Effect of Short-Term Infusive Dobutamine Therapy on Thyroid Hormone Profile and Hemodynamic Parameters in Patients With Acute Worsening Heart Failure and Low-Triiodothyronine Syndrome

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Objectives: Low-triiodothyronine syndrome (LT3S) is a condition characterized by decreased total serum T3 and free T3 (fT3) with normal levels of thyroxine (fT4) and thyrotropin (TSH). Experimental studies have shown that altered thyroid hormones (THs) metabolism modifies cardiovascular homeostasis.

The aim of the study was to evaluate prospectively the reversibility and pathophysiological implications of sick euthyroid syndrome in patients with moderate-to-severe chronic heart failure.

This study should demonstrate the role of short-term acute dobutamine heart failure (HF) treatment in improving thyroid hormone, neuroendocrine profile, and ventricular performance in patients with worsening HF and LT3S.

Methods: During hospitalization for worsening heart failure, fT3, fT4, and TSH levels; brain natriuretic peptide; and echocardiographic and right hemodynamic parameters were recorded on admission, after HF treatment and after dobutamine infusion in patients with LT3S.

Results: We evaluated 60 patients hospitalized for severe acute decompensated HF. Fourteen patients (23%) of the population presented an LT3S. Dobutamine infusion in LT3S patient group evoked a statistically significant cardiac index increase, pulmonary capillary arterial wedge pressure, and right atrial pressure decrease with left ventricle diastolic dysfunction recovery; the hemodynamic and clinical improvement were associated with brain natriuretic peptide reduction and increased fT3 levels. Free T3 levels increased in all of them and normalized in 6 patients (42%). Free T4 and TSH values remained unchanged.

Conclusions: These data suggest that LT3S in patients with acute decompensated HF can be useful in assessing the status and clinical course for this disease. These preliminary results indicate that LT3S reversibility by dobutamine is associated with short-term hemodynamic and neurohormonal improvement in patients with persistent severe heart failure.

Key Words: low-triiodothyronine syndrome (LT3S), heart failure, dobutamine

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Thyroid hormones (THs) have a fundamental role in cardiovascular homeostasis, and the heart is a primary target for TH in both physiological and pathological conditions.

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In heart failure (HF), the main alteration of thyroid function is referred to as low-triiodothyronine syndrome (LT3S), known also as nonthyroidal illness syndrome. This syndrome consists of an impairment of the hypothalamus-pituitary-thyroid axis characterized by decreased total serum T3 and free T3 (fT3) with normal levels of thyroxine (fT4) and thyrotropin (TSH).[1] This condition is found in approximately 30% of patients with severe congestive HF.[2]

Experimental studies have shown that altered THs metabolism modifies cardiovascular homeostasis by inducing alterations of cardiac histology, cardiomyocyte morphology and relaxation, gene expression, determining diastolic and systolic myocardial dysfunction.[3,4]

The improvement of ventricular performance and neuroendocrine profile (reducing adrenaline, aldosterone, and N-terminal-pro-brain natriuretic peptide [BNP] levels) is shown after short-term synthetic Levo-T3 replacement therapy.[5] In addition to T3 infusion replacement, also inotropic therapy seems to have some thyroid hormonal effects. Dopamine infusion induced a reduction in TSH and an increase in fT3 serum levels in surgical risk patients and in critically ill patients,[6,7] and dobutamine lowers TSH concentration in healthy subjects.[8] The effects of dobutamine on FT3 and TSH in patients with HF are still unknown.

AIM OF THE STUDY

To evaluate the effects of short-term treatment with dobutamine in improving TH profile, neuroendocrine pattern, and ventricular performance in patients with worsening acute HF and LT3S.

MATERIALS AND METHODS

We evaluated 60 patients with worsening acute heart failure (AHF) recovered from December 2010 to January 2011. They received standard therapy of AHF according to European Society of Cardiology guidelines for the treatment of AHF.

In all 60 patients, fT3, fT4, and TSH serum levels before and after the standard treatment for AHF were assessed. Fourteen (n = 14) patients with a worsening clinical status presented characteristics of LT3S. These patients with LT3S underwent right heart catheterization and were treated with short-time dobutamine infusive therapy. Exclusion criteria from our protocol included patients with primary overt or latent thyroid disorder, hormone replacement, and thyreostatic and amiodarone therapy.

