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RESEARCH ARTICLE

Heart rate kinetics during exercise in patients with subclinical hypothyroidism

Saulo Peters Almas,[1] Francisco Zacaron Werneck,[2] Emerson Filipino Coelho,[2] Patrícia de Fátima dos Santos Teixeira,[1] and Mario Vaisman[1]

[1]*Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil; and* [2]*Universidade Federal de Ouro Preto (UFOP), Ouro Preto, Brazil*

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Almas SP, Werneck FZ, Coelho EF, Teixeira PF, Vaisman M. Heart rate kinetics during exercise in patients with subclinical hypothyroidism. *J Appl Physiol* 122: 893–898, 2017. First published February 2, 2017; doi:10.1152/japplphysiol.00094.2016.—Studies suggest that patients with subclinical hypothyroidism (SH) have sympathovagal imbalance, which could lead to a slower heart rate (HR) response in the transition from rest to exercise. Thus the objective of this study was to investigate the behavior of the HR kinetics in patients with SH during the transition from rest to exercise. The study included 18 SH women [thyroid stimulating hormone (TSH) = 6.95 ± 2.94 μIU/ml and free thyroxine (FT_4) = 0.96 ± 0.15 ng/dl] and 17 euthyroid women (TSH = 2.28 ± 0.84 μIU/ml and FT_4 = 0.98 ± 0.07 ng/dl). Both groups were matched for physical activity, menopausal status, and age. The HR kinetics was obtained during the course of a constant-load exercise (50 W), for 6 min, in a cycle ergometer, and quantified from the mean response time (MRT), which is equivalent to the time taken to reach 63% of the HR at steady state. SH patients showed slower HR kinetics than the control group (MRT = 48.5 ± 17.6 vs. 36.0 ± 10.3 s, $P = 0.015$). The MRT has been shown to correlate with the level of physical activity ($r = -0.361$; $P = 0.033$) and with the subjective perception of exertion at the end of the exercise ($r = 0.365$; $P = 0.031$). It is concluded that SH patients have slower HR kinetics in the transition from rest to exercise compared with euthyroid women, with this impairment being associated with lower levels of physical activity.

NEW & NOTEWORTHY Subclinical hypothyroidism patients have slower heart rate kinetics in the transition from rest to exercise when performing a constant-load exercise at 50 W.

aerobic exercise; cycle ergometer; mean response time; constant load

SUBCLINICAL HYPOTHYROIDISM (SH) is characterized by a thyroid stimulating hormone (TSH) serum concentration above the upper limit of the reference range and free thyroxine levels within their reference values (28). The prevalence ranges from 4 to 20% (7), being more common in women, at any age group (4). Despite being a subclinical condition, SH patients can present various impairments, such as increased prevalence of atherosclerosis and myocardial infarction (11), in addition to a higher frequency of neuromuscular complaints, such as myalgia and weakness, and reduced muscle strength (22). Some of the studies evaluating the tolerance to physical exercises found that patients show impairment in performing these activities (5, 17, 31).

Address for reprint requests and other correspondence: S. P. Almas, Rua Manoel Diniz da Silva, 08, Francisco Bernardino, Juiz de Fora, MG 36081760, Brazil (e-mail: sauloalmas@hotmail.com).

The transition from rest to exercise leads to heart and metabolic changes necessary for the maintenance of homeostasis and other demands of the body (26). A faster increase in heart rate (HR) can contribute to improve the performance during exercise by increasing the oxygen supply to the muscles and by reducing the peripheral muscle fatigue (2). This HR variation, as a function of time, is given the name HR kinetics. It can be represented by the mean response time (MRT), which identifies the time taken to reach 63% of the HR at steady state (32). In populations with different impairments, it was found that the HR kinetics are slower (6, 19, 21, 30).

A study with SH patients showed lower HR variability, i.e., sympathovagal imbalance (9). The HR kinetics, in the transition from rest to exercise, are modulated by the vagal withdrawal with concomitant increased sympathetic activity (12); therefore, one can assume that, in these patients, the HR kinetics are shown to be impaired. Notwithstanding, no study verified whether there are losses in the HR kinetics of these patients. Therefore, the objective of this study was to investigate the behavior of the HR kinetics in SH patients during exercise.

