The Management of Thyroid Abnormalities in Chronic Heart Failure

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KEYWORDS

• Hypothyroidism • Low T3 syndrome • Heart failure • Cardiac fetal phenotype • Levothyroxine • liothyronine

KEY POINTS

- Normal triiodothyronine (T3) levels are essential to preserve cardiac morphology and function.
- Overt and subclinical hypothyroidism are associated with an increased risk of heart failure, and levothyroxine is able to improve cardiovascular function in hypothyroid patients.
- Low T3 syndrome can develop in patients with advanced heart failure and is associated with a negative prognosis.
- Low T3 syndrome is associated with alterations in thyroid hormone receptors expression, contributing to the development of a cardiac fetal phenotype, leading to cardiac dysfunction.
- The positive effects of treatment with thyroid hormones in patients with low T3 and heart failure support their potential therapeutic approach in heart failure.

INTRODUCTION

It is widely recognized that thyroid hormone (TH) excess (overt hyperthyroidism and subclinical hyperthyroidism) and TH deficiency (overt hypothyroidism and subclinical hypothyroidism [SHypo]) can represent potential causes of the onset or worsening of heart failure (HF).[1–3] Moreover, changes in thyroid function can develop in acute and chronic illnesses (nonthyroidal illnesses), including HF.[4,5]

CELLULAR MECHANISMS OF THYROID HORMONE ACTION ON THE HEART

Triiodothyronine (T3), the active TH, affects heart rate, cardiac contractility, and systemic vascular resistance (SVR).[1,4,5] The physiologic effects of T3 on the cardiovascular (CV) system are in part mediated by genomic mechanisms, which result from the binding of T3 to nuclear TH receptors (TRs).[4,6] These receptors, which are abundant in the human atria and ventricles, regulate the transcription of various cardiac genes expression, ion channels, and cell surface receptors. The transcriptions of α–myosin heavy chain (MHC) isoform, sarcoplasmic reticulum Ca^{2+}-adenosine triphosphatase ATPase (SERCA2), voltage-gated K^+ channels, β_1-adrenergic receptors, guanine nucleotide regulatory proteins, adenylate cyclase, NA^+/K^+-ATPase, atrial brain natriuretic peptide (BNP), and malic enzyme are up-regulated by T3.[1,4,5] On the contrary, the expressions of β-MHC, phospholamban, Na^+/Ca^{2+} exchanger, TR-α1, and adenylyl cyclase types V and VI are down-regulated by T3.[1,4,5] Nongenomic TH actions, which do not involve TR-mediated transcriptional events, are more rapid than genomic effects; they control the effects of T3 on the transport of glucose and amino acids and ion fluxes across the plasma

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membrane; they also regulate the cytoskeleton and mitochondrial functions.[4,6]

Altogether, these direct and indirect effects of TH are important in regulating the cardiac rhythm and CV hemodynamic. Genomic and nongenomic TH actions control the cardiac pacemaker and heart rate, the potential duration and repolarization currents, the response to β-adrenergic receptor, and the interaction with other neurohormonal factors.[1,4,7] Moreover, T3 administration is able to improve the CV hemodynamic by influencing the relaxation and contractile properties of the myocardium and by acting on the cardiac preload and afterload.[1,7] Cardiac volume is increased by T3 administration for the activation of the renin-angiotensin-aldosterone system (RASS); on the contrary, cardiac afterload is reduced because of the T3 effects on the vascular tone.[4] T3 reduces SVR and increases nitric oxide availability, improving endothelial function.[4,5]

THYROID DYSFUNCTION AND HEART FAILURE

Overt hypothyroidism (characterized by increased serum thyrotropin [TSH] and reduced free T3 and free thyroxine levels) is associated with left ventricular diastolic dysfunction.[8] The activity of the $Ca2^{+}$-ATPase within the sarcoplasmic reticulum is decreased, with a consequent reduced reuptake of calcium during diastole.[7,8] Moreover, both systolic and diastolic functions are impaired during effort, leading to an decreased exercise tolerance for the slowed myocardial relaxation and the impaired left ventricular filling and vasodilatation during effort.[9,10] The onset of dyspnea during exercise can be the first symptom of the altered CV hemodynamic in patients with TH deficiency.[9,10]

