

Acute Effects of Triiodothyronine (T₃) Replacement Therapy in Patients with Chronic Heart Failure and Low-T₃ Syndrome: A Randomized, Placebo-Controlled Study

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Context: Low-T₃ syndrome is a predictor of poor outcome in patients with cardiac dysfunction. The study aimed to assess the short-term effects of synthetic L-T₃ replacement therapy in patients with low-T₃ syndrome and ischemic or nonischemic dilated cardiomyopathy (DC).

Design: A total of 20 clinically stable patients with ischemic (n = 12) or nonischemic (n = 8) DC were enrolled. There were 10 patients (average age 72 yr, range 66–77; median, 25–75th percentile) who underwent 3-d synthetic L-T₃ infusion (study group); the other 10 patients (average age 68 yr, range 64–71) underwent placebo infusion (control group). Clinical examination, electrocardiography, cardiac magnetic resonance, and bio-humoral profile (free thyroid hormones, TSH, plasma renin activity, aldosterone, noradrenaline, N-terminal-pro-B-Type natriuretic peptide, and IL-6) were assessed at baseline and after 3-d synthetic L-T₃ (initial dose: 20 μg/m² body surface·d) or placebo infusion.

Results: After T₃ administration, free T₃ concentrations increased until reaching a plateau at 24–48 h (3.43, 3.20–3.84 vs. 1.74, 1.62–1.93 pg/ml; P = 0.03) without side effects. Heart rate decreased significantly after T₃ infusion (63, 60–66 vs. 69, 60–76 beats per minute; P = 0.008). Plasma noradrenaline (347; 270–740 vs. 717, 413–808 pg/ml; P = 0.009), N-terminal pro-B-Type natriuretic peptide (3000, 438–4005 vs. 3940, 528–5628 pg/ml; P = 0.02), and aldosterone (175, 152–229 vs. 231, 154–324 pg/ml; P = 0.047) significantly decreased after T₃ administration. Neurohormonal profile did not change after placebo infusion in the control group. After synthetic L-T₃ administration, left-ventricular end-diastolic volume (142, 132–161 vs. 133, 114–158 ml/m² body surface; P = 0.02) and stroke volume (40, 34–44 vs. 35, 28–39 ml/m² body surface; P = 0.01) increased, whereas external and intracardiac workload did not change.

Conclusions: In DC patients, short-term synthetic L-T₃ replacement therapy significantly improved neuroendocrine profile and ventricular performance. These data encourage further controlled trials with more patients and longer periods of synthetic L-T₃ administration. (*J Clin Endocrinol Metab* 93: 1351–1358, 2008)

A low T₃ syndrome has been documented in patients with dilated cardiomyopathy (DC); its occurrence is an independent predictor of poor outcome (1–5). The effect of decreased T₃ concentrations on myocyte gene expression and cardiac con-

tractility has already been documented in a model of low-T₃ syndrome in which T₃ supplementation normalized both cardiac function and phenotype (6).

The main pathophysiological mechanism underlying low

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Abbreviations: bs, Body surface area; CMR, cardiac magnetic resonance; CO, cardiac output; DC, dilated cardiomyopathy; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HF, heart failure; HR, heart rate; LV, left ventricular; ns, not significant; NT-proBNP, N-terminal pro-brain natriuretic peptide; PRA, plasma renin activity; SV, stroke volume; SVR, systemic vascular resistance.

TABLE 1. HR, blood pressure, and rate pressure product (RPP) at baseline and after 3 d in patients treated with synthetic L-T₃ or placebo infusion

Variables	Patients treated with L-T ₃			Patients treated with placebo		
	Before L-T ₃	After L-T ₃	P value	Basal	After 3 d	P value
HR (bpm)	69 (60–76)	63 (60–66)	0.008	67 (60–74)	70 (59–79)	ns
SBP (mm Hg)	117 (111–127)	118 (113–120)	ns	117 (105–128)	119 (113–128)	ns
DBP (mm Hg)	68 (63–68)	70 (64–78)	ns	76 (68–83)	76 (68–79)	ns
MBP (mm Hg)	94 (86–102)	95 (91–96)	ns	96 (86–101)	95 (92–100)	ns
RPP	8281 (6384–9747)	7498 (6651–7830)	ns	7702 (7226–8609)	8455 (7081–9421)	ns

Data are expressed as median (25th and 75th percentiles). DBP, Diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure.

circulating T₃ is the decreased activity of 5'-monodeiodinase, responsible for converting T₄ into T₃ in peripheral tissues (1, 7).