MATERIALS AND METHODS

Sample. The power calculation was performed using $\alpha = 0.05$, $\beta = 0.20$, and an effect size of 0.994, being calculated from the mean difference in O_2 uptake ($\dot{V}O_2$), in accordance with a previous study with SH patients (31), since data regarding HR kinetics using MRT are not available. The sample size required would be of 17 participants per group. In fact, 18 women with SH and 17 euthyroid women (control group) took part in the study. The volunteers were recruited in the Endocrinology Service of the Hospital and Maternity Therezinha de Jesus of the Faculty of Medical Sciences and Health of Juiz de Fora (HMTJ-FCMS) and examined under the criteria for inclusion and exclusion of the study.

The inclusion criteria for the SH group were as follows: female sex; aged 20–60 yr; two TSH doses above the upper limit of the adopted reference range (0.35–4.94 μIU/ml), with a minimum interval of 4 wk between them; and free thyroxine (FT_4) level within the reference range (0.7–1.48 ng/dl). As for the control group, the criteria were as follows: female sex; aged 20–60 yr; TSH and FT_4 levels within the reference ranges adopted; and negative anti-thyroperoxidase antibody (anti-TPO). The exclusion criteria for both groups were as follows: use of tobacco and/or drugs that could interfere with the thyroid function, the HR or the blood pressure; cardiopulmonary disease; use of levothyroxine; inability to perform physical exercises; or involvement in a regular exercise program.

All selected participants signed the Free and Informed Consent Term (FICT), and the study was approved by the Research Ethics Committee of the FCMS-SUPREMA (no. 0164/10).

Procedures. The participants were evaluated in five steps performed on different days. The first three steps occurred in the HMTJ-FCMS for filling of the FICT and of the physical activity assessment questionnaire, with subsequent blood drawn for hormone assays and echocardiography, respectively. The fourth and fifth steps were performed in the Motor Evaluation Laboratory of the Faculty of Physical Education of the Federal University of Juiz de Fora. In the fourth visit, the anthropometric assessment and two cardiopulmonary tests of constant-load submaximal exercise were carried out, while another test was performed in the last step. The average values of these three tests were used in the study. All steps were performed at intervals of 8–12 days.

Hormone dosage, echocardiography, assessment of the physical activity level, and anthropometry. The dosages of TSH, FT_4, and anti-thyroid hormones were measured using a third-generation chemiluminescent immunometric assay (Beckman Coulter, Access2). For evaluation of the cardiac structure and function, an echocardiogram was performed (Sonos 5500, Hewlett-Packard, Andover, MA), using one- and two-dimensional echocardiography techniques, and pulsed- and continuous-wave Doppler guided by color-flow mapping. Anatomical and functional data were obtained at rest with the use of a 3.5-MHz linear transducer, placed in the third or fourth left intercostal spaces. The measurements were obtained and analyzed in accordance with the standards of the American Society of Echocardiography (10). The systolic function (systolic volume and ejection fraction) was also evaluated. All readings were made by a single cardiologist, who was unaware of which group the volunteer belonged.

Baecke questionnaire validated for Portuguese was used to assess the physical activity level (8). The questionnaire evaluated the habitual physical activity in the previous 12 mo, regarding three components: physical activity at work (questions 1–8), sport during leisure time (questions 9–12), and physical activity during leisure time and transport (questions 13–16). Body mass and height were measured using a stadiometer scale (Filizola).

Experimental protocol. In the 24 h before the performance of the constant-load submaximal tests, the participants were asked to refrain from all strenuous physical activity and from consuming alcohol or caffeine. Before the first test, patients were familiarized with the laboratory environment and with the cycle ergometer. An electromagnetic cycle ergometer (Ergo 167 Cycle®) was used, which allowed the load to remain constant. The HR was continuously monitored through a HR monitor (Polar). Systolic (SBP) and diastolic blood pressure (DBP) were measured at rest, every 3 min of exercise, and 1 min after completion of the test, using the auscultatory method (Narcosul, 1400-C). The subjective perceived exertion was informed by the volunteer every minute of exercise, using the modified Borg scale (CR10) (3). Participants attended the laboratory to carry out the ergometric tests at the same time of the day, to avoid the influence of the circadian rhythm.