CV findings, similar to overt hypothyroidism, also have been reported in patients with SHypo, a condition characterized by increased serum TSH with levels of THs within the reference range, although at their lower limits.[2,3] Several studies using Doppler echocardiography, tissue Doppler, and cardiac MRI suggest that patients with mild TH deficiency or severe TH deficiency can have CV alterations, leading to a higher risk of developing HF when TH deficiency is untreated in the long-term.[2,3,9–14] Moreover, SHypo can be a risk factor for cardiac death in patients with chronic HF.[15]

Treatment of overt hypothyroidism and SHypo with levothyroxine (LT4) is able to prevent the progressive left ventricle dysfunction and improve systolic and diastolic dysfunctions, SVR, and endothelial function, improve cardiac output thereby increasing (CO) and stroke volume.[11,12,16] Therefore, LT4 in replacement doses is recommended by international guidelines and expert opinions in patients with serum TSH above 10 mU/L.[2,3,17,18] This treatment also should be considered when serum TSH is persistently increased in mild disease (TSH 4.5–9.9 mU/L), especially in patients with a high CV background.[2,3,17,18]

THYROID ABNORMALITIES IN NONTHYROIDAL ILLNESS SYNDROME

Nonthyroidal illness syndrome (NTIS) is characterized by decreased serum T3 levels, normal to high levels of reverse T3 (rT3), and inappropriately normal serum TSH or low serum TSH.[19–21] This syndrome can be considered a neuroendocrine response to a severe illness or starvation. Initial abnormalities of NTIS are characterized by decreased serum T3 and increased rT3 levels.[19,20] The pathophysiologic basis of the development of these alterations are related to the following effects: (1) a decreased extrathyroidal conversion of thyroxin (T4) to T3 for the reduced activity of type 2 deiodinase, (2) a decreased transport of T4, and (3) an increased TH catabolism for the enhanced activity of type 3 deiodinase (D3) in the peripheral tissues.[19–22] rT3 is consequently increased due to its reduced peripheral catabolism and clearance.

TSH levels may rise briefly after the onset of the acute disease; however, circulating TSH levels usually remain within the low to normal range. Subsequently, TSH can be decreased as a consequence of a central hypothyroidism due to a reduced serum TSH secretion for abnormalities in thyrotropin-releasing hormone secretion and clearance. The progressive development of a low serum T4 is linked to an increased probability of death.[19–22]

Low levels of T3 are associated with a decreased metabolic rate. Therefore, the changes in TH homeostasis during the acute phase of NTIS have been interpreted as an attempt to save energy expenditure and do not require any intervention. This interpretation of the low T3 syndrome, however, remains controversial and has been debated for many years probably because it may have a different significance in the acute and chronic phases of illness.[21]

Experts suggest that serum TSH and T3 levels should be reassessed within 1 months to 3 months after an acute illness before deciding to start a treatment with replacement doses of TH.[17,19–22]

THYROID ABNORMALITIES IN HEART FAILURE

HF represents a common final condition of severe cardiac diseases.[23]

At the beginning of its onset, HF is characterized by a decreased CO, increased atrial pressure, and inadequate blood volume, which is compensated by the activation of the RAAS and systemic nervous system to preserve blood volume and pressure. A low T3 syndrome can develop in this phase of HF; it could represent an adaptive process to reduce energy expenditure and metabolic demand. Subsequently, the progression of HF is characterized by a persistent neuroendocrine activation, which is associated with an increase in hormonal response (enhanced levels of RAAS, vasopressin, cortisol, insulin, atrial natriuretic peptide, and BNP and reduced levels of growth hormone) and in inflammatory and immunologic mediators (cytokines, such as interleukin 6 and tumor necrosis factor). All these changes are responsible for an increased cardiac overload and myocardial fibrosis with a negative cardiac remodeling and a progressive deterioration and apoptosis of myocytes and endothelial function. In this advanced stage of HF, the administration of β-adrenergic blocking drugs, digitalis, angiotensin-converting enzyme inhibitors, diuretics, and aldosterone antagonists can improve symptoms and CO. Morbidity, mortality, and recurrent hospitalization, however, are always high in patients with advanced HF for the progressive and irreversible cachexia.[23] Therefore, the persistent activation of the hormonal and inflammatory system and the persistent low T3 syndrome represent a maladaptive mechanism inducing cellular, functional, and morphologic negative CV changes with a negative cardiac remodeling. All these factors are responsible for the progression of HF and death.