The pathophysiological role of the progressive decrease in T₃ that occurs in patients with heart failure (HF) has not yet been established (8). It may merely be a marker of the severity of the disease, or it could contribute to the impairment of cardiovascular function. The latter hypothesis is based on the key role of thyroid hormones on the homeostasis of the cardiovascular system by three different routes: 1) direct effect on cardiomyocytes; 2) peripheral effects on the vasculature; and 3) modulation of sympathetic systems (1, 9).

Although potentially promising, the usefulness of synthetic thyroid hormone administration as a new therapeutic strategy during evolution of HF is still debated (1, 10). In patients with DC and low-T₃ state, the short-term (a few hours) iv administration of pharmacological doses of synthetic L-T₃ increased cardiac output (CO) and decreased systemic vascular resistance (SVR) without changes in heart rate (HR) and arterial blood pressure (11). Administration of synthetic L-T₃ had no adverse effects, and, in particular, no arrhythmias were observed. However, data on the effects of replacement doses of L-T₃ in humans are lacking. In addition, very little information is available on the potential link between changes in thyroid hormone state and the other activated neuroendocrine/proinflammatory systems during progression of HF; however, preliminary data on humans seem promising (12).

This study aimed to evaluate the effects of 3-d iv replacement doses of synthetic L-T₃ on clinical status, left ventricular (LV)

function, and neuroendocrine/proinflammatory profile in patients with DC and low-T₃ syndrome.

Patients and Methods

Patients

A total of 500 outpatients with known post-ischemic or nonischemic DC were screened. Post-ischemic DC was diagnosed by angiographically proven coronary artery disease or by documented myocardial infarction; nonischemic DC was diagnosed based on the absence of coronary artery disease on angiography. Inclusion criteria were: 1) ischemic or nonischemic dilated left ventricle, *i.e.* end-diastolic diameter more than 56 mm and ejection fraction (EF) less than 40%, echocardiographically assessed; 2) optimized standard HF medical therapy; 3) New York Heart Association class less than III; and 4) stable thyroid function pattern with low free T₃ levels confirmed on the basis of two consecutive determinations within the last month. Exclusion criteria were: 1) history of primary thyroid disease, 2) amiodarone therapy during the past 6 months, 3) concomitant severe systemic disease, 4) complex ventricular arrhythmias, 5) severe obesity (body mass index > 35 kg/m²), and 6) pregnant women or women undergoing estrogenic therapy.

Based on the aforementioned criteria, a total of 445 patients was excluded. Of the remaining 55 patients, 35 were excluded for the following reasons: 1) rapid, unexpected clinical worsening (n = 8); 2) need for changes in medical treatment (n = 11); and 3) normalization of thyroid pattern (n = 5), refusal of hospitalization, and/or of synthetic L-T₃ infusion (n = 11).

Therefore, the final population consisted of 20 patients (14 male, 6 female), with an average body mass index of 28 kg/m² (range 25–31), and an average body surface area (bs) of 1.89 m² (range 1.81–1.92) with post-ischemic (n = 12) or nonischemic (n = 8) DC, randomly assigned

TABLE 2. Effect of synthetic L-T₃ infusion on cardiac rhythm

Patient no.	No. of PACs		No. of SVTs		No. of PVCs		No. of NSVTs	
	Before T ₃	After T ₃						
1	42	32	6	4	294	100	40	0
2	107	5	42	0	947	2047	6	0
3	1	3	1	0	177	104	0	0
4	35	24	1	2	924	66	0	0
5	5	1	5	0	227	355	0	1
6	2	6	2	1	230	135	0	0
7	45	31	2	2	353	121	48	2
8	8	2	4	0	272	426	0	1
9	50	38	7	5	739	53	0	0
10	86	4	34	0	663	1433	4	1

PAC, Premature atrial contraction; SVT, supraventricular tachyarrhythmia; PVC, premature ventricular contraction; NSVT, nonsustained ventricular tachycardia.

to continuous 3-d iv synthetic L-T₃ infusion. There were 10 patients (mean age 72 yr, range 66–77) who underwent L-T₃ infusion and comprised the study group. The other 10 patients (mean age 68 yr, range 64–71) underwent continuous low-rate (100 ml/d) 3-d iv infusion of saline (placebo) solution and comprised the control group. Standardized medical therapy for HF was optimized before the study; this remained unchanged for at least 15 d before the study was initiated and remained the same throughout the entire 3-d T₃ infusion. Medical therapy consisted of angiotensin-converting enzyme inhibitors (n = 17), diuretics (n = 15), β -blockers (n = 16), and spironolactone (n = 10 patients).