Before each test, the volunteers remained seated on the cycle ergometer, at rest, for 3 min, for the measurement of resting HR. Then they cycled for 6 min at 60 rpm, keeping the constant load at 50 W.

Measurement of the HR kinetics. To measure the HR kinetics, a monoexponential model and the least-squares method were used, according to previous studies (12, 30, 31). For the calculation of the HR kinetics, the following equation was used:

$$HR_{(t)} = HR_b + \Delta HR \cdot \left[1 - e^{-(t-Td)/\tau}\right] \quad (1)$$

$HR_{(t)}$ is the HR to any point of time, while HR_b refers to the HR value immediately before the start of the exercise. ΔHR indicates the HR variation from the beginning to the end of the exercise, τ is the HR response time constant, and Td shows the delay time in the HR response. The kinetics calculation was performed using the sum of the delay time and the time constant, which is called MRT ($= Td + \tau$). In addition to these variables, the value of the steady-state HR was also calculated, by the average values between the 3rd and 6th min of exercise.

Statistical analysis. The Shapiro-Wilk test showed that all continuous variables presented normal distribution, except the TSH. For the analyses that involved the TSH measurement, nonparametric tests of Mann-Whitney and Spearman were used. The others continuous variables were compared using the *t*-test for independent samples, and Pearson's correlation coefficient was used for the correlation between variables. As for the categorical variables, χ^2 test was used. The effect size was calculated by Cohen's *d*, where the value of 0.2 was considered as small, 0.5 was considered as average, and 0.8 was considered as high (20). All analyses were performed using the software SPSS 20 (IBM, Armonk, NY). The level of significance was set at 0.05.

RESULTS

The SH group showed 44.4% patients with positive anti-TPO and TSH levels higher than the control group ($P < 0.001$). Nonetheless, the groups were similar with respect to age, body mass index, FT_4, physical activity level, menopause status, and physical activity practice ($P > 0.05$) (Table 1).

At rest, the control and SH groups were similar for the variables HR, SBP, DBP, ejection fraction, and systolic volume ($P > 0.05$). Yet, during exercise, no differences were observed between the groups regarding steady-state HR, ΔHR, HR, SBP, and DBP measured at the end of the exercise ($P > 0.05$); however, the SH group had higher MRT values ($P = 0.015$, $d = 0.86$), which reveals slower HR kinetics during the transition from rest to exercise compared with the control group. There were also differences between the groups on the Borg scale ($P = 0.036$, $d = 0.74$), which shows greater exertion perception of patients when carrying out the exercise (Table 2). From a practical point of view, the effect size suggests a difference of great magnitude on the HR kinetics, and of medium magnitude on the exertion perception. Figure 1 shows the HR kinetics in representative woman from the SH group, and Fig. 2 shows the HR kinetics in representative woman from the control group. The adjustment of HR data to the monoexponential curve proved to be satisfactory for the SH and control groups ($R^2 = 0.94 \pm 0.07$ vs. 0.91 ± 0.12).

The MRT correlated negatively with the physical activity level ($r = -0.361$; $P = 0.033$) and positively with the Borg scale ($r = 0.365$; $P = 0.031$), but did not correlate with ejection fraction ($r = 0.155$; $P = 0.367$), systolic volume ($r = 0.012$; $P = 0.943$), TSH levels ($r = 0.313$; $P = 0.067$), and FT_4 levels ($r = -0.139$; $P = 0.427$). When the level of physical activity was controlled, no correlation was found between MRT and TSH ($r = 0.235$; $P = 0.180$).

Table 1. *Sample characterization*

	SH Group	Control Group	*P* Value
n	18	17	
Age, yr	39.7 (11.7)	38.8 (8.1)	0.805
Level of physical activity	6.9 (0.8)	7.5 (1.2)	0.109
BMI, kg/m^2	26.3 (6.0)	27.2 (5.6)	0.620
TSH, μIU/ml	6.9 (2.9)	2.3 (0.8)	<0.001
FT_4, ng/dl	0.96 (0.1)	0.98 (0.1)	0.570
Status of menopause, no. "yes" frequence	3	4	0.691
Physical activity, no. "yes" frequence	4	6	0.471
Anti-TPO antibodies, no. "positive" frequence	8	0	0.003

Values are means (SD), except for the categorical variables; *n*, no. of subjects. BMI, body mass index; TSH, thyroid stimulating hormone; FT_4, free thyroxine; SH, subclinical hypothyroidism.