In physiologic conditions, TH controls cardiac growth and maturation; its deficiency in the low T3 syndrome is associated with alterations in expression of TRs, contributing to the development of a cardiac fetal phenotype, leading to cardiac dysfunction.[24–29]

The hypoxia and the inflammatory response to HF are able to reduce the type 2 deiodinase activity in the cardiomyocytes, which results in a decrease of intracellular T3 bioavailability.[24] Changes in the deiodinase activities are associated with the increase in proinflammatory cytokines; they can modulate the cardiac levels of T3, contributing to a local low T3 state in the failing heart. Hypoxia also is able to induce the expression of D3 in cardiomyocytes. In a rat model of right ventricular (RV) hypertrophy and failure, D3 activity increased in the chronically overloaded RV, whereas no changes were observed in the LV of the same heart.[25]

The abnormalities in TRs and the decreased deiodinase activities could both lead to the development of important changes in cardiac gene expression, which are similar to those observed in hypothyroidism. The induction of D3 in the cardiomyocytes is associated with a decrease in the T3 concentrations in the tissue and in the T3-dependent gene expression with TRα 1 overexpression.[26–29] In a rat model of starvation-induced low T3 syndrome, the mRNA content of the α-MHC and SERCA2 was reduced.[27,29,30] Propylthiouracil-induced hypothyroidism in rats was responsible for a reduction of the myocyte cross-sectional area, leading to cardiac atrophy. Similarly, T3 deficiency induces alterations in the myocyte shape typical of progressive HF.[31,32] Therefore, long-term T3 deficiency is responsible for the negative effects on myocardial function, histology, and morphology, inducing cellular fibrosis and a negative cardiac remodeling with cellular and structural changes similar to those observed in the progression of HF[31,32] (**Table 1**). All these findings suggest that T3 has an important role in regulating myocyte transverse shape and wall stress and could play a key role during the progression of HF in patients with low T3 syndrome.[24–32]

Up to 30% of patients with HF have low serum T_3 levels; they are associated with CV changes in humans. Although the α-MHC isoform is prevalently expressed in the human heart, changes in the MHC isoform expression can occur in the human atria in patients with congestive HF and in severe hypothyroidism.[33,34] These changes also are linked to a decreased expression of SERCA 2 and increased cytoskeletal abnormalities, with consequent modifications in contractility, wall stress, chamber diameters, and wall thickness.[34]

Studies in humans have demonstrated that low serum T_3 levels correlate with the severity of HF when assessed by the New York Heart Association (NYHA) classification.[35–37] Low T3

Table 1
Main findings in heart failure and effects of low T_3 syndrome on the cardiovascular system

	Heart Failure	Heart Failure + Low T3 Syndrome
LV systolic function	↓	↓ ↓
LV diastolic function	↓	↓ ↓
SVR	↑	↑ ↑
Cardiac contractility	↓	↓ ↓
Renal function	↓	↓ ↓
CO	↓	↓ ↓
Alterations in the myocyte shape	↑	↑ ↑

syndrome occurs with a higher incidence in patients with NYHA classes III and IV compared with NHYA I and NYHA II.[34–37] In addition, the negative prognostic role of the low T3 is enhanced in patients with higher BNP concentration, both in acute decompensated HF and chronic compensated HF.[37] The abnormal TH pattern in patients with HF is associated with a high incidence of fatal events. In a large cohort of cardiac patients with ischemic HF and nonischemic HF, T3 levels and left ventricular ejection fraction (LVEF) were the only independent predictive variables of both cardiac and cumulative deaths at multivariate analysis.[36] Patients with low T3 levels and reduced LVEF had the highest mortality compared with patients with similar LVEF but normal T3 levels.[36] These results suggest that T3 levels can be useful to identify patients at high risk for death.

