 (24.6 – 42.8)	35.3 (21.3 – 39.6)	36.0 (24.6 – 43.8)	41.0 (33.5 – 49.0)	< 0.01	0.04 [§]
Δ HR _{peak - 3rd min rec} (bpm)	40.5 (30.0 – 44.8)	38.5 (29.8 – 43.6)	42.3 (27.0 – 50.0)	48.0 (40.5 – 55.5)	< 0.01	< 0.01 [§]
Δ HR _{peak - 4th min rec} (bpm)	42.0 (30.0 – 49.0)	41.3 (30.4 – 48.1)	42.5 (26.0 – 51.0)	50.0 (45.5 – 58.0)	< 0.01	< 0.01 [‡]
Δ HR _{peak - 5th min rec} (bpm)	45.0 (34.0 – 48.5)	45.0 (34.8 – 47.0)	42.5 (26.5 – 53.5)	53.5 (46.0 – 60.0)	< 0.01	< 0.01 [‡]

min = minute; rec = recovery.

Results are presented as median (25th and 75th percentiles).

† Mann-Whitney U-test; SCH patients vs. euthyroid subjects; statistical significance set at p < 0.05.

* Kruskal-Wallis test; SCH patients TSH < 0.1 vs. SCH patients TSH ≥ 0.1 vs. euthyroid subjects; statistical significance set at p < 0.05. The differences were identified by the Mann-Whitney U-test.

‡ Mann-Whitney U-test; SCH patients TSH < 0.1 ≠ euthyroid subjects and SCH patients TSH ≥ 0.1 ≠ euthyroid subjects; statistical significance set at p < 0.05.

§ Mann-Whitney U-test; SCH patients TSH < 0.1 ≠ TSH ≥ 0.1; SCH patients TSH < 0.1 ≠ euthyroid subjects; statistical significance set at p < 0.05.

Table 4. Blood pressure parameters at rest, during exercise and recovery

Parameter	SCH Patients (n = 29)	SCH Patients TSH < 0.1 (n = 17)	SCH Patients TSH ≥ 0.1 (n = 12)	Euthyroid Subjects (n = 35)	p-value†	p-value*
SBP _{rest} (mmHg)	130.0 (120.0 – 140.0)	130.0 (120.0 – 140.0)	125.0 (112.5 – 141.5)	120.0 (110.0 – 130.0)	0.20	0.34
SBP _{peak} (mmHg)	182.0 (166.0 – 200.0)	180.0 (170.0 – 200.0)	197.0 (162.5 – 200.0)	170.0 (158.0 – 200.0)	0.28	0.34
Δ SBP _{peak - rest} (mmHg)	60.0 (40.0 – 70.0)	60.0 (40.0 – 70.0)	59.0 (50.0 – 77.5)	52.0 (40.0 – 76.0)	0.64	0.61
Δ SBP _{peak - 1st min rec} (mmHg)	0.0 (0.0 – 10.0)	0.0 (0.0 – 10.0)	3.0 (0.0 – 11.5)	10.0 (0.0 – 20.0)	0.01	0.06
Δ SBP _{peak - 3rd min rec} (mmHg)	23.0 (20.0 – 37.0)	26.0 (19.8 – 35.5)	27.0 (20.0 – 39.5)	30.0 (20.0 – 50.0)	0.04	0.20
Δ SBP _{peak - 5th min rec} (mmHg)	40.0 (22.0 – 50.0)	41.0 (32.8 – 50.0)	44.0 (22.0 – 50.0)	50.0 (32.0 – 60.0)	0.05	0.27
DBP _{rest} (mmHg)	80.0 (80.0 – 98.0)	80.0 (80.0 – 98.0)	82.0 (80.0 – 100.0)	84.0 (80.0 – 90.0)	0.60	0.68
DBP _{peak} (mmHg)	92.0 (90.0 – 100.0)	90.0 (90.0 – 100.0)	94.0 (90.0 – 100.0)	90.0 (84.0 – 90.0)	0.05	0.05
Δ DBP _{peak - rest} (mmHg)	10.0 (0.0 – 13.0)	10.0 (0.0 – 18.0)	10.0 (5.0 – 13.5)	8.0 (4.0 – 10.0)	0.64	0.72
Δ DBP _{peak - 1st min rec} (mmHg)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.0)	0.0 (0.0 – 1.5)	4.0 (0.0 – 10.0)	0.03	0.06
Δ DBP _{peak - 3rd min rec} (mmHg)	7.0 (0.0 – 10.0)	8.0 (0.0 – 10.0)	6.0 (0.0 – 10.0)	10.0 (4.0 – 12.0)	0.07	0.21
Δ DBP _{peak - 5th min rec} (mmHg)	10.0 (2.0 – 10.0)	10.0 (3.0 – 10.0)	10.0 (2.0 – 14.0)	12.0 (10.0 – 20.0)	< 0.01	0.01 [‡]
DP _{peak} (bpm.mmHg)	27540.0 (23320.0 – 31255.0)	27360.0 (23120.0 – 30600.0)	28425.0 (25391.3 – 32185.0)	26910.0 (24240.0 – 32220.0)	0.63	0.64