Table 2. *Hemodynamic variables during rest and exercise and HR kinetics in the transition from rest to exercise*

	SH Group	Control Group	*P* Value
n	18	17	
Rest			
Resting HR, beats/min	78.8 (10.9)	80.5 (13.3)	0.685
Resting SBP, mmHg	114.9 (9.1)	109.2 (13.2)	0.147
Resting DBP, mmHg	74 (7.4)	70.3 (6.2)	0.121
Ejection fraction, %	70.1 (6.8)	71.6 (5.4)	0.465
Systolic volume, ml	73.7 (16.4)	73.9 (19.3)	0.979
Exercise			
HR at steady state, beats/min	119.9 (14.0)	119.5 (7.5)	0.906
ΔHR, beats/min	41.1 (10.1)	38.9 (9.1)	0.516
MRT, s	48.5 (17.6)	36.0 (10.3)	0.015
HR in the 6th min, beats/min	124.1 (15.1)	121.8 (9.8)	0.597
SBP in the 6th min, mmHg	138.8 (14.3)	135.1 (16.6)	0.485
DBP in the 6th min, mmHg	76.2 (8.9)	75.1 (7.3)	0.674
Subjective perception of exertion in the 6th min (Borg CR10)	2.8 (0.7)	2.3 (0.5)	0.036

Values are means (SD); *n*, no. of subjects. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MRT, mean response time; SH, subclinical hypothyroidism.

DISCUSSION

The results showed that women with SH exhibit slower HR kinetics during constant-load submaximal exercise compared with euthyroid women. Such difference is highlighted by the performance of the analysis of three different ergometric tests, to minimize major confounding factors such as the adaptation to the cycle ergometer and the impact of possible nutritional influences or daily life in the 24 h preceding the test. This was not done in different studies evaluating exercise in patients with SH (1, 5, 17, 18). Moreover, as both groups had similar levels of physical activity, the difference found for the HR kinetics is not due to a condition other than the SH. Thus it is possible that studies with larger sample sizes evidence that higher TSH levels imply slower HR kinetics.

The transition from rest to exercise enhances the cardiac contractility and the HR to meet the energy demands imposed by the exercising muscles (25). This process is modulated by the autonomic nervous system (23), and the delay in the HR increase indicates impaired parasympathetic withdrawal and/or sympathetic activation (1, 12), which only occurs in more intense exercises (12). Previous studies have shown that, in patients with SH, there may be impairment in both the para-