Experimental protocol

All enrolled patients were admitted to the Institute of Clinical Physiology in Pisa and hospitalized to perform the study protocol. All patients gave informed consent for hospitalization and L-T₃ infusion. The study was approved by the local ethics review committee and conformed to the principles outlined in the Declaration of Helsinki. Synthetic L-T₃ was continuously infused (initial dose 20 $\mu\text{g}/\text{m}^2$ bs·d diluted in 100 ml saline); we used this dosage, which is slightly higher than the measured T₃ production rate in normal humans ($16 \pm 3 \mu\text{g}/\text{m}^2$ bs·d, mean \pm SD) (13), to restore normal T₃ levels as rapidly as possible while avoiding potential side effects. Starting on the first day after the beginning of infusion, on the basis of measured T₃ levels, the dose was adjusted to maintain T₃ circulating levels within the normal range (see *Thyroid function pattern throughout L-T₃ infusion*). Clinical signs and symptoms, bio-humoral profile, and cardiac magnetic resonance (CMR) were evaluated at baseline and at the end of L-T₃ infusion. Continuous electrocardiographic monitoring was maintained during the entire L-T₃ infusion period to detect arrhythmias. Systolic/diastolic and mean blood pressure as well as HR were measured five times per day; the reported values of these parameters at baseline and after T₃/placebo administration (see *Results*) represent the average value of the measures. Rate pressure product was calculated as the product between HR and systolic blood pressure.

Neuroendocrine and proinflammatory bio-humoral profile

Basal blood samples were taken at 0800 h from an antecubital vein after a 30-min rest in supine position. Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured with a fully automated “sandwich” electrochemiluminescence method using an Elecsys 2010 analyzer (Roche Diagnostics, Basel, Switzerland), as previously described (14). The low detection limit of the NT-proBNP assay was 4.2 pg/ml (0.50 pmol/liter), whereas the functional sensitivity was 22 pg/ml (2.60 pmol/liter). Plasma renin activity (PRA) (ng/ml·h) and aldosterone (pg/ml) were measured by RIA (Dia Sorin S.r.l., Saluggia, Italy); for the assay, blood samples were immediately put into ice-chilled tubes containing EDTA, and then plasma was rapidly separated by centrifugation at 4 C and frozen at –20 C (15). Serum TSH, free T₃, and free T₄ were measured using an AIA 21 analyzer (Eurogenetics-Tosho, Turin, Italy). The reference intervals for our laboratory were: free T₃, 2.1–4.2 pg/ml (3.4–6.5 pmol/liter); free T₄, 7.1–18.5 pg/ml (9.2–24 pmol/liter); and TSH, 0.30–3.80 $\mu\text{IU}/\text{ml}$. Measured functional sensitivity for the TSH assay was 0.12 $\mu\text{IU}/\text{ml}$. For the measurement of plasma norepinephrine (pg/ml), we used the HPLC method as previously described in detail (15). Levels of IL-6 (pg/ml) were measured by a high-sensitivity ELISA technique (Diaclone Research, Besançon, France).

Assessment of cardiac morphology and function

CMR imaging was performed with a 1.5 T Signa Excite Scanner (GE Medical System, Waukesha, Wisconsin) using an eight-element phased array cardiac receiver coil. To evaluate LV function, images were acquired in short axis views, from the mitral annulus to the ventricular apex (thickness 8 mm, no spacing) using a breath-hold gradient-echo pulse sequence triggered to electrocardiogram. For each image the myocardium was defined by manually tracing the endocardium to assess end-diastolic volume (EDV) (ml/m² bs), end-systolic volume (ESV) (ml/m² bs), stroke volume (SV) (ml/m² bs), and EF (%). CO (liter/min) was obtained as the product of SV and HR. SVR (dyne/sec \times cm) was com-

puted as the mean arterial blood pressure divided by CO. Internal and external cardiac works were calculated as follows: internal cardiac work = $\text{ESV} \times \text{HR} \times (\text{systolic blood pressure}/2)$; and external cardiac work = $\text{SV} \times \text{HR} \times \text{mean blood pressure}$. Total cardiac work was calculated as the sum of the internal and external cardiac work.

Statistical analysis

All variables are expressed as median plus 25th and 75th percentile, unless otherwise indicated. Continuous data were analyzed by the non-parametric Wilcoxon test. A *P* value less than 0.05 was considered statistically significant. ANOVA and *post hoc* comparison tests for repeated measures were performed with the Friedman test and Bonferroni adjusted Wilcoxon test to assess the differences of thyroid hormones and TSH circulating levels during the 3-d L-T₃ and placebo infusion. All analyses were performed using SPSS for Windows (version 11.00; SPSS, Inc., Chicago, IL).

