37 - IMPACT OF LEVOTHYROXINE REPLACEMENT ON OXYGEN UPTAKE KINECTICS DURING EXERCISE IN SUBCLINICAL HYPOTHYROIDISM PATIENTS

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INTRODUCTION

Subclinical hypothyroidism (SH) is a minor thyroid dysfunction in which the patient presents increased serum thyroid-stimulating hormone (TSH) and normal concentration of triiodothyronine (T3) and free thyroxin (T4) (BIONDI & COOPER, 2008). The prevalence of SH may reach 20%, depending on the patients and the age group which is being investigated, it is more frequent on elderly women (SURKS et al., 2004). Besides, the SH is associated to ischemic heart disease and the cardiovascular mortality (RAZVI et al., 2008). The main organic-functional changes observed on SH patients are: increased systemic vascular resistance, diastolic dysfunction, reduced systolic function and shorter myocardial contractility (BIONDI & COOPER, 2008), leading to low tolerance to effort and reduced functional capacity (KAHALY, 2000; KAHALY, KAMPMANN & MOHR-KAHALY, 2002).

Studies reveal that the return to the euthyroidism condition, through levothyroxine (L-T4) replacement, reverts the observed cardiovascular implications in the SH (MONZANI et al., 2001; RAZVI et al., 2007; BIONDI & COOPER, 2008). However, there isn't an agreement related to the L-T4 replacement hypothesis as a mean to improve the functional capacity of these patients (AREM et al., 1996; KAHALY, 2000; BRENTA et al., 2003; CARACCIO et al., 2005; MAINENTI et al., 2009). The functional capacity is the efficiency of the integrated response of the respiratory, cardiovascular and muscular systems to the exercise, and can be measured by ergoespirometry. This direct analysis method of the gas exchanges allows the evaluation of the necessary physiological adjustments to get, transport and utilization of the oxygen by the active muscles (WASSERMAN et al., 2005). The oxygen uptake ($\dot{V}$ O2) increases according to the work load. The $\dot{V}$ O2 kinetics represents the physiological mechanism which is responsible for the velocity of the response of the oxygen uptake during the exercise; it is an important tool for disease diagnosis and prognosis (POOLE, KINDIG & BEHNKE, 2005). Various studies demonstrate that individuals who present cardiovascular dysfunctions present slower $\dot{V}$O2 kinetics during the exercise and recovering (COHEN-SOLAL et al., 1990; MYERS et al., 1991; KOIKE et al., 1992; COHEN-SOLAL et al., 1997; MEYER et al., 1998; REGENSTEINER et al., 1998; MATSUMOTO et al., 1999; GRASSI et al., 2009; AKCAKOYUN et al., 2010). On the other hand, few studies focus on this theme related to patients with thyroid dysfunction (BEN-DOV et al., 1991; KIMURA et al., 1996; KAHALY et al., 1998; AKCAKOYUN et al., 2010), especially in SH. Therefore, the purpose of the present study is to analyze the effect of L-T4 replacement on ventilatory kinetics during progressive exercise in SH patients.

MATERIALS AND METHODS

PATIENTS

Twenty-five women were recruited from a population study and led to the Endocrine Clinic of the University Hospital Clementino Fraga Filho, Federal University of Rio de Janeiro (HUCFF/UFRJ). Inclusion criteria were: untreated LT4 women, aged between 25 and 60 years old, presenting elevated serum TSH levels (>4,0 µUI/ml) and T4 values within the normal range (0,8 a 1,9 ng/dl), in two blood samples (with interval of at least four weeks). The excluding criteria were: use of drugs or substances that could influence thyroid function, heart rate (bpm) and blood pressure (BP); diagnosed cardiac disease or systemic arterial hypertension; presence of pain or other physical problems that could interfere with the walking. The final population was constituted by 20 women (age: 45±8,1 years; BMI: 28,4±5,7; Fat%: 32,4±6,6; 75% sedentary). All subjects signed a free and explained consent and the protocol was approved by the local Research Ethics Committee of HUCFF/ Medical School of UFRJ (n° 012/01).