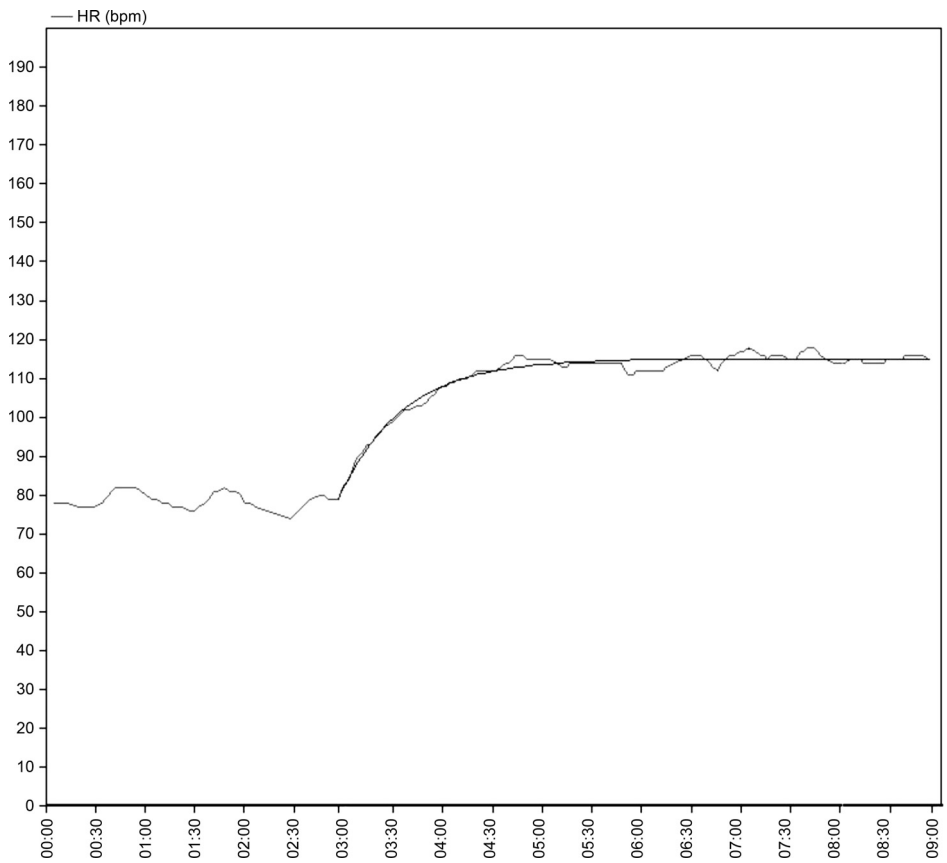

Fig. 1. Heart rate kinetics and its monoexponential fit in a representative woman of the subclinical hypothyroidism (SH) group. This participant had a mean response time (MRT) of 47.9 s.

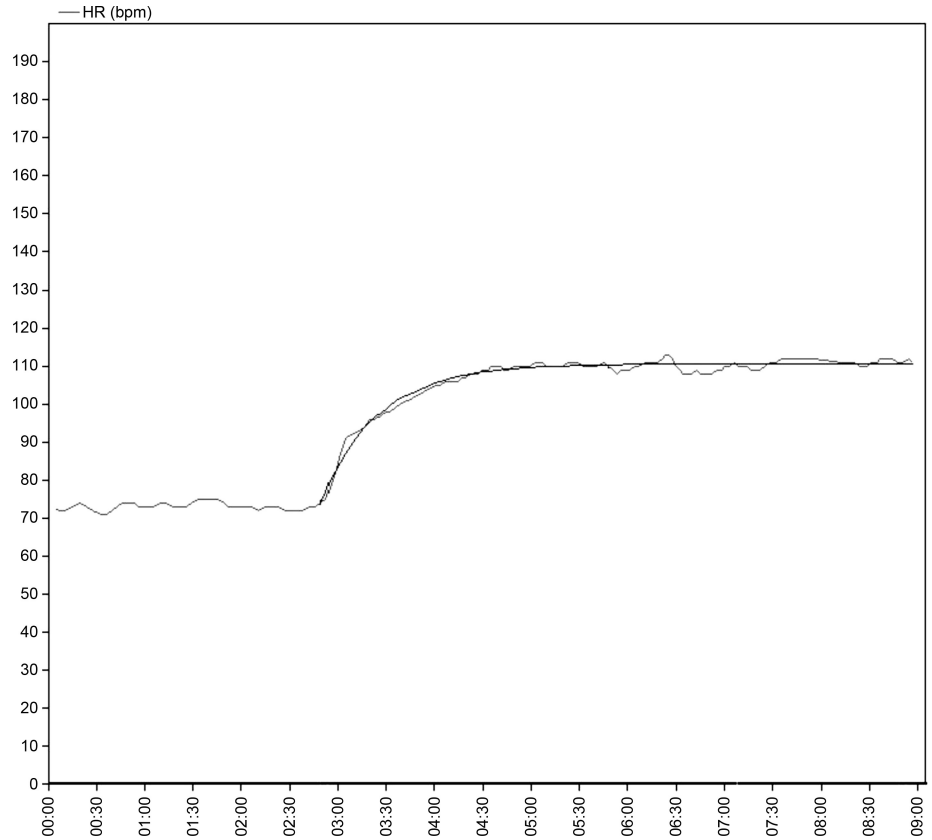

Fig. 2. Heart rate kinetics and its monoexponential fit in a representative woman of the control group. This participant had a mean response time (MRT) of 36.1 s.

sympathetic and the sympathetic activity (1, 9, 13, 16), in addition to systolic and/or diastolic dysfunctions (13, 29), which could explain the slower HR kinetics of that group.

