Usefulness of L-Thyroxine to Improve Cardiac and Exercise Performance in Idiopathic Dilated Cardiomyopathy

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The short-term effects of L-thyroxine (100 μg/day, 10 patients) and placebo (10 patients) on idiopathic dilated cardiomyopathy were compared. Before and at the end of the treatment, a hemodynamic study was performed in the control state and during dobutamine infusion. A cardiopulmonary exercise test was also performed with hemodynamic monitoring. An echocardiogram was recorded in the control state and during acute changes of left ventricular afterload. Plasma levels of triiodothyronine, thyroxine, thyroid-stimulating hormone and norepinephrine were measured.

Placebo was ineffective. After administration of L-thyroxine all patients had normal thyroid function. The increase in left ventricular ejection fraction and the rightward shift of the slope of left ventricular ejection fraction/end-systolic stress relation ($p < 0.05$) indicated an improvement in the cardiac inotropic state. This proved to be independent of adrenergic influences by the unchanged β_1 response to dobutamine. A decrease in resting systemic vascular resistances and an increase in cardiac output ($p < 0.05$) were also observed. Cardiopulmonary effort parameters improved ($p < 0.05$) without hemodynamic changes at peak exercise. It is concluded that L-thyroxine short-term administration improves cardiac and exercise performance in patients with chronic heart failure, without modifying the adrenergic support to the heart and the circulatory parameters at peak exercise.

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Together with the occasional encounter with low plasma levels of thyroid hormone in heart failure,[1–3] several physiologic actions of thyroxine justify testing its use in this disorder. First, thyroid hormone stimulates protein synthesis, particularly in muscle. In myocardium, it can induce physiologic hypertrophy and increase the contractility.[4,5] Second, it increases the response of both heart and vessels to adrenergic stimulation. Although this action is poorly understood,[6] it has been demonstrated that thyroid hormone reduces circulating norepinephrine levels[7] and causes "up-regulation" of β_1 receptors,[8,9] events that are opposite to those observed in heart failure.[10,11] Finally, thyroid hormone reduces systemic vascular resistances, particularly in skeletal muscle[12–14] where perfusion and metabolic activity are affected in chronic heart failure.[15–17]

METHODS

Patients: Twenty patients (11 men and 9 women, mean age 53 years, range 46 to 78) participated in the study. Echocardiogram and coronary angiography confirmed the presence of idiopathic dilated cardiomyopathy. Patients were in New York Heart Association functional class II ($n = 6$) and III ($n = 14$) and in stable clinical condition. Left ventricular ejection fraction (echocardiography) was <40% (mean 27 ± 8) in all subjects.

Study design: The study was approved by the local ethics committee. All patients were hospitalized for ≥2 weeks and gave informed consent to the investigation. L-thyroxine (100 μg/day orally) or placebo were administered in a randomized fashion for 1 week. At the beginning and end of the study we measured plasma values of triiodothyronine, thyroxine, thyroid-stimulating hormone and norepinephrine. We also evaluated exercise performance by cardiopulmonary exercise test, hemodynamic parameters by cardiac catheterization at rest, during dobutamine infusion and exercise, and left ventricular anatomy and function by echocardiography.

Cardiopulmonary exercise evaluation: Before treatment, 2 cardiopulmonary exercise tests were performed: the first to make patients familiar with the equipment. The cardiopulmonary exercise test, performed on a cycloergometer (Collins Pedalmate) started with 60 seconds of unloaded pedaling, followed by 25 W increments every 180 seconds; patients were instructed and encouraged to exercise until exhaustion. Exhaled gases were collected on a breath-by-breath basis (Sensor Medics MMC 4400); anaerobic threshold was determined by carbon dioxide production/oxygen consumption analysis (V slope).[18] Oxygen consumptions at peak

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and at the anaerobic threshold were calculated (ml/min/kg) in the 30 seconds in which peak oxygen consumption and the anaerobic threshold occurred, respectively. In the L-thyroxine group the exercise test was performed in the catheterization laboratory, recording hemodynamic parameters at rest and peak exercise. Results of the tests in each patient were analyzed by 3 independent experts who were unaware of the study protocol.