STUDY PROTOCOL

The SH patients were randomly assigned into two groups according to the purposed intervention in a blinded manner: TrP (treated patients with levothyroxine replacement L-T4) and UntrP (untreated patients). Each TrP patient received an accurate count of L-T4 tablets with an initial dosage of 0, 75 µg/kg per day according to the patient's weight. After that, the doses were gradually adjusted in order to achieve serum TSH normalization, checked every two months during clinical visits. The patients were instructed to take the medication once a day in the morning, at least 30 minutes before breakfast. UntrP patients did not receive any medication or intervention. After the first procedures, the patients were led to the Exercise Physiology Laboratory at the Physical Education and Sports School of UFRJ, where the ergospirometry tests referring to the baseline state, were performed (before randomizing the group). After six months this test was performed again in both TrP and UnTrP groups.

MEASUREMENTS

A medical history questionnaire was applied in order to check information such as: sedentary lifestyle, smoking habits and prior diseases. Anthropometry took place in the same Lab as a mean to characterize the group: weight (kg), height (m), Body Mass Index (BMI, kg/m2) and relative body fat (%BF) estimated by skinfold thickness. Before taking the ergospirometry test, the patients were instructed to avoid exertive physical activities, drinking alcohol, taking caffeine (for a day) and smoking (for at least four hours before the exam). The gas exchange analysis was done by Medical Graphics - VO2000 equipment, using the average of registrations which were taken every 10 seconds. The test was performed with a treadmill (Ecafix - EG 700.2), and the modified

Balke protocol was used (constant velocity of 4,8 km/h and increase 3% inclination every 2 minutes). The vital signs of the patients were monitored during the whole test (ECG - Ecafix Cardio Perfect; blood pressure - Narcosul, 1400-C) and subjective exertion perception (Borg Scale). The test was characterized by limitation symptoms, all patients were informed about the test interruption criteria, they were asked to inform the presence of any discomfort. The following variables were analyzed: Minute Ventilation ($\dot{V}$ E, l.min-1, STPD), Oxygen uptake ($\dot{V}$ O2, ml.kg.min-1, STPD) carbon dioxide production ($\dot{V}$ CO2, ml.kg.min-1, STPD). The $\dot{V}$ O2peak was determined as the highest $\dot{V}$O2 level measured at the end of the test. For the kinetics calculation of the ventilatory variables, the following ratios were used: Δ $\dot{V}$ O2/Δt, Δ $\dot{V}$ CO2/Δt, Δ $\dot{V}$E/Δt [(the peak value of the ventilatory variable minus the initial test value)/(test duration in minutes)]. On progressive tests performed on ergometric bikes up to exertion, the linear regression of the $\dot{V}$ O2-Work load relation provides the $\dot{V}$ O2 kinetics (Δ $\dot{V}$O2/ΔW slope), being typically linear for intensities below the anaerobic threshold (MEYER et al., 1998; WASSERMAN et al., 2005). In our case, since the treadmill was used, the ΔW was replaced by Δt, once the intensity is increased during the test. The T1/2 $\dot{V}$ O2 (necessary time to reach 50% of the difference of $\dot{V}$. O2 at rest and the $\dot{V}$ O2peak) was calculated in differently manner from the prior studies. For the T1/2 $\dot{V}$ O2 calculation, a $\dot{V}$ O2-time curve relationship was created for each patient, making use of all values registered during the test. A linear logarithm function was used, with a test duration on the axis x and $\dot{V}$ O2 on axis y, with the means of the following equation: $\dot{V}$ O2(t) = aLn(x) + b (R2=0,72; p<0,001), where a = slope of the curve coefficient, denominated Δ $\dot{V}$ O2/Δt slope; Ln(x) = natural logarithm of time, in minutes; b = initial $\dot{V}$ O2.

