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ORIGINAL ARTICLE

Endurance training improves heart rate on-kinetics in women with subclinical hypothyroidism: a preliminary study

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Abstract

Purpose The aim of the study was to evaluate the effect of endurance training on heart rate (HR) on-kinetics in patients with subclinical hypothyroidism (SH).

Methods Eighteen women were randomly assigned to trained group (TG) or control group (CG). Both groups performed three tests at 50 W in a cycle ergometer for 6 min. HR kinetics was obtained during the tests and the mean response time (MRT), which is equivalent to the time taken to reach 63% of the HR at steady state, was extracted. The TG was then submitted to 12 weeks of endurance training (50 min, 3x/week, intensity between 70 and 85% of the maximum HR predicted for the age). Statistical analysis was performed by the mixed analysis of variance.

Results At baseline, TG and CG were similar for TSH (7.7 ± 3.1 vs. 6.9 ± 3.3 mUI/L, $p = 0.602$, respectively) and FT4 (12.31 ± 1.51 vs. 12.20 ± 1.89 pmol/L, $p = 0.889$, respectively). After adjustment for body mass index and age, interactions between moment (baseline or after 12 weeks) and group (trained or control) were only significant for MRT (TG: 39.6 ± 10 to 28.9 ± 8.4 s, CG: 53.6 ± 20.3 to 55 ± 19.7 s, $p = 0.001$) and physical activity level (CG: 7.3 ± 0.7 to 8 ± 0.9, CG: 6.8 ± 0.8 in both moments, $p = 0.005$).

Conclusion The preliminary results suggest that 12 weeks of endurance training improve HR on-kinetics and physical activity level in SH.

Keywords Endurance · Training · Subclinical hypothyroidism · Heart Rate · Kinetics

Introduction

The transition from rest to exercise is essential for the adjustment of physiological and metabolic processes to the demand imposed by the activity performed [1]. One way to assess the adequacy of these adjustments is by analyzing the heart rate (HR) variation as a function of time during exercise (HR on-kinetics).

The HR on-kinetics is regulated by the autonomic nervous system through sympathetic activity, responsible for the increase in HR, and parasympathetic (or vagal) activity, responsible for the deceleration in HR [2]. Thus, during exercise, there is a gradual vagal withdrawal and an increase in sympathetic activity [3].

Subclinical hypothyroidism (SH) is a condition in which thyroid stimulating hormone (TSH) concentrations are elevated, but free thyroxine (FT4) and free triiodothyronine (FT3) concentrations are normal [4]. Some studies have detected sympathovagal imbalance in people with SH [5–7], which could impair HR kinetics during exercise. Previously, evidence of slower HR on-kinetics was found in individuals with SH [8], but we did not identify studies that evaluated ways to accelerate this HR response during exercise in this population.

A few studies have shown improvements in physical performance after levothyroxine replacement in SH [9, 10], but the analysis of oxygen consumption (VO_2) kinetics, for example, showed no benefit after levothyroxine use [11, 12]. While the efficacy of levothyroxine replacement in improving HR in SH in yet to be tested, endurance training is an effective intervention in improving several comorbidities associated with SH, which has already been demonstrated

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by some research [13–16]. The aim of the study was to evaluate the effect of 12 weeks of endurance training on HR on-kinetics during submaximal exercise in patients with SH after 12 weeks of endurance training.

Materials and methods

Sample

The inclusion criteria were: women sex, age between 25 and 60 years, SH defined as TSH levels above the upper limit of the adopted reference range (0.35–4.94 mUI/L) and normal FT4 values (9–19 pmol/L) confirmed in two consecutive samples taken at the Laboratory of the Pé da Serra Intermunicipal Health Cooperation Agency (ACISPES) – Suprema with a minimum interval of 4 weeks. The exclusion criteria were: use of drugs or substances that interfere with thyroid function to the point of altering serum dosages (levothyroxine, lithium, amiodarone, glucocorticoids, among others); presence of diseases that interfere with circulating levels of thyroid hormones (nephrotic syndrome, renal failure, liver failure, AIDS); active infectious disease; infarction and/or angina in the last 3 months; potentially serious arrhythmias; use of medication that interferes with HR and/or blood pressure, such as diuretics, ACE inhibitors, beta-blockers, vasodilators; pain or other physical problems that prevent walking or cycling; systolic blood pressure (SBP) higher than 200 mmHg and/or diastolic blood pressure (DBP) higher than 110 mmHg at the time of the test, and non-attendance at least 75% of the scheduled workouts and/or absence in three consecutive sessions.