The slower HR adjustment is responsible for increasing the time required to reach the steady state, in addition to increasing the oxygen deficit (12), the tissues' need for blood while performing the exercise (24), and the peripheral muscle fatigue (2). These factors could trigger the lower tolerance of these patients to exercise, which has been shown by some studies (5, 14, 17, 18, 31), although not all patients show the same pattern (1, 27). This incongruity can be due to the fact that not all studies match the SH and control groups with respect to intervening variables, or still to the differences in the duration or intensity of the exercise in the protocols used. In our study, as there was control of the variables possibly related to the HR kinetics, the result is due to the SH. The evaluation of the HR kinetics has outstanding importance, since it has been shown that the slower increase in HR during the beginning of the exercise is associated with increased mortality from all causes (15).

Diabetic patients who exercised at 30 W for 7 min in a cycle ergometer showed HR kinetics of 40.7 s (21), which is quite close to that found for patients with SH. Another study, with patients who had received abdominal organ transplants, found a MRT of 41 s during a 6-min walk test (30). Yet morbidly obese women showed HR kinetics slower than that presented by patients with SH. Notwithstanding, 4 mo after gastric bypass surgery and without physical training, the MRT was reduced to 41 s (6). Together, these data indicate that losses in the HR kinetics of SH patients are comparable to those of other clinical populations. In addition, the effect size of 0.86 shows that ~80.5% of patients showed kinetics slower than the average of the control group, and that 33.3% of patients had HR kinetics values unlikely to be achieved by women in the control group.

The correlation between the physical activity level and the $\dot{V}O_2$ kinetics is established in the literature and has been shown in patients with SH (31). Nonetheless, the correlation of the physical activity level with the HR kinetics had not been shown for this group and indicates that more active individuals have faster kinetics. Thus physical training can be an effective measure to improve the HR kinetics in patients with SH. The correlation of the $\dot{V}O_2$ kinetics with the TSH levels has also been shown, including after controlling for the physical activity level (31). In the present study, however, the HR kinetics were not associated with the TSH, regardless of the control of the physical activity level. Nevertheless, the value found for the correlation between MRT and TSH ($r = 0.313$; $P = 0.067$) reveals a moderate effect size, and the P value is close to the significance level of 5%.

The highest values obtained by the patients in the Borg scale show that they subjectively identified the need to make greater efforts to perform the exercise, although physiologically there is no difference. The values are comparable to those obtained by another study in patients with SH (31). The effect size of 0.74 indicates that ~77% of the patients had higher values of subjective perceived exertion than the average of the control group, and that 28.9% of the patients had values of subjective perceived exertion improbable to be achieved by women in the control group.

The values of HR, SBP, and DBP, at rest, were similar between the groups, which corroborates previous findings that

verified no impairment in the hemodynamic variables at rest (1, 5, 27, 31). During the exercise, there was also no difference between groups for the hemodynamic variables, which has been shown previously (1, 17, 31). These results suggest that the SH does not influence both resting and exercise hemodynamics. However, in the transition from rest to exercise, the increase in HR is slower for the SH group. The limitations of this study are due to the sample being composed only of women, with no assessment of the cardiac output, of the autonomic function, and of other variables that may contribute to the impairment of the HR kinetics.

Conclusion. The HR kinetics of SH women are slower in the transition from rest to constant-load submaximal exercise compared with that of euthyroid women. Furthermore, the kinetics are shown to be inversely correlated with the physical activity level and directly correlated with the perceived exertion.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

S.P.A., F.W., and E.C. performed experiments; S.P.A. and F.W. analyzed data; S.P.A. interpreted results of experiments; S.P.A. drafted manuscript; S.P.A., F.W., E.C., P.T., and M.V. approved final version of manuscript; F.W., E.C., P.T., and M.V. edited and revised manuscript.