STATISTICAL ANALYSIS

Attending the parametric analysis conditions, the Student t test was used for independent measurements, to test the significance of the difference between the measurements taken before and after the six month period of the TrP and UnTrp. The t and X2 tests were used to verify the equivalence between groups on the measurements before the treatment. The data is presented as average ± standard deviation. The adopted significance level was p<0,05.

RESULTS

Randomization was performed to guarantee similar pre test conditions for both treated and untreated patients on the following variables: Age (years), BMI (Kg/m2), TSH (mU/l), L-T4 (ng/dl), Sedentary lifestyle (%), Menopause (%) and Smoking (%) – p>0,05. The time interval between the randomization and the second evaluation after six months of euthyroidism was 10,6±2,5 months for TrP and 10,1±2,5 months for UnTrP. Due to the levothyroxine replacement, the TrP achieved normal TSH levels (before: 7,70 x after: 2,84 mU/l). The UnTrP also presented TSH level decrease (7,43 x 5,10 mU/l), however insufficient to obtain normal levels of this hormone.

There were no significant changes on the anthropometric (BMI %BF), ventilatory ($\dot{V}$E,$\dot{V}$ O2,$\dot{V}$ CO2) and hemodynamic (SBP,DBP, HR) measurements at rest and peak of the exercise, for both groups when measurements were analyzed before and after six months (p>0,05). The peak values observed on the untreated patients (UnTrP) were:$\dot{V}$O2 (before: 29,3 ± 10,7 x after: 26,8 ± 11,0 ml/Kg/min); % $\dot{V}$ O2max reached (81,1 ± 25,4 x 75,8 ± 29,4%); Inclination (16,6 ± 2,8 x 15,4 ± 4,0%); Test duration (11,4 ± 3,9 x 10,3 ± 2,9min). On treated patients (TrP) the peak values were:$\dot{V}$ O2 (30,8 ± 9,8 x 24,5 ± 6,6 ml/Kg/min); % $\dot{V}$ O2max reached (88,6 ± 31,8 x 67,5 ± 17,7%); Inclination (15,2 ± 2,1 x 15,0 ± 2,7%); Test duration (9,7 ± 3,3 x 10,0 ± 2,5min). No significant differences related to the ventilatory kinetics were observed between the groups - Table 1 and Picture 1.

Table 1: Mean and Standard Deviation of the Ventilatory Response kinetics, during progressive test on the treadmill with SH patients before and after six months of observation or TSH normalization

Parameters	Untreated Group (UnTrP) n=10		Treated Group (TrP) n=10		p-value*
	Before	After-6months	Before	After-6months	
$\Delta\dot{V}E_2$ (L/min)	25,2 ± 12,9	22,8 ± 8,3	24,2 ± 16,3	23,6 ± 6,1	0,77
$\Delta\dot{V}O_2$ (mL/min)	1470,0 ± 818,0	1275,0 ± 452,6	1472,0 ± 803,0	1187,0 ± 305,8	0,80
$\Delta\dot{V}CO_2$ (mL/min)	1294,0 ± 607,9	1063,0 ± 307,3	1338,0 ± 762,0	1108,0 ± 221,2	0,99
$\Delta\dot{V}E/\Delta t$ (L/min^2)	2,2 ± 1,2	2,3 ± 0,9	2,7 ± 2,2	2,4 ± 0,6	0,71
$\Delta\dot{V}O_2/\Delta t$ (mL/min^2)	131,7 ± 65,2	130,0 ± 61,2	165,1 ± 107,4	124,1 ± 33,3	0,36
$\Delta\dot{V}CO_2/\Delta t$ (mL/min^2)	119,7 ± 60,1	108,5 ± 44,1	149,3 ± 102,0	116,0 ± 28,3	0,53
$\Delta\dot{V}O_2/\Delta t$ slope	4,3 ± 2,1	4,2 ± 1,4	4,5 ± 1,4	3,5 ± 0,9	0,33

*non significant differences (p>0, 05).