Results

Clinical status

The main clinical characteristics of patients are shown in Table 1. Plasma protein and albumin levels before L-T₃ infusion were normal (6.9, 6.4–7.2 g/dl, and 4.2, 3.1–6.2 g/dl, respectively). Synthetic L-T₃ infusion was well tolerated, and no side effects were reported. HR decreased significantly, whereas blood pressure and body weight remained unchanged. Continuous electrocardiographic monitoring showed no increase either in

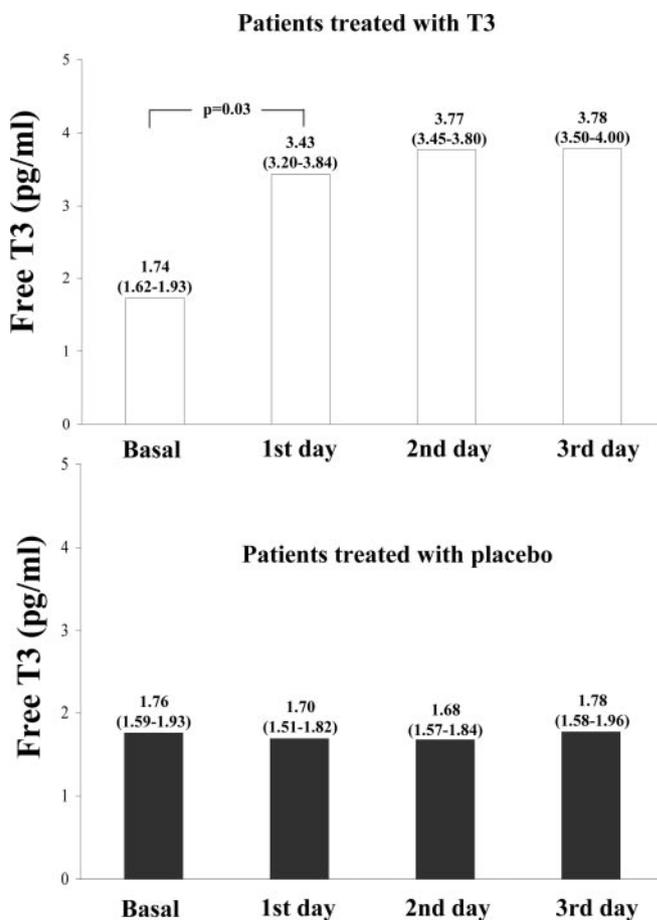


FIG. 1. Free T₃ levels in patients treated with L-T₃ (upper panel) and in patients treated with placebo (lower panel).

the number of ventricular premature beats (Table 2) or in the appearance of ischemic episodes. QT intervals did not change during L-T₃ infusion [before T₃ 437, 429–477 msec vs. after T₃ 439, 413–478; P = not significant (ns)].

Thyroid function pattern throughout L-T₃ infusion

At baseline all patients showed a typical low-T₃ syndrome with free T₃ plasma levels lower than the limit of reference range. After starting T₃ replacement iv therapy, free T₃ concentrations rapidly increased until reaching the upper level of the physiological range, then remained stable throughout the entire infusion time (ANOVA P < 0.001) (Fig. 1). Starting from the second day of infusion, the mean dose of administered T₃ was 1.10 ± 0.11 µg (mean ± SD) per hour (range 0.8–1.2), which corresponds to 24.2 µg/d (range 19.2–28.8), i.e. 13.4 µg/m² bs·d, on average. A typical example of the adjustment of L-T₃ infusion rate in a patient with elevated FT₃ concentrations after the first day of administration is reported in Fig. 2. During treatment there was a concomitant decrease in free T₄ and even more in TSH levels (ANOVA P < 0.001 for TSH), although the concentrations of both hormones still remained within the normal range (Fig. 3). In the placebo-treated patients, no significant change was observed in the circulating levels of thyroid hormones and TSH.

Routine laboratory and neuroendocrine/proinflammatory profile

Synthetic L-T₃ infusion did not induce any significant change in the main routine laboratory variables. At the end of T₃ infusion, there was a significant decrease in noradrenaline, NT-proBNP, and aldosterone plasma levels (Fig. 4), whereas PRA and IL-6 remained unchanged. Neurohormonal profile did not change after placebo infusion in the control group.