Study design

A third-generation chemiluminescent immunometric assay (Beckman Coulter®, Access2®, USA) was used to measure serum TSH, FT4 and anti-thyroid peroxidase (anti-TPO) antibodies. FT4 intra-assay coefficient of variation (CV) ranged from 2.3 to 5.3% while FT4 inter-assay CV ranged from 3.7 to 7.8%, both depending on the mean concentration values. After two consecutive tests demonstrating elevated TSH and normal FT4, the subjects signed the Term of Free and Informed Commitment and filled out the Baecke's Questionnaire validated for Portuguese, which was used to evaluate the level of physical activity [17].

To evaluate cardiac structure and function, the ultrasonic echocardiogram (Sonos 5500, Hewlett-Packard, Andover, MA, USA) was performed, utilizing one- and two-dimensional echocardiography techniques and pulsatile and continuous Doppler guided by color flow mapping. The anatomical and functional data were obtained at rest using a 3.5 MHz linear transducer placed in the third or fourth left intercostal spaces and were analyzed according to the standards of the American Society of Echocardiography [18]. The measurements extracted were those related to left ventricular morphology and function, specifically: left ventricular size in diastole and systole, left ventricular area, ejection fraction, left ventricular mass, systolic volume, and end-systolic volume. All tests were taken by a single cardiologist, who was unaware of which group the subject was participating in.

Subsequently, subjects were referred to Faculdade de Educação Física e Desportos of Universidade Federal de Juiz de Fora (FAEFID-UFJF) for anthropometric measurements (body mass and height), using a scale with a stadiometer (Filizola®, Brazil) and for 2 submaximal exercise cardiopulmonary tests with constant load were performed, and on another day, a third constant-load cardiopulmonary test was conducted. The mean values of these three tests were used in the study. All steps were performed within an interval of 8 to 12 days.

In the 24 h before the tests, the participants were instructed not to perform strenuous physical activities or consume alcohol or caffeine. Before the first test, the patients familiarized themselves with the laboratory environment and with the electromagnetic cycloergometer, which allows the load to remain constant (Ergo-167, Germany). The HR was continuously monitored through a cardiofrequency meter (Polar F4™, Polar®, Finland). SBP and DBP were measured at rest, every 3 min of exercise and 1 min after the end of the test, through auscultatory method (Narcosul, 1400-C, Brazil). The subjective perception of effort was reported by the subject at each minute of exercise, using the modified Borg scale (CR10) [19]. The participants came to the laboratory at the same time of the day for the ergometric tests to reduce the influence of the circadian rhythm.

Prior to each test, the subjects seated on the cycloergometer, without pedaling for three minutes to measure resting HR. Then, they pedaled for 6 min at 60 rpm, with a constant load of 50 W.

Measurements of heart rate kinetics

To measure HR kinetics, the monoexponential model and the least squares method were used [6, 8, 16, 20]. This method aims to find the best fit for a set of data points by minimizing the sum of the residuals of points from the plotted curve. For the HR on kinetics of calculation, the following equation was used:

$$HR_{(t)} = HR_0 + \Delta HR_{on} * \left(1 - e^{-\frac{t - Td}{\tau}}\right)$$

HR(t) represents the HR for any point in time, HR_0 refers to the HR value immediately before the beginning of exercise, ΔHR_{on} indicates the HR variation from the beginning to the end of the exercise, τ represents the time constant of

the HR response, and Td shows the time delay in the HR response. The kinetics calculation was performed using the sum of the delay time and the time constant, which is called the mean response time (MRT = Td + τ). The MRT is a way to assess HR kinetics and corresponds approximately to the time required to reach 63% of the HR range [21].

Endurance training

To verify the effect of endurance training on HR on-kinetics, the patients were randomly divided into two groups: the trained group (TG), which underwent physical training, and the control group (CG), which did not undergo any intervention.