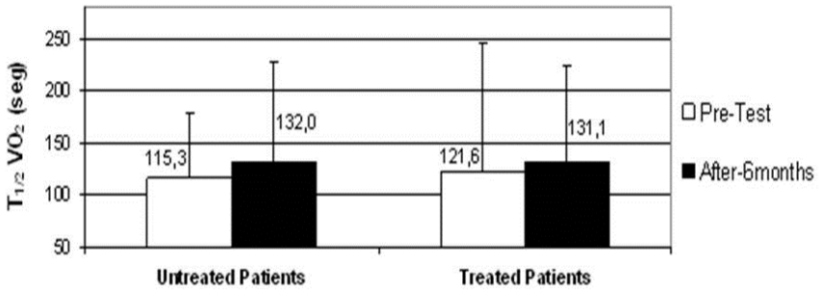

Figure 1: Oxygen Uptake kinetics ($T_{1/2}$VO2) during progressive exercise on treadmill in SH patients before and after six months of observation or Levothyroxine replacement (LT4)

DISCUSSION

The present study showed that the TSH normalization through hormone replacement was not able to improve the ventilatory response kinetics during progressive exercise on the treadmill in SH patients, after six months of euthyroidism. Studies on the impact of levothyroxine replacement on the heart and vascular functions demonstrate that the medication therapy reverts the adverse effects of SH (KAHALY, 2000; MONZANI et al., 2001), generally improving the tolerance to exertion after a determined time of euthyroidism, especially when analyzing the submaximal indicators of the functional capacity (MAINENTI et al., 2009). In the same manner, in hyperthyroidism, greater working efficiency ($\Delta \dot{V}O2/\Delta W$) was verified, after returning to the euthyroidism condition with the use of propranolol (KIMURA et al., 1996; KAHALY et al., 1998).

These patients reached lower $\dot{V}O2$ amplitude on the first twenty seconds of exercise and they take more time to reach the T1/2 $\dot{V}O2$ when compared to healthy people (BEM-DOV, SIETSEMA & WASSERMAN, 1991). It is possible that the six month euthyroidism period used in the present study may not have been sufficient to observe a $\dot{V}O2$ kinetics improvement. Another factor that may have contributed is the small difference of the TSH levels observed among the treated and untreated patients. It is impossible to affirm that the same results would be found with patients presenting more discrepant TSH values. Some studies reveal that the more severity the disease is related to the greater implications on the functional capacity (COHEN-SOLAL et al., 1997; MEYER et al., 1998).

Studies on $\dot{V}O2$ kinetics are generally performed with constant load exercise protocol where T1/2 $\dot{V}O2$ for healthy people is around 25 to 40sec, varying according to the physical skill (BARSTOW et al., 2000).

Individuals with greater $\dot{V}O2max$ present a faster $\dot{V}O2$ kinetics, while heart patients may take up to 3minutes to reach half of the $\dot{V}O2$ of the steady-state, depending on the exercise intensity and severity of the disease. Considering the methodological differences between the results, in the present study, SH patients took about 2 minutes to reach 50% of the $\dot{V}$-O2peak final amplitude on the progressive test. The consequence of a slower kinetics is the greater O2deficit taken in the beginning of the exercise, leading to a greater inner cell disturbance, greater glycolytic activity and the premature fatigue appearance. This result is similar to T1/2 $\dot{V}O2$ of the recovering patients with chronic heart failure (COHEN-SOLAL et al., 1997). The cardiovascular dysfunctions and low physical aptitude observed in SH patients are possible causes of a much slower -$\dot{V}O2$ response during the exercise.

In the progressive load test, most studies made use of bicycle ergometric, calculating the $\Delta \dot{V}O2/\Delta W$ (KOIKE et al., 1992; KIMURA et al., 1996; KAHALY et al., 1998; MATSUMOTO et al., 1999; BARSTOW et al., 2000; GRASSI et al., 2009; AKCAKOYUN et al., 2010). In average, the $\dot{V}O2$ is 10 ml/min/w. In the present study, since the treadmill was used, the calculation was made with the use of Δt. In this case, the $\dot{V}O2$ average increase due to the test duration was 137mL per minute in each minute (137ml/min2). One of the advantages of the $\dot{V}O2$ kinetics evaluation is that it does not demand the maximum performance, making it a sensitive method to identify problems on the O2 transportation and usage systems. This is particularly important in patients with low tolerance to effort, such as SH patients.