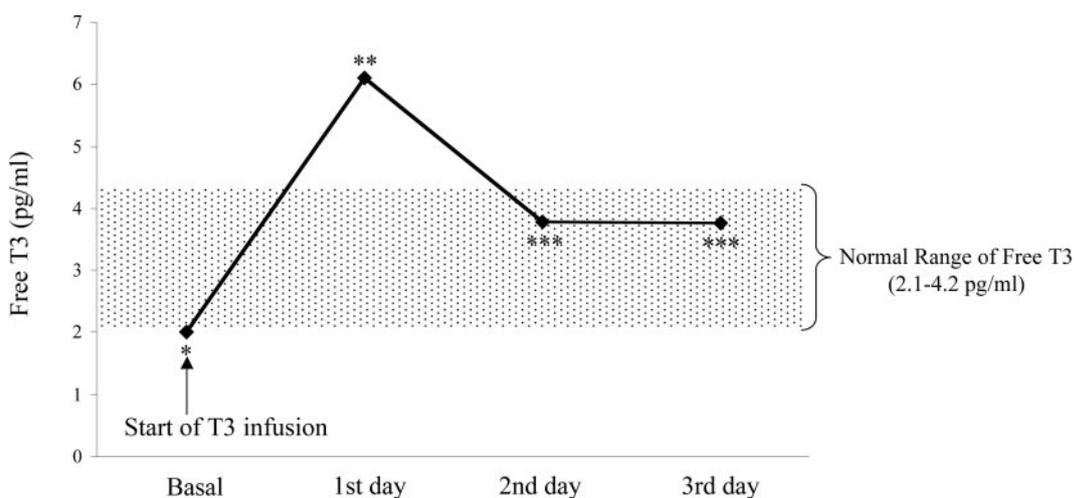
Cardiac function

End-diastolic LV volume and SV increased significantly, whereas EF, CO, SVR, external, internal, and total cardiac workload did not change (Table 3).

Discussion

In our study we assessed the effects of the iv infusion of replacement doses of L-T₃ on cardiac function and on the activated neuroendocrine system in patients with stable ischemic or non-ischemic LV dysfunction and low-T₃ syndrome. The L-T₃ infusion regimen adopted rapidly restored T₃ levels to within normal range and was associated with a significant decrease in TSH level, which still remained, however, in the normal range. A similar TSH pattern was observed in the study by Moruzzi et al. (16), in which a replacement dose of L-T₄, i.e. 0.1 mg/d, was used.

Our main finding was that L-T₃ infusion induced a positive cardiac and neuroendocrine resetting characterized by improved SV of the left ventricle and deactivation of the neuroendocrine profile, resulting from the significant reduction in vasoconstrictor/sodium retaining noradrenaline, aldosterone, and in the counterpart NT-proBNP plasma levels. The protocol we adopted for synthetic L-T₃ administration offers two main advantages: 1) constant infusion of substitutive doses of L-T₃ makes it possible to rapidly establish stable T₃ levels within the physiological range (Fig. 1), which is at variance with multiple bolus injections or an oral regimen; and 2) constant infusion of substitutive doses of L-T₃ is more effective in promoting nuclear action of T₃ and T₃-mediated transcription in the myocardium when compared with multiple bolus injections (14) or to an oral regimen (17–19). However, previous studies on euthyroid patients with DC showed that short- and medium-term treatment



- *Synthetic L-T₃ infusion rate: 20 µg/m² b.s. x 1.78 m² = 35.6 µg/day
- ** Synthetic L-T₃ infusion rate reduced to 60% of initial dose i.e. to 21.3 µg/day
- *** Synthetic L-T₃ infusion rate = 21.3 µg/day

FIG. 2. A typical example of adjustment of synthetic L-T₃ infusion rate throughout the 3-d experimental protocol.