Hemodynamic evaluation: Circulatory measurements at rest were obtained in fasting patients in the supine position. A 7Fr triple-lumen Swan-Ganz catheter was inserted percutaneously under local anesthesia into an antecubital vein, floated to the pulmonary artery and, when necessary, to the wedge position, to measure pulmonary artery and wedge pressures. Pulmonary pressures were measured with a Statham P23 Db transducer and recorded on a Hewlett-Packard 480 recorder. Cardiac output was obtained by thermodilution (mean of ≥5 consecutive measurements). Systemic arterial pressure was measured by a 23-gauge Teflon™ catheter intro-

TABLE I Laboratory Data

	Placebo		L-Thyroxine	
	Control	Treatment	Control	Treatment
Triiodothyronine (ng/ml)	1.0 ± 0.1	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.3
Thyroxine (μg/dl)	9.3 ± 2.0	9.1 ± 2.3	9.1 ± 2.1	11.2 ± 2.6*
Thyroid-stimulating hormone (μU/ml)	1.2 ± 0.5	1.1 ± 0.7	1.1 ± 0.6	0.7 ± 0.8*
Norepinephrine (pg/ml)	300 ± 230	310 ± 252	338 ± 267	284 ± 202

*p <0.05 versus control.
Laboratory parameters obtained in the placebo and L-thyroxine groups in the control state and after treatment. Data are mean ± SD.

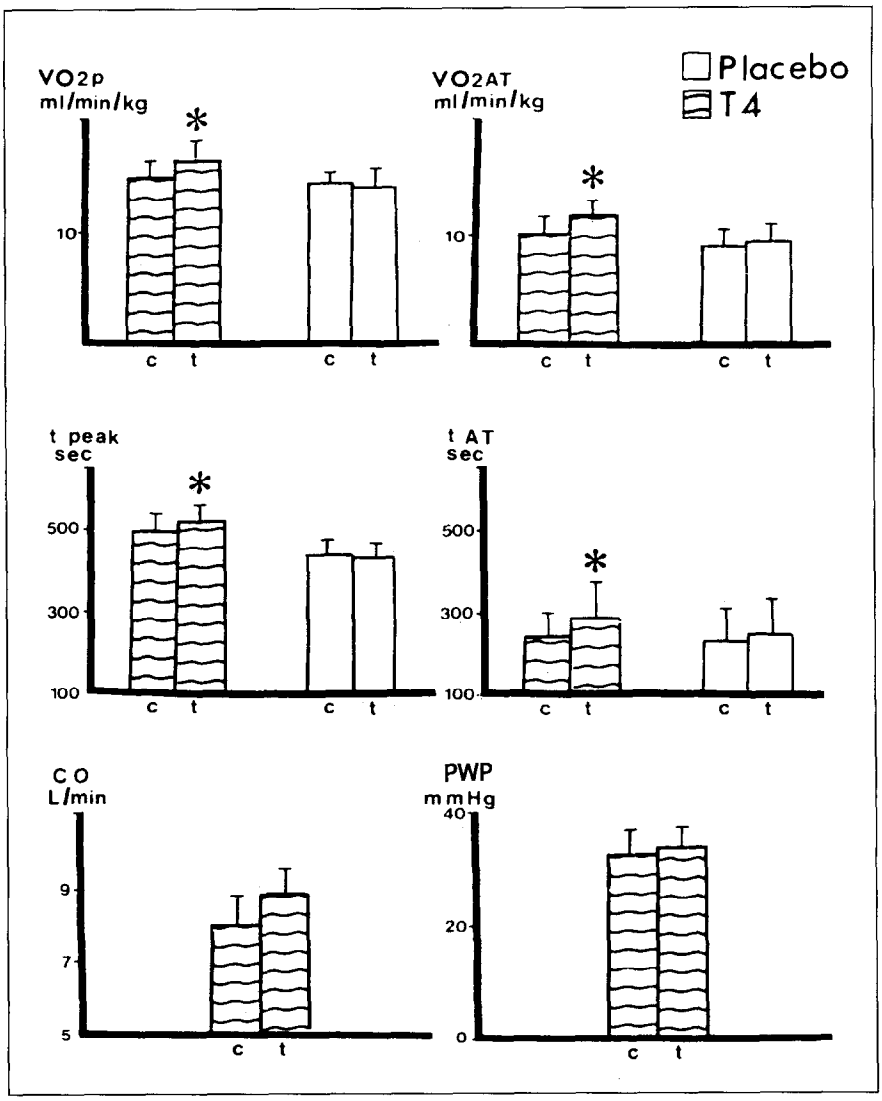

FIGURE 1. Data are mean ± SD. *p <0.05 versus control. c = control condition; CO = cardiac output; PWP = pulmonary artery wedge pressure; t = treatment; t AT = time to the anaerobic threshold; t peak = time to peak exercise; T4 = L-thyroxine; VO_2AT = oxygen consumption at the anaerobic threshold; VO_2p = oxygen consumption at peak exercise.