The limitations shown on the present study are: the reduced population, the absence of a control group and the absence of a test to measure the reproducibility of the ventilatory kinetics. New studies are recommended based on bigger population, comparing patients and healthy people, both male and female, with different physical skills. The use of T1/2 $\dot{V}O2$ as the kinetics measure during the progressive exercise needs to be better investigated, comparing adjustments on the linear and non linear curves. An important gap in literature is about the effect of physical training on SH patients.

CONCLUSION

The study concluded that the TSH normalization with levothyroxine replacement was not efficient on the improvement of the ventilatory kinetics ($\dot{V}E$, $\dot{V}O2$ e $\dot{V}CO2$) in subclinical hypothyroidism patients during progressive exercise on treadmill.

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IMPACT OF LEVOTHYROXINE REPLACEMENT ON OXYGEN UPTAKE KINECTICS DURING EXERCISE IN SUBCLINICAL HYPOTHYROIDISM PATIENTS

ABSTRACT

The present study aimed to analyze the effect of levothyroxine replacement (LT4) on the ventilatory response kinetics during progressive exercise on patients with subclinical hypothyroidism (SH). Twenty SH women (TSH=7,5±2,2mU/l; L-T4=1,1±0,3ng/dl) were randomized into two groups: UnTrP (untreated, n = 10) e GT (treated, n = 10). Ergoespiromety on treadmill was used, with the modified Balke protocol, in order to observe the ventilatory curves, before the treatment and six months after the TSH normalization or observation. No significant differences were observed between the groups referring to the variation amplitude of the ventilatory variables ($\Delta \dot{V}$O2 and $\Delta \dot{V}$ CO2), in T1/2 $\dot{V}$ O2 and on the ratios $\Delta \dot{V}$ O2/Δt, $\Delta \dot{V}$ CO2/Δt and $\Delta \dot{V}$E/Δt. The study concludes that the LT4 replacement does not improve the ventilatory response kinetics on SH patients during progressive exercise after six months of euthyroidism. New studies are necessary due to the lack of literature on $\dot{V}$ O2 kinetics in SH.

KEYWORDS: Subclinical Hypothyroidism; Exercise; Oxygen Uptake Kinetics.

IMPACT DE LÉVOTHYROXINE REMPLACEMENT DANS LA CINÉTIQUE DE CONSOMMATION D'OXYGÈNE DURANT L'ANNÉE CHEZ LES PATIENTS AVEC SUBCLINIQUE HYPOTHYROÏDIE.

RÉSUMÉ

L'objectif de cette étude était d'analyser l'effet de repositionnement de lévothyroxine (LT4) sur la cinétique de ventilatoire courbes pendant progressiste exercer chez les patients avec subclinique hypothyroïdie (HS). Vingt femmes avec (TSH=7,5±2,2mU/l; L-T4=1,1±0,3ng/dl) ont été randomisés en deux groupes: GNT (non traités, n = 10) et du GT (traités, n = 10). Utilisé-si le spiromrie en mat, avec le s. Balke protocole modifié, d'obtenir les courbes ventilatoire changements avant la transformation, et après six mois de la normalisation de TSH ou d'observation. N'étaient pas observé des différences significatives entre les groupes d'amplitude de variation de ventilatoire variables ($\Delta \dot{V}$ E, $\Delta \dot{V}$ O2 e $\Delta \dot{V}$ CO2), dans le T1/2 $\dot{V}$ O2 et des raisons $\Delta \dot{V}$ O2/Δt, $\Delta \dot{V}$ CO2/Δt e $\Delta \dot{V}$ E /Δt. Conclut-que le repositionnement de L-T4 pas améliorer la cinétique de ventilatoire réponse chez les patients avec HS pendant progressiste exercice après six mois de eutireoidismo. De nouvelles études sont nécessaires dans le visage de la rareté de la littérature sur cinétique de $\dot{V}$ O2 dans le HS.