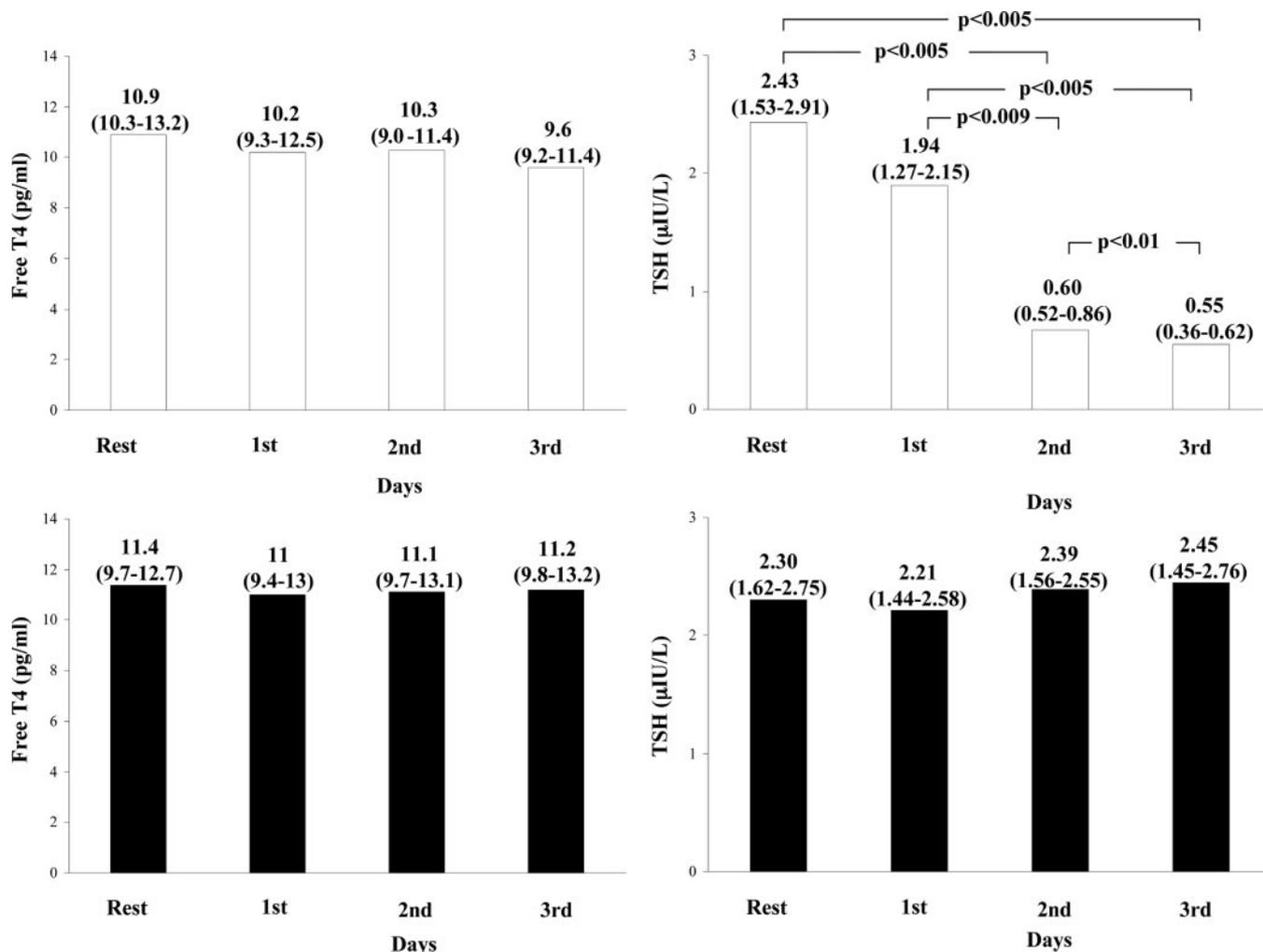


FIG. 3. Free thyroid hormones (left panels) and TSH circulating levels (right panels) before and during L-T₃ treatment.

with 0.1 mg/d synthetic L-T₄ increased CO and reduced SVR in the absence of significant changes in HR and catecholamine circulating levels (16). A similar hemodynamic finding has been shown in our previous study in patients with subclinical hypothyroidism and without cardiac disease (20). In that study, SV, EF, and CO significantly increased after synthetic L-T₄ replacement therapy, whereas blood pressure values did not change. On the contrary, the absence of a decrease in SVR after T₃ infusion observed in our low-T₃ cardiomyopathic patients could be related to the significant decrease in HR associated with a significant reduction in noradrenaline levels, neither documented in any of the previous studies cited (16), thus causing an unchanged CO despite the documented significant increase in SV.

In addition, we preferred to administer T₃ instead of the pro-hormone T₄ because in a previous study on hypothyroid animals, the restoration of serum biologically active T₃ by constant infusion of T₄ was unable to normalize all tissue levels of T₃, including the myocardium (21). This could be even more evident in the presence of an impaired peripheral conversion of T₄ into T₃, as observed in low-T₃ syndrome.

The main novel finding of this study is the evidence for a deactivation of the vasoconstrictor/sodium-retaining neuroendocrine system that occurs after L-T₃ infusion, with NT-proBNP,

noradrenaline, and aldosterone all decreasing significantly when compared with baseline values and with corresponding hormonal levels after placebo infusion. The neuroendocrine rearrangement may be interpreted as an indirect rather than direct T₃-mediated action, very likely linked to the improved cardiac performance as documented by increased LV SV. In fact, T₃ “*per se*” is able to increase rather than decrease catecholamines, BNP, and aldosterone release. This effect is mediated by promoting BNP gene transcription (22) or by regulating the rate of transcription of the β -1-adrenergic receptor gene (23). Accordingly, increased and decreased NT-proBNP levels have been observed in patients with hyperthyroidism or hypothyroidism, respectively (24), and parallel changes in the levels of catecholamine and catecholamine metabolites have been shown in cardiac muscle of rats with thyroid disorders (25). Similarly, decreased aldosterone circulating levels have been observed in hypothyroid patients treated with synthetic thyroid hormones (26). Further evidence in favor of an indirect positive effect of T₃ on neuroendocrine resetting is the observation of a decreased HR. Interestingly, the improvement in cardiac performance induced by T₃ did not correspond to increased myocardial oxygen consumption, as indirectly estimated by calculation of the rate pressure product as well as total cardiac work.