Echocardiography

All patients underwent a complete echocardiography-Doppler examination (VIVID 7 echocardiograph General Electric Medical Systems, Horten, Norway) on admission and after treatment. Left ventricle end-diastolic and end-systolic volumes, left

ventricle end-diastolic and end-systolic diameters, and ejection fraction were measured. The Doppler method was used to calculate early and late transmitral flow velocities (E- and A-wave components) and deceleration time. The ratio of early transmitral flow velocity to early mitral annular velocity (E/E′) was measured by tissue Doppler imaging.

Swan-Ganz Catheterization

A triple lumen Swan-Ganz catheter was inserted percutaneously through the internal jugular vein and positioned in the pulmonary artery to obtain hemodynamic measurements. Cardiac output was measured using the termodilution method. Derived hemodynamic variables were calculated using standard formulas.[9]

Blood Chemistry

All patients underwent brain natriuretic peptide (BNP) and fT3, fT4, and TSH plasmatic measurements. Brain natriuretic peptide serum levels were obtained using a commercial kit (Triage, Biosite Diagnostics, San Diego, CA) (normal values <100 pg/mL). Free T3 (normal values, 2.4–4.7 pg/mL), fT4 (normal values, 7–18 pg/mL), and TSH (normal values, 0.270–4.2 mU/L) were all measured by a chemiluminescence assay (Architech, Abbott Laboratories, North Chicago, IL).

RESULTS

Sixty patients with ischemic (n = 39 [65%]) and idiopathic dilated cardiomyopathy (n = 21 [35%]) with a mean ± SD age of 70 ± 13 years and a mean ± SD left ventricle ejection fraction of 27% ± 6% were admitted to our intensive unit coronary care with acute decompensated HF (AHF). Immediately after the initial clinical evaluation, all patients were treated with AHF optimized therapy: all patients received infusive therapy with diuretics and nitrates. No patients underwent ultrafiltration, noninvasive mechanical ventilation treatment, and no other inotropic infusive drugs were used.

At clinical presentation, 48 patients (80%) were in New York Heart Association (NYHA) class IV, whereas the remaining 12 patients (20%) were in NYHA class III HF.

After the HF treatment, 46 patients (77%) had improved clinical and hemodynamic status, with an improvement in NYHA class (38 patients passed from NYHA class IV to NYHA class II, and 8 patients passed from NYHA class III to NYHA class II). Furthermore, a significant decrease of BNP blood levels was observed (from 1000 ± 684 pg/mL to 284 ± 180 ng/mL; $P < 0.001$).

Fourteen patients (23%) did not show an early clinical improvement after HF treatment: 10 patients (71%) remained in NYHA class IV and 4 patients (29%) remained in NYHA class III.

All patients underwent thyroid hormone and TSH serum level assessment on admission; and after that, they underwent the standard therapy for HF. The 46 patients with clinically and hemodynamically improvement after treatment showed no changes in thyroid hormonal plasmatic values.

The 14 patients who did not improve after HF treatment also presented a LT3S profile. These patients had a mean ± SD age of 68 ± 15 years, and the mean ± SD left ventricle ejection fraction was 24 ± 7%. Fifty-seven percent of patients were affected by ischemic cardiomyopathy instead of the 43% by idiopathic cardiomyopathy. All the other general characteristics of the LT3S population are summarized in Table 1. This group of patients with a more unstable clinical and hemodynamic status were treated with short-time dobutamine infusion (5–20 μg/kg per minute) for a mean ± SD duration of 60 ± 36 hours.

Dobutamine infusion in this group of patients with HF-LT3S evoked a statistically significant improvement in all the major hemodynamic parameters measured with right ventricle catheterization. Cardiac index increased (from 1.7 ± 0.3 to 2.2 ± 0.4 L/min per square meter; $P < 0.05$), whereas pulmonary capillary arterial wedge pressure decreased (from 35 ± 8 to 17 ± 5 mm Hg; $P < 0.05$) and right atrial pressure was reduced (from 18 ± 4 to 8 ± 5 mm Hg; $P < 0.05$) with left ventricle diastolic dysfunction recovery, as was shown by the reduction of E/E′ wave ratio and E/A wave ratio measured through transthoracic echocardiography (from 25 ± 8 to18 ± 5 and from 2.8 ± 0.7 to 0.96 ± 0.4, respectively; $P < 0.05$).

TABLE 1. Baseline Characteristics of Patients With HF With LT3S

Variables	Patients Without LT3S (n = 46)	Patients With LT3S (n = 14)
Weight, kg	68 ± 7	66 ± 5
LV ejection fraction, %	30 ± 5	24 ± 7*
Age, yrs	67 ± 10	68 ± 15
NYHA class, n		
III	8 (18)	4 (29)
IV	38 (82)	10 (71)
Etiology		
Ischemic cardiomyopathy	25 (55)	8 (57)
Idiopathic cardiomyopathy	21 (45)	6 (43)
Creatinine, mg/dL	1.4 ± 2	1.5 ± 3
Hemoglobin, g/dL	12 ± 1	11 ± 2

Data are expressed as mean ± SD or frequencies (n [%]).
*$P < 0.05$.
LV indicates left ventricle; NYHA, New York Heart Association.