min = minute; rec = recovery.

Results are presented as median (25th and 75th percentiles).

† Mann-Whitney U-test; SCH patients vs. euthyroid subjects; statistical significance set at p < 0.05.

* Kruskal-Wallis test; SCH patients TSH < 0.1 vs. SCH patients TSH ≥ 0.1 vs. euthyroid subjects; statistical significance set at p < 0.05. The differences were identified by the Mann-Whitney U-test.

‡ Mann-Whitney U-test; SCH patients TSH < 0.1 ≠ euthyroid subjects and SCH patients TSH ≥ 0.1 ≠ euthyroid subjects; statistical significance set at p < 0.05.

DISCUSSION

On this cross-sectional study, SCH patients on TSH-suppressive therapy with LT_4 for thyroid carcinoma were evaluated for cardiopulmonary and hemodynamic function on exercise and its recovery. SCH was associated with impaired exercise capacity, characterized by premature achievement of anaerobic threshold, lower peak median values of $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}O_2/HR$, in addition to shorter duration of exercise for the same fatigue perception and metabolic stress level. These results mean that SCH patients had higher and premature anaerobic energy production to supplement aerobic energy production (which was deficient) when compared to euthyroid subjects, paired for gender, age, and menopause status. Such abnormalities (except for $\dot{V}O_2/HR$) were present in both patient subgroups (with a lesser and a higher degree of TSH suppression) in comparison to euthyroid subjects, indicating that the state of being SCH, i.e., presenting serum TSH level below the lower limit of reference range with normal FT_4 and T_3 levels and not the level of TSH suppression is associated with cardiopulmonary impairments.

Thyroid hormones have relevant effects on the cardiovascular and ANS systems (5,7,8). Overt hyperthyroidism is associated with alterations in cardiac function and structure such as left ventricular hypertrophy, increased systolic function, diastolic dysfunction, impaired exercise capacity, tachycardia and sympathovagal imbalance (5,22). In SCH, however, these manifestations are less clear. Some factors such as different etiologies of SCH (endogenous or exogenous), different duration of TSH-suppressive therapy with LT_4 and the use of drugs that could interfere with the cardiovascular system, such as β -blockers, contribute to raise difficulties in the comparison of these studies.

During exercise, muscle bioenergetics is stressed while both the cardiovascular and pulmonary systems should respond to support the increased gas exchange requirements of the active muscle cells. So, a finely coordinated integration of these systems is necessary in order to permit muscle contractions (11,21).

Maximal oxygen consumption ($\dot{V}O_{2max}$) is the most reliable variable to predict functional capacity of a subject. It represents the capacity of capitation (lungs), transport (heart and vessels), and use (muscles) of oxygen during exercise (10). It is obtained when a plateau of $\dot{V}O_2$ is established, despite further increases in work rate. Usually, untrained and/or diseased people

stop exercise testing before the achievement of this plateau (21,23), as our study sample did. Because of this, $\dot{V}O_{2peak}$ was considered in the present analysis.

When metabolic demands of exercise begin to exceed oxygen delivery to working muscles, anaerobic metabolism ensues in order to supplement aerobic energy production (20,21). Anaerobic threshold occurs at a higher percentage of $\dot{V}O_{2max}$ or $\dot{V}O_{2peak}$ according to how much trained and/or healthy the subject is. Patients with impaired cardiovascular function have insufficient oxygen delivery to their active muscles at low work rates (11). Therefore, anaerobic threshold in these patients occurs at a low $\dot{V}O_{2max}$ or $\dot{V}O_{2peak}$ or work rate.