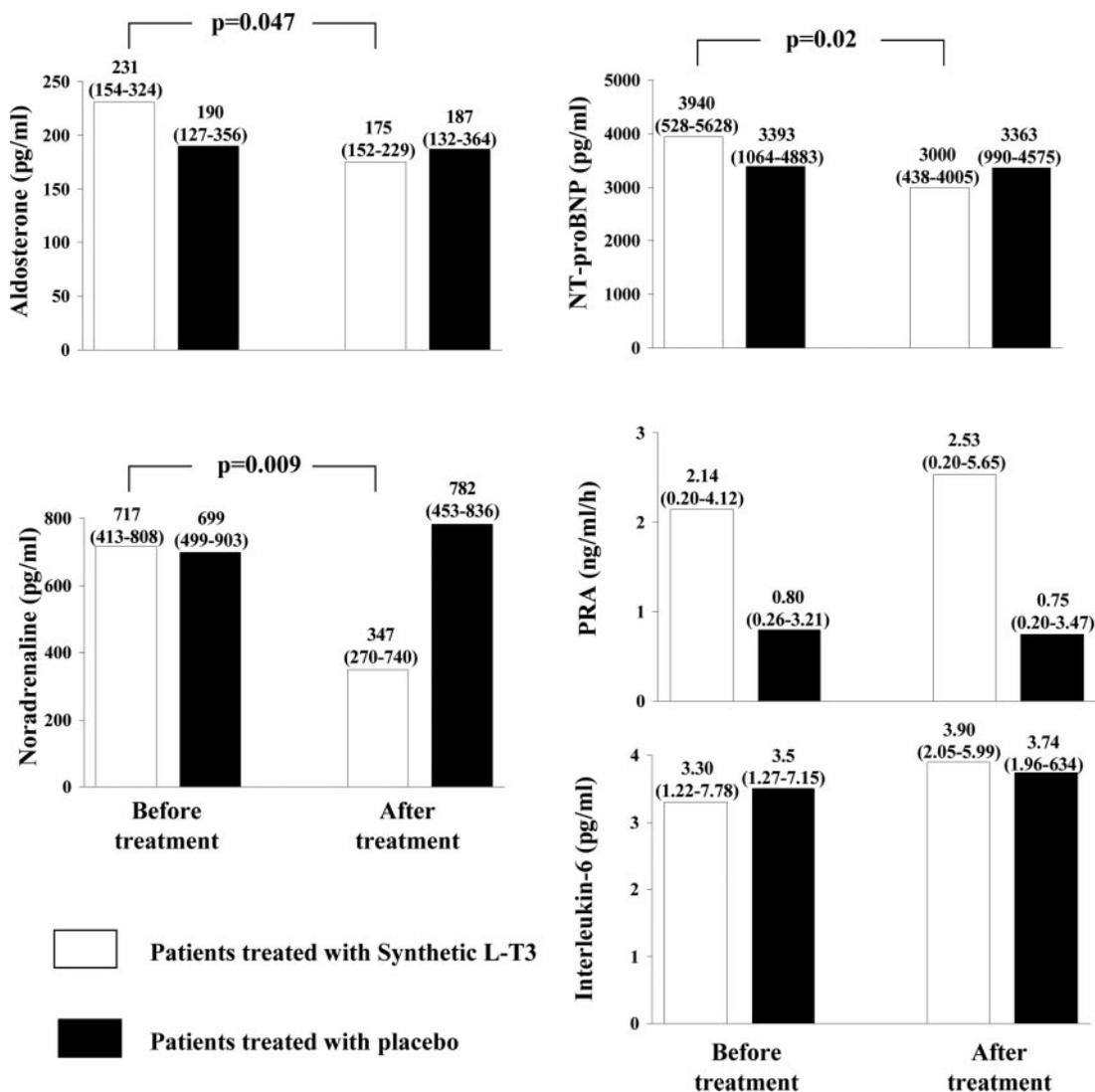


FIG. 4. Aldosterone, noradrenaline, NT-proBNP, PRA, and IL-6 levels in patients treated with L-T₃ and in patients treated with placebo.