All the hemodynamic and clinical improvements (Table 2) were associated with BNP reduction (from 996 ± 246 to 356 ± 128 pg/mL; $P < 0.05$). In all these patients, fT3 levels increased (from 1.6 ± 0.4 to 2.3 ± 0.5 pg/mL; $P < 0.05$) and normalized in six (reference range, 2.4–4.7 pg/mL). Free T4 and TSH values slightly changed (from 12 ± 5 to 13 ± 4 pg/mL and from 2.1 ± 7 to 2.0 ± 6 mU/L, respectively; ns). There were no observed differences between increase of fT3 levels and dobutamine dosages and the duration of treatment. All the other hemodynamic and clinical parameters are summarized in Table 2.

DISCUSSION

Approximately 30% of patients with severe congestive HF[1] are affected by LT3S. It is characterized by decreased total serum T3 and fT3 with normal levels of fT4 and TSH.[2] It is well known that THs have a crucial role in cardiovascular homeostasis and the heart is a primary target for THs in both physiological and pathological conditions. However, LT3S reducing cardiac output may have potential negative effects, contributing to the progressive deterioration of cardiac function and myocardial remodeling in HF and representing a powerful predictor of mortality in patients with HF.[10]

In our study, we showed that a short-term dobutamine treatment in patients affected by acute decompensated HF without clinical improvement after optimized HF therapy and with LT3S improves not only in the hemodynamic parameters but also in thyroid hormone profile. Short-term dobutamine treatment infusion resulted in the increase of fT3 values, with a normalization in 6 patients with LT3S. Furthermore, for the first time, we documented a concomitant significant decrease of BNP values. Accordingly, serial measurements of THs and BNP levels may be

TABLE 2. Results of Dobutamine Infusion in Patients With HF-LT3S

Variables	Basal	After HF Therapy
NYHA class	3.5 ± 0.5	2.5 ± 0.5*
fT3, pg/mL	1.6 ± 0.4	2.3 ± 0.5*
fT4, pg/mL	12 ± 5	13 ± 4
TSH, mU/L	2.1 ± 7.0	2.0 ± 6.0
BNP, pg/mL	996 ± 246	356 ± 128*
DT, ms	102 ± 13	158 ± 12*
E/E′	25 ± 8	18 ± 5*
E/A	2.8 ± 0.7	0.96 ± 0.4*
SAP, mm Hg	90 ± 10	110 ± 8*
HR, beats per minute	78 ± 15	87 ± 14 *
CI, L/min per m^2	1.7 ± 0.3	2.2 ± 0.4*
PCWP, mm Hg	35 ± 8	17 ± 5*
RAP, mm Hg	18 ± 4	8 ± 5*
SVR, $dynescm^{-5}$	1.711 ± 516	1.114 ± 396*
LVEF, %	24 ± 7	25 ± 6

Basal means before HF therapy.

Data are expressed as mean ± SD.

*$P < 0.05$ basal versus therapy.

CI indicates cardiac index; DT, deceleration time; E′, tissue Doppler early diastolic myocardial velocity; E/A, early and atrial LV diastolic velocity wave ratio; HR, heart rate; LVEF, left ventricle ejection fraction; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SAP, systemic arterial pressure; SVR, systemic vascular resistance.

considered 2 coins of the same medal and may be used in clinical practice, in the follow-up of patients with HF. Based on the results reported herein, the serum THs levels seem to represent a repeatable, relatively inexpensive and reliable marker of severe CHF, which seems to be related to hemodynamic abnormalities and might reflect the effects of the acute treatment.