REFERENCES

1. **Akcakoyun M, Emiroglu Y, Pala S, Kargin R, Guler GB, Esen O, Karapinar H, Say B, Esen AM.** Heart rate recovery and chronotropic incompetence in patients with subclinical hypothyroidism. *Pacing Clin Electrophysiol* 33: 2–5, 2010. doi:10.1111/j.1540-8159.2009.02567.x.
2. **Amann M, Calbet JA.** Convective oxygen transport and fatigue. *J Appl Physiol (1985)* 104: 861–870, 2008. doi:10.1152/japplphysiol.01008.2007.
3. **Borg GA.** Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 14: 377–381, 1982. doi:10.1249/00005768-198205000-00012.
4. **Canaris GJ, Manowitz NR, Mayor G, Ridgway EC.** The Colorado thyroid disease prevalence study. *Arch Intern Med* 160: 526–534, 2000. doi:10.1001/archinte.160.4.526.
5. **Caraccio N, Natali A, Sironi A, Baldi S, Frascerra S, Dardano A, Monzani F, Ferrannini E.** Muscle metabolism and exercise tolerance in subclinical hypothyroidism: a controlled trial of levothyroxine. *J Clin Endocrinol Metab* 90: 4057–4062, 2005. doi:10.1210/jc.2004-2344.
6. **Castello-Simões V, Polaquini Simões R, Beltrame T, Bassi D, Maria Catai A, Arena R, Azambuja NC Jr, do Nascimento Ortega J, Borghi-Silva A.** Effects of aerobic exercise training on variability and heart rate kinetic during submaximal exercise after gastric bypass surgery—a randomized controlled trial. *Disabil Rehabil* 35: 334–342, 2013. doi:10.3109/09638288.2012.694575.
7. **Cooper DS, Biondi B.** Subclinical thyroid disease. *Lancet* 379: 1142–1154, 2012. doi:10.1016/S0140-6736(11)60276-6.
8. **Florindo AA, Latorre MR, Jaime PC, Tanaka T, Zerbini CA.** [Methodology to evaluation the habitual physical activity in men aged 50 years or more]. *Rev Saude Publica* 38: 307–314, 2004. doi:10.1590/S0034-89102004000200022.
9. **Galetta F, Franzoni F, Fallahi P, Rossi M, Carpi A, Rubello D, Antonelli A, Santoro G.** Heart rate variability and QT dispersion in patients with subclinical hypothyroidism. *Biomed Pharmacother* 60: 425–430, 2006. doi:10.1016/j.biopha.2006.07.009.
10. **Gottdiener JS, Bednarz J, Devereux R, Gardin J, Klein A, Manning WJ, Morehead A, Kitzman D, Oh J, Quinones M, Schiller NB, Stein JH, Weissman NJ; American Society of Echocardiography.** American Society of Echocardiography recommendations for use of echocardiography in clinical trials. *J Am Soc Echocardiogr* 17: 1086–1119, 2004.10.1016/j.echo.2004.07.013.
11. **Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC.** Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med* 132: 270–278, 2000. doi:10.7326/0003-4819-132-4-200002150-00004.
12. **Javorka M, Zila I, Balhárek T, Javorka K.** On- and off-responses of heart rate to exercise - relations to heart rate variability. *Clin Physiol Funct Imaging* 23: 1–8, 2003. doi:10.1046/j.1475-097X.2003.00460.x.
13. **Kahaly GJ.** Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid* 10: 665–679, 2000. doi:10.1089/10507250050137743.
14. **Lankhaar JA, de Vries WR, Jansen JA, Zelissen PM, Backx FJ.** Impact of overt and subclinical hypothyroidism on exercise tolerance: a systematic review. *Res Q Exerc Sport* 85: 365–389, 2014. doi:10.1080/02701367.2014.930405.
15. **Leeper NJ, Dewey FE, Ashley EA, Sandri M, Tan SY, Hadley D, Myers J, Froelicher V.** Prognostic value of heart rate increase at onset of exercise testing. *Circulation* 115: 468–474, 2007. doi:10.1161/CIRCULATIONAHA.106.666388.
16. **Mahajan AS, Lal R, Dhanwal DK, Jain AK, Chowdhury V.** Evaluation of autonomic functions in subclinical hypothyroid and hypothyroid patients. *Indian J Endocrinol Metab* 17: 460–464, 2013. doi:10.4103/2230-8210.111642.