The TG was submitted to a 12-week training program involving endurance exercise on treadmill and bicycle ergometer. The training consisted of three weekly sessions lasting 60 min. Each session was composed of 5 min of warm-up, 50 min of exercise with intensity between 70 and 85% of the maximum HR predicted for age, and 5 min of cool-down. The training intensity was monitored by a HR monitor (Polar F4™, Polar®, Finland) and a modified Borg scale (0–10). The absolute training load was continuously adjusted to maintain the prescribed relative intensity. The training sessions were supervised by a Physical Education professional.

At the end of 12 weeks, the subjects were reevaluated, following the same phases of the initial testing protocol. There was no loss of subjects during the follow-up period in either group.

Statistical analysis

To verify the effect of training on the variables studied, mixed analysis of variance was used. The purpose of this analysis is to understand if the dependent variable is influenced by the moment (baseline or after 12 weeks), the group (trained or control) or if there is an interaction between both moment and group. Chi-square test was used for the categorical variables. All analyses were performed in SPSS 20 software (IBM Corp., Armonk, NY) and the significance level was set at 0.05.

Results

At baseline, 5 patients in the TG and 4 patients in the CG were anti-TPO positive ($p = 0.637$) and only one woman in each group was postmenopausal ($p = 1.000$). These results remained unchanged after 12 weeks of follow-up.

The physical activity level increased from 7.3 ± 0.7 to 8 ± 0.9 in the TG and remained the same (6.8 ± 0.8) in the CG ($p = 0.001$ for moment; $p = 0.031$ for group; $p = 0.005$ for interaction). FT4 concentration decreased from 12.31 ± 1.51 to 11.93 ± 1.17 pmol/L in the TG, and increased from 12.20 ± 1.89 to 13.27 ± 1.54 pmol/L in the CG ($p = 0.303$ for the moment; $p = 0.363$ for the group; $p = 0.038$ for interaction). The MRT in the TG decreased from 39.6 ± 10 to 28.9 ± 8.4 s, and increased from 53.6 ± 20.3 to 55 ± 19.7 s in the CG ($p = 0.004$ for the moment; $p = 0.013$ for the group; $p = 0.001$ for interaction). However, after adjusting for body mass index (BMI) and age, the interaction between group and moment remained significant for physical activity level ($p = 0.039$) and MRT ($p = 0.005$), but not for FT4 ($p = 0.148$). Figure 1 shows the effect of endurance training on physical activity level (Panel A) and MRT (Panel B). Table 1 displays the results for the other hemodynamic, hormonal, and submaximal test-related variables. Table 2 shows the results for the echocardiographic variables studied, which showed no interaction between moment and group. Figure 2 shows the change in HR behavior of the TG before and after undergoing training.

Discussion

The results indicate that 12 weeks of endurance training improved HR on-kinetics during a constant load (50 W) test. In addition, training caused the MRT of patients with SH to reach a lower value than that previously found for euthyroid

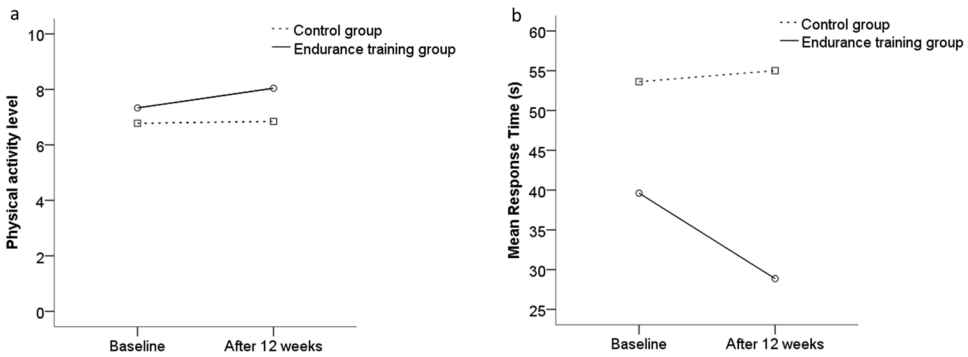

Fig. 1 Effect of training on physical activity level (Panel A), and mean response time (Panel B)