TABLE II Hemodynamic and Echocardiographic Data

	Placebo		L-Thyroxine	
	Control	Treatment	Control	Treatment
Hemodynamics				
Cardiac output (L/min)	3.6 ± 0.6	3.5 ± 0.5	3.7 ± 0.7	4.1 ± 0.3*
Systemic vascular resistances (dynes s cm^{-5})	2,002 ± 342	2,050 ± 324	2,051 ± 323	1,720 ± 192*
Pulmonary artery wedge pressure (mm Hg)	19 ± 9	19 ± 8	18 ± 10	17 ± 9
Mean systemic arterial pressure (mm Hg)	98 ± 8	97 ± 9	99 ± 14	92 ± 10
Heart rate (beats/min)	92 ± 8	90 ± 8	91 ± 7	84 ± 8
Δ cardiac output dobutamine 10 μg/min/kg (L/min)	+1.4 ± 0.8	+1.4 ± 0.9	+1.5 ± 0.7	+1.9 ± 1.4
Δ cardiac output dobutamine 15 μg/min/kg (L/min)	+2.8 ± 0.9	+2.8 ± 0.9	+2.9 ± 1.0	+3.0 ± 1.0
Echocardiography				
Left ventricular diastolic diameter (mm)	67 ± 9	68 ± 9	68 ± 10	68 ± 9
Left ventricular mass index (g/m^2)	260 ± 98	268 ± 70	267 ± 101	243 ± 74
Left ventricular ejection fraction (%)	28 ± 11	28 ± 10	27 ± 8	31 ± 10*

*p < 0.05 versus control.
Hemodynamic and echocardiographic parameters obtained in the placebo and L-thyroxine groups in the control state and after treatment. Data are mean ± SD.

duced into the omeral artery. After baseline measurements, dobutamine was infused intravenously at the rate of 10 μg/min/kg for 10 minutes and 15 μg/min/kg in the next 10 minutes to evaluate cardiac response to β_1-adrenergic stimulation.

Echocardiogram: M-mode and cross-sectional echocardiograms were recorded with a cross-sectional unit (Hewlett-Packard model Sonos 1000). End-diastolic and end-systolic left ventricular diameters and wall thickness were measured from the M-mode tracings, and left ventricular mass index was calculated.[19] Left ventricular ejection fraction was calculated either using the Teichholz formula[20] or, during conduction disturbances, from the apical 2-chamber view using the area-length method for left ventricular volume calculations.[21] All measurements were means of ≥5 consecutive beats. The same variables were obtained during the control state and after acute changes in blood pressure by the cold pressor test and nitroprusside infusion (graduated to reduce systolic blood pressure by 20 mm Hg). Data obtained during left ventricular load modulation were used to build the relation between left ventricular ejection fraction and end-systolic stress[22] in order to evaluate cardiac contractility.

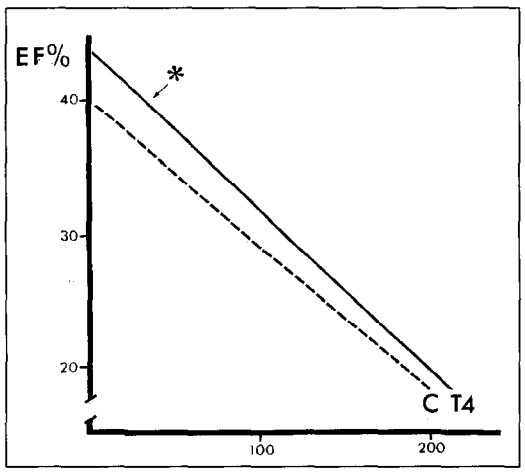

FIGURE 2. Left ventricular ejection fraction (EF%) versus end-systolic stress in control condition (C) and after treatment with L-thyroxine (T4). Data are obtained by echocardiography during acute changes in left ventricular afterload. *p <0.05.

Statistical analysis: Reported data are expressed as mean ± SEM. Differences were analyzed by the paired Student's *t* test. Left ventricular ejection fraction/end-systolic stress relation (obtained by afterload modulation) was also analyzed by the Student's *t* test. In each patient the slope of the ejection fraction/end-systolic stress relation was calculated. The slopes of the relations obtained with both treatments for each patient were not significantly different. Therefore, we calculated a mean slope of the relations that, together with values of ejection fraction and end-systolic stress, allowed us to calculate the y intercept value in the control state and after treatment in each patient. The values of y were then compared using the paired Student's *t* test.

RESULTS

All patients completed the study and none complained of adverse effects.

Before the study, plasma values of triiodothyronine, thyroxine, thyroid-stimulating hormone and norepinephrine were normal in the 2 groups (Table I). Laboratory tests showed values in the normal range after treatment. In particular, all patients remained euthyroid, and significant changes in thyroxine and thyroid-stimulating hormone values were observed only in patients treated with L-thyroxine.