Deactivation of the neuroendocrine system is a crucial goal in the therapeutic management of HF. The potential clinical relevance of T₃-induced neuroendocrine deactivation in patients with LV dysfunction is clearly deducible from an analysis of reported data in the literature showing highly beneficial effects of aldosterone and β-adrenergic antagonists in terms of survival, rate of hospitalization, symptoms, cardiac remodeling, and performance (27). Indeed, after L-T₃ administration, in addition to neuroendocrine deactivation, we found a parallel increase in SV and EDV in the absence of any significant change in LV EF. The increased EDV can be considered an expression of the recruitment of residual ventricular filling reserve, which is a fundamental compensatory mechanism for maintaining CO in patients with HF (28). This finding may result from the positive effects of biologically active T₃ on diastolic relaxation secondary to the increase in calcium ATPase of the sarcoplasmic reticulum pump and to the inhibition of its counter-regulatory phospholamban (10). Studies have also shown an improved cardiac function and LV remodeling after replacement doses of L-T₃ (29). Future studies are needed to clarify whether the observed positive acute changes in terms

of both neuroendocrine profile and hemodynamics will be maintained during chronic L-T₃ administration.

Limitations of the study

The study’s main limitation was the small number of patients. Therefore, results regarding the potential safety of L-T₃ administration cannot be considered conclusive; another limitation is that our results cannot be extended to all patients with HF because we enrolled only highly selected and clinically stable patients with LV dysfunction and low-T₃ syndrome. The complexity and high cost of the protocol, including hospitalization and CMR, along with the multiplicity of inclusion and exclusion criteria adopted were the main reasons for the low number of patients finally enrolled for L-T₃ administration. Another limitation of the study was the lack of assessment of the effects of synthetic L-T₃ on the diastolic function of the left ventricle. However, previous studies have clearly shown the improvement in diastolic function induced by synthetic thyroid hormone administration (30, 31). Another limitation was that the potential total body catabolic effects of T₃ were determined only indirectly by assessing

TABLE 3. CMR parameters at baseline and after 3 d in patients treated with synthetic L-T₃ or placebo infusion

Parameters	Patients treated with L-T ₃			Patients treated with placebo	
	Before L-T ₃	After L-T ₃	P value before L-T ₃ vs. after L-T ₃	Basal	P value before L-T ₃ vs. basal
LV EDV (ml/m ² bs)	133 (114–158)	142 (132–161)	0.02	130 (117–153)	ns
LV ESV (ml/m ² bs)	103 (84–127)	108 (89–124)	ns	91 (86–115)	ns
LV SV (ml/m ² bs)	35 (28–39)	40 (34–44)	0.01	36 (29–48)	ns
CO (liter/min)	4.1 (3.3–5.4)	4.8 (3.4–5.4)	ns	4.7 (4.0–5.3)	ns
CI (liter/m ² bs × min)	2.2 (1.7–2.8)	2.5 (1.9–2.7)	ns	2.5 (2.1–2.9)	ns
LV EF (%)	25 (18–32)	28 (22–32)	ns	27 (23–41)	ns
SVR (dyne/sec × cm)	2.07 (1.92–3.13)	2.10 (1.87–2.48)	ns	2.03 (1.86–2.36)	ns
Elastance	1.36 (0.93–1.63)	1.27 (0.91–1.36)	ns	1.32 (0.97–2.14)	ns
External cardiac work (ml × mm Hg × bpm)	201,226 (161,084–3,002,307)	226,519 (169,276–266,388)	ns	253,950 (190,929–306,180)	ns
Internal cardiac work (ml × bpm × mm Hg/2)	401,849 (348,910–534,505)	396,885 (343,080–473,613)	ns	360,260 (314,153–440,763)	ns
Total cardiac work	626,859 (492,291–787,522)	592,085 (540,060–756,684)	ns	599,945 (538,645–748,639)	ns

Data are expressed as median (25th and 75th percentiles). bpm, Beats per minute; CI, cardiac index.

blood urea nitrogen levels, and not directly by calorimetry. However, in this context it has already been shown that an increased catabolic rate occurs not only when circulating T₃ levels are kept within normal range, but also during supra-physiological L-T₃ administration (10), when circulating T₃ exceeds the upper limit of the reference interval.

Conclusions

Altogether, our data indicate that short-term administration of substitutive doses of synthetic L-T₃ state reduces activation of the neuroendocrine system and improves LV SV in patients with ventricular dysfunction and low-T₃ syndrome. Future studies will clarify whether this approach may truly be considered a novel tool in the therapeutic strategies for managing cardiac failure.

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