MOTS-CLÉS: Hypothyroïdie Subclinique; L'exercice; Cinétique de Consommation D'oxygène.

IMPACTO DE LA SUSTITUCIÓN DE LEVOTIROXINA EN LA CINÉTICA DEL CONSUMO DE OXÍGENO DURANTE EL EJERCICIO EN PACIENTES CON HIPOTIREOIDISMO SUBCLÍNICO

RESUMEN

El objetivo de este estudio fue analizar el efecto de la levotiroxina sustitución (L-T4) sobre la cinética de curvas de ventilación en ejercicio progresivo en pacientes con hipotiroidismo subclínico (HS). Veinte mujeres con HS (TSH=7,5±2,2mU/l; L-T4=1,1±0,3ng/dl) fueron asignados aleatoriamente en dos grupos: GNT (no tratadas, n = 10) y GT (tratadas, n = 10). El ergoespirometria fue usado en carrera, con el protocolo de Balke modificado, para obtener las curvas ventilatórias, antes del tratamiento y después de seis meses de normalización de TSH o de la observación. Las diferencias importantes no fueron observadas entre los grupos en el ancho de la variación de las variables ventilatórias ($\Delta \dot{V}$ E, $\Delta \dot{V}$ O2 e $\Delta \dot{V}$ CO2), en T1/2 $\dot{V}$O2 y en las razón $\Delta \dot{V}$ O2/Δt, $\Delta \dot{V}$ CO2/Δt e $\Delta \dot{V}$ E /Δt. La conclusion es que la sustitución de L-T4 no mejora la cinética del respuesta ventilatória en pacientes con la HS durante el ejercicio progresivo después de seis meses de eutireoidismo. Los nuevos estudios son necesarios debido a la escasez de literatura sobre cinética del $\dot{V}$ O2 en la HS.

PALABRAS CLAVE: Hipotireoidismo Subclínico; Ejercicio; Cinética del Consumo de Oxígeno.

IMPACTO DA REPOSIÇÃO DE LEVOTIROXINA NA CINÉTICA DO CONSUMO DE OXIGÊNIO DURANTE O EXERCÍCIO EM PACIENTES COM HIPOTIREOIDISMO SUBCLÍNICO

RESUMO

O objetivo do presente estudo foi analisar o efeito da reposição de Levotiroxina (LT4) sobre a cinética das curvas ventilatórias durante exercício progressivo em pacientes com hipotireoidismo subclínico (HS). Vinte mulheres com HS (TSH=7,5±2,2mU/l; L-T4=1,1±0,3ng/dl) foram randomizadas em dois grupos: GNT (não tratadas, n = 10) e GT (tratadas, n = 10). Utilizou-se a ergoespirometria em esteira, com o protocolo de Balke modificado, para obtenção das curvas ventilatórias, antes do tratamento e após seis meses de normalização do TSH ou de observação. Não foram observadas diferenças significativas entre os grupos na amplitude de variação das variáveis ventilatórias ($\Delta \dot{V}$ E, $\Delta \dot{V}$ O2 e $\Delta \dot{V}$ CO2), no T1/2 $\dot{V}$ O2 e nas razões $\Delta \dot{V}$ O2/Δt, $\Delta \dot{V}$ CO2/Δt e $\Delta \dot{V}$ E /Δt. Conclui-se que a reposição de LT4 não melhora a cinética da resposta ventilatória em pacientes com HS durante exercício progressivo após seis meses de eutireoidismo. Novos estudos são necessários diante da escassez de literatura sobre cinética do $\dot{V}$ O2 no HS. Palavras-Chave: Hipotireoidismo Subclínico; Exercício; Cinética do Consumo de Oxigênio.