Until this moment, only three studies in the literature have investigated the effect of SCH on functional capacity. Two groups have reported similar results to those shown in the present study. Mercurio and cols. (24) found significantly reduced exercise tolerance, $\dot{V}O_{2peak}$ and premature anaerobic threshold in 19 patients receiving long-term TSH-suppressive therapy with LT_4 (5.7 ± 3.5 years) at a fixed daily dose ranging from 1.8 to 4.0 $\mu g/kg$. Such abnormalities, however, improved when LT_4 therapy was individually tailored to the lowest dose required to keep serum TSH below reference range. In the same manner, Biondi and cols. (25) observed an impaired maximal exercise capacity, i.e., both reduced peak workload and exercise duration, in SCH patients on TSH-suppressive therapy with LT_4 for 5.0 – 9.0 years who underwent a cycloergometer test. Conversely, in a previous study, our group did not find any abnormality in exercise performance of 14 SCH patients. Peak $\dot{V}O_2$, $\dot{V}CO_2$ and exercise duration were similar between SCH patients and healthy controls and the anaerobic threshold was achieved at the same percentage of peak $\dot{V}O_2$. Their patients however, were younger than ours (median = 40.5 years; interquartile range = 28.6 – 48.0) and they also presented lower median disease duration (3.0 years; interquartile range = 1.2 – 7.3). It may be hypothesized that age and time in TSH suppressive therapy may contribute to abnormalities in cardiopulmonary function in SCH (26).

The cardiovascular system is modulated by the ANS through sympathetic and parasympathetic stimulus. Basically, HR response to exercise may be described in three phases: a) initial tachycardia from rest to exercise (initial transient) which depends principally on a vagal withdrawal; b) rise in HR during progressive effort, which is associated to the combination of sympathetic

activation and parasympathetic withdrawal; and c) fall in HR after cessation of exercise, which is a hall marker of the reactivation of the parasympathetic nervous system (27,28). Autonomic imbalance, i.e., reduced vagal tone and increased sympathetic activity has been shown to be an independent risk factor of all-cause mortality even in patients without a history of heart disease (29).

In the present study, SCH patients presented signs of autonomic imbalance defined by three parameters: elevated resting HR, abnormal HR response during exercise, and slower HR recovery immediately after exercise. Different from the findings observed in cardiopulmonary parameters, the level of TSH suppression seems to play an important role in determining these abnormalities, as they were predominantly present in patients with serum TSH < 0.1 μ UI/mL. Using different methods of analysis, Eustatia-Rutten and cols. (8) evaluated the autonomic nervous system of SCH patients on TSH-suppressive therapy with LT_4 . They found higher urinary excretion of catecholamines and lower heart rate variability among SCH patients, when compared to healthy subjects. Such characteristics were maintained even after six-months of restoration of euthyroidism. Petretta and cols. (9), evaluating time and frequency domain measures of heart-rate variability (24-h holter recordings) observed that SCH patients showed cardiac parasympathetic withdrawal compared to healthy controls, but such alteration was less severe when SCH patients were compared to patients with overt hyperthyroidism. In another study, nonelderly female SCH patients who were submitted to the tilt test with electrocardiographic record at rest, during expiratory sinus arrhythmia (RSA) maneuvers and after tilting, presented reduced vagal reserve at RSA maneuvers and blunted vagal response to sympathetic stimulus (7).

Among the different available noninvasive techniques for assessing the ANS, electrocardiogram analysis from rest to peak of exercise and its recovery can be easily incorporated in the clinical daily routine, in addition to its cost-effectiveness. It permits to evaluate HR response during different phases of exercise, each one with its prognostic value. Elevated resting HR, which was detected in the present study, is one of the most consistent abnormalities described in SCH (5,30). This abnormality has been proven to be associated with a higher risk of myocardial infarction and coronary deaths, even in healthy populations (14). Equally, abnormal HR recovery during the first minute after exercise reflects diminished vagal tone, which is also a strong