TREATMENT WITH THYROID HORMONES

Hypothyroid cardiac alterations in the failing heart can be reversible with TH replacement therapy. The T3 supplementation in the culture of neonatal cardiomyocytes was associated with a positive change in the myocyte shape, with an increased ratio of the major to minor cell axis and an increase in the synthesis of α-MHC.[38–41] Treatment with physiologic doses of T3 also normalized the SERCA2 contents of cardyomyocytes, improving systolic and diastolic functions and heart performance.[38–41]

This Opinion is supported by the Following consideration: (1) the evidence that T3 has positive effects on the CV function, (2) the observation that even mild TH deficiency is associated with a worse outcome in cardiac patients, (3) the negative prognostic impact of the low T3 syndrome, and (4) the improvement of the cardiac dysfunction after TH administration. On this basis, LT4, LT3, and TH analogs have been administered to improve the prognosis of patients with HF.

Some studies used LT4 in patients with HF or dilated cardiomyopathy. Moruzzi and colleagues[42,43] performed 2 randomized placebo-controlled studies to evaluate the short-term and long-term CV effects of oral LT4 at a dose of 0.1 mg per day. In both of these studies, LT4 was able to significantly improve cardiac contractility, resting LVEF, CO, and exercise capacity.[42,43] Similar results were observed by Malik and colleagues,[44] who administered intravenous LT4 (20 μg/h) in 10 consecutive patients with severe systolic HF, which progressed to cardiogenic shock. These patients had a significant improvement in cardiac index, pulmonary capillary wedge pressure, and mean arterial pressure after 24 hours and 36 hours of LT4 administration.

The first study that used LT3 was performed by Hamilton and colleagues.[45] In a small nonrandomized trial, these investigators used an intravenous bolus of liothyronine (LT3) followed by LT3 infusion in patients with advanced HF and low T3 syndrome.[45] CO improved significantly 2 hours after T3 administration. Moreover, SVR significantly decreased without considerable changes in blood pressure. Comparable findings were observed by Pingitore and coworkers.[46,47] They administered physiologic doses of LT3 (20 μg/d/m^2 body surface) for a period of 96 hours in 6 patients with advanced HF and low T3 syndrome.[46] A progressive reduction in SVR, an increase in LVEF, and an improvement of CO were observed after T3 administration. These positive results were confirmed in a placebo-controlled study by the same investigators.[47] They administered a 3-day LT3 infusion in patients with chronic and stable dilated cardiomyopathy and low T3 syndrome. Their results showed an improved cardiac performance and an increase in total cardiac work, which were associated with a concomitant improvement of the neuroendocrine pattern (decreased noradrenaline plasma levels and N-terminal prohormone of BNP).[47]

All these studies demonstrated that THs were well tolerated with no occurrence of major or minor side effects and without any increase in atrial arrhythmias or heart rate.

THYROID HORMONE ANALOGS IN HEART FAILURE

3,5-diiodothyropropionic acid (DITPA), a TH analog with a cardiac inotropic selectivity, was tested in humans to treat congestive HF in a randomized clinical trial.[48] DITPA was able to improve cardiac index and diastolic function and decrease SVR; it also improved total cholesterol and LDL cholesterol values and triglycerides. Its use, however, was not associated with an improvement of CHF symptoms and generally was poorly tolerated by the patients because of an average weight loss of 11 kg. This decrease in weight was not related to the gastrointestinal side effects, which were common in patients treated with DITPA.[48] DITPA also suppressed the hypothalamic-pituitary-thyroid axis and had a negative effect on bone by increasing bone turnover.[48] Unfortunately, these several adverse events caused the withdrawal of DITPA from clinical trials.

SUMMARY

Large prospective multicenter studies are needed to assess the usefulness of THs in treating and/or

preventing the evolution of HF. Further research is needed to establish which drugs (T3, T4, or analogs) could be useful in treating patients with HF. The timing of TH administration and the best schedule for therapy (their dosage and route of administration intravenous or orally) also should be assessed.

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