Table 1 Hemodynamic, hormonal characteristics, heart rate behavior and subjective perceived exertion at baseline and after 12 weeks

Variables	Baseline	After 12 weeks	Moment	Group	Interaction
TSH (µUI/mL)					
Control	6.9 ± 3.3	5.4 ± 2.2	< 0.001	0.700	0.521
Trained	7.7 ± 3.1	5.6 ± 3.2			
HR at rest (bpm)					
Control	75.1 ± 12.5	75.3 ± 10.4	0.417	0.260	0.345
Trained	71.9 ± 5.8	69 ± 7.1			
SBP at rest (mmHg)					
Control	110.2 ± 11.4	104.2 ± 10.3	0.006	0.285	0.687
Trained	115.6 ± 7.9	107.8 ± 8.7			
DBP at rest (mmHg)					
Control	70.9 ± 7.9	64.9 ± 5.1	0.057	0.087	0.057
Trained	73.8 ± 9.4	73.8 ± 7			
BMI (kg/m^2)					
Control	24.1 ± 5.5	24.2 ± 5.6	0.350	0.107	0.167
Trained	28.1 ± 3.6	27.7 ± 3.4			
HR at the start of exercise (bpm)					
Control	80.3 ± 10.7	81.1 ± 7.6	0.999	0.873	0.646
Trained	80.3 ± 9.8	79.5 ± 13.3			
Delta of HR (bpm)					
Control	44.3 ± 11.9	38.8 ± 8.1	0.001	0.097	0.493
Trained	36.2 ± 7.4	32.4 ± 8.2			
HR at stable-state (bpm)					
Control	124.6 ± 15.5	119.9 ± 10.9	0.024	0.192	0.984
Trained	116.5 ± 13.1	111.9 ± 12.5			
SBP at 6th minute (mmHg)					
Control	138.2 ± 13.2	135.8 ± 14.4	0.112	0.525	0.561
Trained	136.4 ± 9	131.3 ± 6.6			
DBP at 6th minute (mmHg)					
Control	71.3 ± 9.5	71.8 ± 7.3	0.805	0.087	0.657
Trained	78.9 ± 9.6	77.3 ± 9.2			
BORG at 6th minute					
Control	2.9 ± 0.6	2.4 ± 0.5	0.035	0.006	0.747
Trained	2.2 ± 0.4	1.9 ± 0.6			
HR at 6th minute (bpm)					
Control	127.7 ± 17.6	126.1 ± 13.3	0.040	0.073	0.162
Trained	119 ± 13	111.6 ± 8.7			

TSH thyroid stimulating hormone, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *BORG* subjective perception of exertion by Borg scale

Table 2 Evolution of echocardiographic variables before and after 12 weeks of training or follow-up

Variables	Baseline	After 12 weeks	Moment	Group	Interaction
Left ventricle in diastole (mm)					
Control	47.4 ± 4	48.5 ± 3.6	0.735	0.318	0.555
Trained	49.7 ± 4.3	49.4 ± 3.9			
Left ventricle in systole (mm)					
Control	28.3 ± 4	28.8 ± 2.2	0.534	0.365	0.922
Trained	29.4 ± 4.5	30.1 ± 2.2			
Left ventricular area (cm^2)					
Control	23.8 ± 6.6	24.5 ± 6.5	0.489	0.236	0.853
Trained	27.4 ± 6.3	27.8 ± 5			
Ejection fraction (%)					
Control	70.67 ± 6	70.7 ± 2.8	0.630	0.487	0.607
Trained	70.33 ± 7.2	68.6 ± 3.7			
Mass of the left ventricle (g)					
Control	156.9 ± 42	184.4 ± 27.9	0.036	0.313	0.503
Trained	179.4 ± 40.2	194.3 ± 41.9			
Systolic volume (mL)					
Control	76.3 ± 15.6	79.1 ± 14.2	0.991	0.518	0.573
Trained	82.9 ± 15.5	80.2 ± 17.9			
End-systolic volume (mL)					
Control	29.6 ± 8.7	32.2 ± 5.7	0.463	0.216	0.766
Trained	34.6 ± 12.5	35.6 ± 6.5			