17. **Mainenti MRM, Teixeira PFS, Oliveira FP, Vaisman M.** [Impact of subclinical hypothyroidism in cardiopulmonary response during effort and its recovery]. *Arq Bras Endocrinol Metabol* 51: 1485–1492, 2007. doi:10.1590/S0004-27302007000900011.
18. **Maor E, Kivity S, Kopel E, Segev S, Sidi Y, Goldenberg I, Olchovsky D.** Differences in heart rate profile during exercise among subjects with subclinical thyroid disease. *Thyroid* 23: 1226–1232, 2013. doi:10.1089/thy.2013.0043.
19. **Massin MM, Leclercq-Foucart J, Sacre JP.** Gas exchange and heart rate kinetics during binary sequence exercise in cystic fibrosis. *Med Sci Monit* 6: 55–62, 2000.
20. **McGough JJ, Faraone SV.** Estimating the size of treatment effects: moving beyond p values. *Psychiatry (Edgmont)* 6: 21–29, 2009.
21. **Regensteiner JG, Bauer TA, Reusch JE, Brandenburg SL, Sippel JM, Vogelsong AM, Smith S, Wolfel EE, Eckel RH, Hiatt WR.** Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus. *J Appl Physiol (1985)* 85: 310–317, 1998.
22. **Reuters VS, Buescu A, Reis FA, Almeida CP, Teixeira PFS, Costa AJL, Wagman MB, Ferreira MM, de Castro CL, Vaisman M.** [Clinical and muscular evaluation in patients with subclinical hypothyroidism]. *Arq Bras Endocrinol Metabol* 50: 523–531, 2006. doi:10.1590/S0004-27302006000300016.
23. **Rowell LB, O'Leary DS.** Reflex control of the circulation during exercise: chemoreflexes and mechanoreflexes. *J Appl Physiol (1985)* 69: 407–418, 1990.
24. **Rumenig E, Bertuzzi RC, Nakamura FY, Franchini E, Matsushigue KA, Kiss MAPD.** [Kinetics and variability of heart rate by predominantly aerobic physical exercise: influence of intensity and time of analysis]. *Rev Bras Educ Fís Esporte* 21: 205–218, 2007.
25. **Sietsema KE, Daly JA, Wasserman K.** Early dynamics of O_2 uptake and heart rate as affected by exercise work rate. *J Appl Physiol (1985)* 67: 2535–2541, 1989.
26. **Simões RP, Bonjorno JC Jr, Beltrame T, Catai AM, Arena R, Borghi-Silva A.** Slower heart rate and oxygen consumption kinetic responses in the on- and off-transient during a discontinuous incremental exercise: effects of aging. *Braz J Phys Ther* 17: 69–76, 2013. doi:10.1590/S1413-35552012005000056.
27. **Sunita, Mahajan AS, Jain A, Singh N, Mishra T.** Heart rate and blood pressure response to exercise and recovery in subclinical hypothyroid patients. *Int J Appl Basic Med Res* 3: 106–110, 2013. 10.4103/2229-516X.117076.
28. **Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ.** Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 291: 228–238, 2004. doi:10.1001/jama.291.2.228.
29. **Teixeira PS, Reis FA, Reuters VS, Almeida CP, Vaisman M.** [Subclinical hypothyroidism and cardiovascular risk]. *Revista da SOCERJ* 17: 50–57, 2004.
30. **Tomczak CR, Warburton DE, Riess KJ, Jendzjowsky NG, Esch BT, Liang Y, Haennel RG, Haykowsky MJ.** Pulmonary oxygen

uptake and heart rate kinetics during the six-minute walk test in transplant recipients. *Transplantation* 85: 29–35, 2008. doi:10.1097/01.tp.0000296056.00863.f0.

31. **Werneck FZ, Coelho EF, de Lima JR, Laterza MC, Barral MM, Teixeira PF, Vaisman M.** Pulmonary oxygen uptake kinetics during exercise in subclinical hypothyroidism. *Thyroid* 24: 931–938, 2014. doi:10.1089/thy.2013.0534.
32. **Whipp BJ, Ward SA, Rossiter HB.** Pulmonary O_2 uptake during exercise: conflating muscular and cardiovascular responses. *Med Sci Sports Exerc* 37: 1574–1585, 2005. doi:10.1249/01.mss.0000177476.63356.22.