In literature, it is known that THs regulate the expression of cardiac genes by means of thyroid hormone response elements in the promoter regions of genes for α- and β-myosin heavy chain (MHC) and SERCA2 ATPase.[4,11] Thyroid hormone deficiency in adult rodent heart is characterized by a shift in expression of the α-MHC isoform to the β-MHC isoform and a decrease of SERCA2 enzyme activity. These changes result in a reduction of systolic function owing to the slower rate of adenosine triphosphate hydrolysis of β-MHC and reduction of diastolic function owing to the minor relaxation of the cardiomyocytes leading to reduced calcium ion uptake by SERCA2 during diastole.[4] Some clinical observational studies have shown that this form of secondary thyroid dysfunction have a negative prognostic impact in patients with HF and consider LT3S an independent predictor of death. Pfister et al.[12] demonstrated that fT3 (hazard ration [HR], 0.58; 95% confidence interval [CI], 0.34–0.98) and LT3S (HR, 3.0; 95% CI, 1.4–6.3) were significantly related to NT-pro-BNP in patients with HF but were predictors of mortality independently of NT-pro-BNP and other known cardiovascular risk factors. Iervasi et al.[13] proved that LT3S was a predictor of cumulative death (HR, 3.582; $P < 0.0001$) followed by the common cardiovascular risk factors (dyslipidemia: HR, 2.955; $P = 0.0023$; age: HR, 1.051; $P < 0.005$) and by ejection fraction (HR, 1.037; $P = 0.006$). Similarly, Pingitore et al.[14] have shown a relationship between low T3 levels and all-cause mortality (HR, 0.6, CI, 0.5–0.8; $P < 0.02$) and cardiac mortality (HR, 3.5 CI, 1.7–13; $P < 0.04$) in patients with chronic HF.

Reversal of this low-T3 phenotype with physiological replacement of T3 has been shown to be beneficial with ejection fraction and contractile performance improvement in an animal model of HF.[15] Hamilton and Lynne.[16] showed also that immediate intravenous administration of T3 in patients with advanced congestive HF improves cardiac output and reduces peripheral vascular resistances. Other clinical studies evidenced significantly improved ventricular performance and neuroendocrine profile (reducing adrenaline, aldosterone, and NT-pro-BNP levels) after short-term synthetic L-T3 replacement therapy in patients with dilated cardiomyopathy.[5]

However, in other chronic diseases, reversion of the underlying condition is associated with sick euthyroid syndrome reversibility, as shown by the increase in serum THs observed after cardiac transplantation.

Opasich et al.[17] evaluated thyroid hormone measurements in 6 of the 9 patients with sick euthyroid syndrome with severe CHF who underwent cardiac transplantation. Total fT3 serum level increased in all of them and normalized in 5 of them after heart transplant.

Moreover, it is possible that the correction of sick euthyroid syndrome offers therapeutic advantages resulting in cardiac and exercise performance in patients with chronic HF.

In addition, few studies showed that inotropes such as dopamine, used in the treatment of HF to increase cardiac output, can reduce the levels of TSH and increase T3 levels.[17] The effects of dobutamine, commonly used in the setting of severe illness and HF, on THs are unknown. In only one study, 30 healthy subjects were treated with high-dose dobutamine infusion, and TSH concentration decreased in both dobutamine and control subjects; but there was an additional statistically significant effect of dobutamine treatment to decrease TSH. These results indicate that immediate administration of high-dose dobutamine lowers TSH by an unknown mechanism.[8] In one other study in the literature, in high-risk surgical patients, dobutamine produced fewer effects on thyreotropin serum concentrations in comparison with dopamine when used in equivalent dosages.[6] Dobutamine is a synthetic catecholamine that acts primarily through myocardial β1 adrenergic receptor with weak stimulatory effect on peripheral β2 and α receptor without effects on dopamine receptors.[18] The mechanism through which dobutamine acts on thyroid function is unknown. Some studies have attempted to demonstrate dobutamine action on the thyroid function and in general on hormonal function. Several hypotheses were made such as that dobutamine may increase TSH clearance or it may decrease production and/or secretion of either thyrotropin realizing hormone, TSH, or both.[19] Another theory is that dobutamine acting on adrenergic receptor may regulate the secretion of TSH, reducing it.[20] It is well established that dopamine may rapidly lower TSH level acting on dopaminergic receptor[21]; similarly, dobutamine may stimulate the same receptors but only at toxic dosages.[22]

Our preliminary data suggest that LT3S in patients with acute decompensated HF can be useful in assessing the status and clinical course for this disease. These results indicate that a rapid LT3S reversibility is associated with short-term hemodynamic and neurohormonal improvement. Interestingly, the restoration of an increase of T3 plasma levels was associated with an increase in stroke volume and a decrease of systemic vascular resistance. These beneficial effects on functional parameters were further reinforced by the evidence of a positive neuroendocrine reset, with a significant decrease in BNP plasma levels. In conclusion, determinations and fluctuations of T3 serum levels may be considered as an easy-to-determine marker of severity and an additional tool to monitor the therapy in the management of

patients with severe HF without hormonal replacement therapy needed. However, additional pathophysiological studies are needed to confirm these preliminary results in a larger HF population.

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