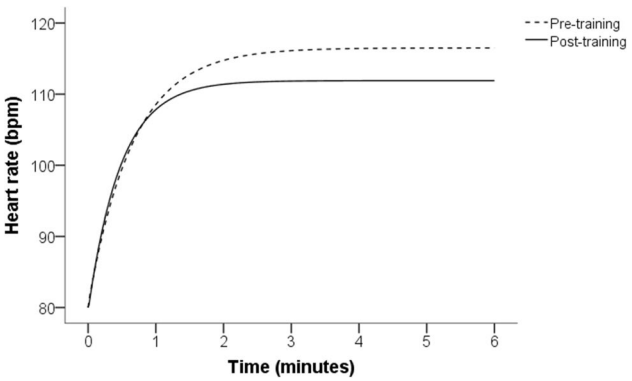

Fig. 2 Graphical representation of heart rate kinetics during submaximal exercise (50 W), before and after endurance training

women without training, respectively 28.9 and 36 s [8]. This may indicate that exercise improves HR on-kinetics to the point of making it faster than that of individuals without thyroid impairment and that SH does not impair the response to training, different from the postulated by other authors [13]. One hypothesis for this divergence in results is that HR on-kinetics may be a more sensitive measure to changes generated by endurance training.

The mechanism of autonomic control of HR is already well established in the transition from rest to exercise. During rest, there is a vagal predominance, which is gradually reduced with the beginning of exercise [22]. In the initial seconds, vagal withdrawal contributes to improve cardiac contractility and the depolarization wave conduction from the atrioventricular node until, depending on the intensity of the effort (> 100 bpm), the sympathetic function becomes predominant leading to an increase in HR and

norepinephrine concentration and vasoconstriction in visceral organs [3]. The behavior of HR during the beginning of exercise seems to be a marker of autonomic function, being important, for example, for the diagnosis of risk in patients with coronary artery disease [23].

Some studies have evaluated the effect of training on autonomic function and on HR on-kinetics in different populations. One of them found no improvement in the autonomic function of women with systemic lupus erythematosus after 12 weeks of aerobic training [24] and other found that 4 weeks of aerobic training were enough to improve the autonomic control, SBP and DBP of sedentary and hypertensive women [25]. Individuals with metabolic syndrome improved autonomic function after exercising three times per week for 16 weeks, at high intensity (85–95% of peak HR or 15–17 on the Borg scale of 6–20), with a duration of only 4 min per session [26]. This result may be of great practical relevance as it indicates that a small weekly volume of training can generate cardiovascular protection, although the required intensity is not suitable for everyone. The studies that evaluated the response of HR on-kinetics to exercise training found similar results. Women with obesity who underwent gastric bypass and 12 weeks of aerobic training improved their HR on-kinetics, making it similar to the eutrophic group, while those who underwent surgery but did not undergo training improved their HR on-kinetics, but not to the same extent as the first group [27]. Another study, conducted in male subjects with type 2 diabetes, identified improvement in HR on-kinetics after 12 weeks of endurance training [28]. However, to our knowledge, no previous study tested the effect of endurance training on HR on-kinetics in subclinical hypothyroid patients.

Endurance training can alter HR behavior by increasing venous return, myocardial contractility, ventricular size at end-diastole, left ventricular mass, systolic volume, and cardiac output, by improving sympathovagal balance and by decreasing intrinsic HR [29, 30]. The increase in vagal activity and the reduction in sympathetic activity should lead to a decrease in resting HR [31]. One study, however, stated that the reduction in resting HR after exercise training is due to the electrophysiological change in the sinus node and not the change in autonomic activity [32]. This would explain the improvement in HR on-kinetics after endurance training, even without a change in resting HR. On the other hand, the percentage reduction in resting HR and HR during submaximal exercise (4% for both after training), despite not reaching significant values, was similar to that found for individuals without thyroid impairment, with a decrease of 5% and 6%, respectively [31].