Cardiopulmonary exercise test: Figure 1 summarizes the parameters obtained at peak exercise and at the anaerobic threshold. Before treatment, effort functional class, according to the classification of Janiki and Weber,[23] did not differ in the placebo and L-thyroxine group (peak oxygen consumption = 19.2 ± 3.6 and 19.8 ± 4.3 ml/min/kg, respectively). After treatment, oxygen consumption at peak exercise varied from 19.2 ± 3.6 to 18.8 ± 3 ml/min/kg with placebo and from 19.8 ± 4.3 to 21.1 ± 4 ml/min/kg with L-thyroxine. Exercise tolerance time remained unchanged after placebo and increased after L-thyroxine from 488 ± 179 to 512 ± 171 seconds. Differences were significant ($p < 0.05$) only for the changes observed in the L-thyroxine group.

Before and after placebo, oxygen consumption and duration of exercise to the anaerobic threshold did not change significantly. After L-thyroxine the same parameters showed a significant improvement (from 14.9 ± 3.8 to 16.3 ± 2.9 ml/min/kg and from 238 ± 141 to 286 ± 150 seconds).

Hemodynamic evaluation: In the L-thyroxine group, at peak exercise cardiac output was 8.0 ± 2.2 and 8.4 ± 2 liters/min, heart rate was 140 ± 25 and 144 ± 28 beats/min, and pulmonary artery wedge pressure was 32 ± 8 and 33 ± 10 mm Hg before and after treatment, respectively; differences were not significant (Figure 1). Hemodynamic parameters during exercise were not recorded in the placebo group.

Hemodynamic parameters recorded at baseline and during dobutamine infusion are reported in Table II: In both groups, mean values of resting circulatory parameters were slightly altered. A significant difference with treatment was observed only after L-thyroxine: a reduction in systemic vascular resistances and increased cardiac output. The increases in cardiac output at any rate of dobutamine infusion were comparable to those obtained before treatment both with placebo and L-thyroxine.

Echocardiography: Table II also reports echocardiographic parameters: left ventricular internal diameters and mass index were not significantly different compared with control conditions during placebo and L-thyroxine therapy. A significant difference was seen only after L-thyroxine: an increase in left ventricular ejection fraction. The echocardiographic parameters recorded during cold pressor testing and nitroprusside infusion were used to obtain the left ventricular ejection fraction/end-systolic stress relation (Figure 2). In the L-thyroxine group the values of y intercept of the relation changed with treatment from 40.3 ± 13 to 44 ± 13 ($p < 0.05$), with a shift to the right indicating an improvement in cardiac inotropic state. The values of y intercept before and after placebo were 44.5 ± 2.5 and 45 ± 3 ($p = NS$).

DISCUSSION

The absence of signs and symptoms of thyroid hyperfunction (anxiety, tremor, weight loss or tachycardia) after L-thyroxine was probably due to variation of thyroid hormone plasma levels within the normal range. Changes observed in hemodynamic, echocardiographic and effort parameters may be interpreted either as a physiologic effect or as the result of the correction of a "de facto" hypothyroidism, possibly induced by target organ hyporesponsiveness to thyroid hormone.[1]

The cardiac inotropic state was improved by L-thyroxine, as shown by increased left ventricular ejection fraction and rightward shift of the ejection fraction/end-systolic stress relation. This improvement was independent of adrenergic influences, since sympathetic activity, as reflected from norepinephrine plasma levels, was reduced (although insignificantly), in agreement with the absence of a tachycardic reaction (Table II). Moreover, L-thyroxine did not change β_1 response to dobutamine, possibly because the low hormone dose and short-term treatment were not able to induce a detectable resynthesis of cardiac β_1 receptors. In addition, our patients had little alteration in hemodynamic parameters and normal plasma values of norepinephrine in the control condition, a situation in which important β_1-receptor down-regulation is unlikely. It can be suggested that these patients were in a stage mainly characterized by sole myocardial involvement, without decreased adrenergic sensitivity of the heart.[24] A metabolic effect of L-thyroxine on cardiac muscle could then explain the improved inotropic state. This hypothesis is in agreement with the cellular actions of thyroid hormone, and among them an increased synthesis in the heart muscle of V1 form of myosin isozyme[5] and intracellular enzymes with adenosine triphosphatase activity,[9] and an increase in calmodulin bioactivity.[25]

The cardiopulmonary exercise test showed a clear improvement in exercise performance that was not due to an improvement in hemodynamic parameters at peak exercise; cardiac output and pulmonary artery wedge pressure were unchanged. A higher oxygen consumption at peak exercise without increment in maximal cardiac output can be attributed to improved oxygen uptake from skeletal muscles.[26] Redistribution of blood flow to leg muscles through vasodilation[5] or improvement in muscle metabolism through a local action of L-thyroxine, which occurs with training,[26,27] can explain this finding.

Our data are in agreement with the reported increases in exercise performance and serum thyroxine in patients with congestive heart failure receiving low-dose amiodarone.[28,29] We suggest that the effect of amiodarone may also be a consequence of increased L-thyroxine production.

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