predictor of cardiovascular risk and all-cause mortality. HR recovery immediately after exercise analysis, as a predictor of mortality, was first described by Cole and cols. (19). They followed 2.428 adults without pacemakers and without a history of heart failure or coronary revascularization for six years. The patients were encouraged to reach symptom-limited maximal exercise on a treadmill and after achieving peak workload all of them spent at least two minutes in an active cool-down period. An abnormal HR recovery was predictive of death in various subgroups, including the elderly and women, where higher prevalence of thyroid carcinoma is observed. In this investigation, abnormal HR recovery was present in 17.2% of SCH patients, most of them with TSH < 0.1 μ UI/mL. Finally, electrocardiogram analysis allows identification of individuals with attenuated HR response to progressive effort, known as chronotropic incompetence. A two-year follow-up cohort study revealed that subjects who failed to reach 85% of their age-predicted maximum HR were more likely to die and, similarly, subjects who had a low chronotropic index had a higher death rate (18). In the Framingham Heart Study, a smaller increase in HR during exercise, the failure to achieve target HR and low chronotropic index were predictive of total mortality and coronary heart disease development (31). In the present study, SCH patients presented lower chronotropic index when compared to euthyroid subjects, in addition to a higher proportion of subjects who failed to achieve 85% of the target HR, reinforcing that SCH patients, mainly those with TSH < 0.1 μ UI/mL compose a group with a higher risk of developing cardiovascular disease.

As for resting SBP and DBP, no differences were observed between SCH patients and euthyroid controls, which means that resting blood pressure is not affected by SCH. This finding is in accordance with two population-based surveys that showed that SCH is not associated with changes in blood pressure (32,33). SCH also seems to be unassociated with peak blood pressure during exercise, since no differences were found in both SBP and DBP between SCH patients and euthyroid subjects, as reported by other studies (24,26).

Immediately after exercise however, SCH presented a delayed SBP and DPB recovery compared to euthyroid subjects. Blood pressure is determined by an interplay between peripheral vascular resistance and cardiac output (heart-rate x stroke volume) and the ANS plays an important role in its modulation during exercise and at rest (34). Smith and cols. (35) demons-

trated that the increase of sympathetic activity occurs in parallel with the increase of blood pressure. It was observed that normotensive subjects with elevated blood pressure presented higher sympathetic activity compared to normotensive subjects with normal blood pressure. In hypertensive patients, sympathetic activity exacerbation contributes to the increase and maintenance of blood pressure (35). The increased sympathetic activity observed in this study, demonstrated by elevated resting heart-rate and slower HR recovery after exercise compared to euthyroid subjects may explain the slower decline in SBP and DBP.

Major limitations to the present study were the small number of participants and the cross-sectional design. The first limitation may be consequence of the rigid inclusion and exclusion criteria which, however, these criteria generated homogeneous baseline characteristics and permitted the comparability between different studied groups. Moreover, the selection of SCH patients from LT₄ suppressive therapy determined a homogeneous duration time of established disease, different from what generally happens with patients with endogenous SCH. Finally, all cardiopulmonary exercise testing measures were made in a non-blinded manner when comparing euthyroid subjects with SCH patients. This last limitation did not influence the comparisons according to the two subgroups of SCH patients because both the patients and skilled professionals who performed the cardiopulmonary tests were blinded in respect to serum TSH determinations.

In summary, the main results of this study were that SCH patients on TSH-suppressive therapy with LT₄ for thyroid carcinoma had impaired functional and hemodynamic response to graded exercise testing. This was demonstrated by premature achievement of anaerobic threshold, lower peak values of $\dot{V}O_2$, $\dot{V}CO_2$, and $\dot{V}O_2/HR$, elevated HR_{rest}, chronotropic incompetence, and attenuated HR and blood pressure recovery immediately after exercise. The level of TSH suppression seems to play an important role in determining heart-rate abnormalities, different to what was seen with cardiopulmonary variables, where no differences were found between the subgroups of SCH patients, according to TSH suppression.

Early diagnosis is important to select the most appropriate intervention method. That may include use of beta-blockers and the adjustment of LT₄ doses, besides non-pharmacological strategies, such as physical activity which has been proven to enhance physical fitness

and reduce HR (36). All these actions taken together will contribute to a better patient-perceived health status and quality of life.

Acknowledgements: This study was supported by research grants from the National Council of Technological and Scientific Development (CNPq).

Disclosure: no potential conflict of interest relevant to this article was reported.

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