Some studies have verified the effect of physical training on patients with SH. Previously, it was found that physical training and calorie restriction decreased BMI of these patients, but did not contribute to the improvement of VO_2 peak [13]. Few studies identified no change on FT4 concentrations after training [15, 33], while another identified an increase in FT4 concentrations when comparing only the trained group [34]. This same study, however, found no interaction between group and moment, indicating that the increase was due to time and not the training itself [34]. One of these studies lasted 6 months, used a wider FT4 reference range (9.10–25.60 pmol/L), with a duration ranging from 25–30 to 40–45 min per day and weekly frequency ranging from 3 to 6 days [15] while another lasted 12 weeks, had a weekly frequency of 4 days of training and included resistance, stretching and aerobic exercises every session [35]. The third study also lasted 12 weeks and had a weekly frequency of 3 days, but featured stretching and muscle strengthening exercises [36]. Inter- and intra-assay CV could explain, at least in part, the decrease of FT4 after training in our study. Nevertheless, the non-significant interaction between moment and group after adjustment for BMI and age may indicate that changes of FT4 levels were not caused by the endurance training. Previously, the reduction of SBP, but not of DBP, was detected in patients with SH submitted to exercise training [33]. Although this study did not use a control group composed of patients who did not undergo training, which makes it difficult to compare the results, it can be stated that there is similarity with our results, since we also identified a reduction in SBP ($p = 0.006$), but not in DBP ($p = 0.057$) at the end of the study.

Levothyroxine replacement reduced HR by 7 bpm in the fifth minute of submaximal treadmill test [9], which is similar to what we found after training. Regarding echocardiography, 1 year of levothyroxine replacement improved only the left ventricular systolic diameter [36]. These results combined show that levothyroxine replacement generates similar effects as endurance training on HR behavior during submaximal exercise and on resting echocardiogram. Our results indicate that exercise training did not alter cardiac morphology or HR during rest or exercise, corroborating the findings of other authors who found that the changes in HR after training are explained by alterations in heart size [36]. Furthermore, the magnitude of the training effect on HR during rest, exercise, and recovery appears to be associated with training intensity [37]. Levothyroxine replacement has previously been cited as a strategy to prevent myocardial dysfunction in patients with SH [38]. However, physical training can also be a strategy and it is inexpensive, has fewer side effects (if any), and still acts on several other risk factors. Thus, patients with SH should be encouraged to exercise regularly as, in addition to the improvement in HR on-kinetics, endurance training can improve quality of life [14, 16], functional capacity [13] and several cardiovascular risk factors commonly present in this population. This is

particularly important given that, following cardiovascular events, patients with SH had a 2 times higher risk of mortality than euthyroid individuals [39].

The improvement of the physical activity level in the group that underwent training was expected, because the physical training itself would justify this increase. However, it is also interesting to note that other physical activities during leisure time, for example, could have been reduced to compensate for the increase generated by training and not leading to a real increase in the physical activity level [40]. On the other hand, untrained patients could also have altered the frequency of these activities in a way that impacted the level of physical activity, but this was not evidenced by our results.

The advantages of using HR on-kinetics are the low cost and the relative ease of data acquisition and analysis. Unlike spirometry, which requires high-value devices and constant calibration, HR kinetics requires only a cardiofrequencimeter or smartwatch that has the HR monitoring function. However it is required to verify the accuracy of the data obtained through these devices.

One of the positive points of this study is the evaluation of the averages of three tests in the cycloergometer, which contributed to prevent daily activities and adaptation to the equipment from influencing the results. The use of submaximal tests is also advantageous for several reasons, including: the low tolerance to exertion in several clinical populations; similarity between the test and daily activities; and independence of the evaluated individual's motivation to perform the exercise, since the load is well tolerated [11].

Among the limitations of the study, we highlight: the small sample size, the sample being composed only of females, which prevents the generalization of the results to males, and the impossibility of establishing the mechanisms by which the HR on-kinetics responded positively to training. Future studies may verify whether the slowness in HR on- kinetics is predictive of cardiovascular risk, in addition to determining whether physical training contributes in reducing cardiovascular events and/or mortality from these events in patients with SH.

It can be concluded that patients with SH improved HR on-kinetics and increased physical activity level after 12 weeks of endurance training.

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Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. The research was approved by the Research Ethics Committee of FCMS-SUPREMA (No. 0164/10).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication All authors approved the final version of article for publication.

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