Thyroid hormone and heart failure: from myocardial protection to systemic regulation

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Heart failure (HF) is an intriguing model of chronic disease. It starts as an organ disorder developing, in its progression, into a systemic disease in which the dysfunction of other organs plays a relevant clinical and prognostic impact. Furthermore, continuous activation of systemic pathways plays a role in disease progression, switching their effect from protective to harmful. In this combination of organ dysfunction and systemic derangement, thyroid hormone (TH) have an important regulative impact from cardiovascular to systemic level and from molecular/cellular processes to clinical setting. Whether it is accepted to include TH and thyroid stimulating hormone assessment in the clinical HF course, the next challenge will be to ascertain the benefit of TH replacement therapy in HF patients, taking into consideration the type of hormone to administer, dosage and treatment schedule.

**KEYWORDS:** heart failure • hypothyroidism • integrin • low T3 syndrome • thyroid hormone • thyroid hormone receptors

The thyroid hormone (TH) system regulates several organ-specific functions directly through genomic and non-genomic actions and indirectly by modulating hormonal and tissue molecular pathways. Further toward the interaction of TH with systemic pathways, that is hormones, inflammatory central and autonomic nervous system pathways facilitate the liaison and the integration of the actions among different organs and systems. A proof of this is the physiological relevance of TH system in the processes of growth, cell differentiation and protection and in the pathophysiological and clinical impact of an altered TH profile in different disease states. Relaxation and contractile properties of the myocardium are both interfered by TH through regulation of the calcium handling and myosin heavy chain (MHC) expression, respectively. Also the effects of TH on the cardiac dynamics are indirectly mediated by TH-induced reduction in peripheral vascular resistance that improves cardiac loading conditions and ventricle–arterial coupling, thus leading to a more favorable balance for the heart work. Beyond these well-known cardiac functional effects, more recently new evidences have redefined the heart/thyroid liaison with the introduction of new physiological and pathophysiological concepts consisting of regeneration and redifferentiation processes and protection.

Heart failure (HF) is an intriguing model of chronic disease. First, it starts as a single-organ disorder developing, in its progression, into a systemic disease in which the dysfunction of other organs plays a relevant clinical and prognostic impact. Second, systemic pathways, continuously activated, play a central role in the progression of the disease, switching their effect from protective to harmful (Figure 1). In this milieu of organ dysfunction and systemic derangement, TH plays a fine from cardiovascular to systemic tuning role, whose potential is not completely understood, but that rises up if we consider the negative impact of mild or overt TH abnormalities in the molecular and cellular processes as experimentally documented, and the negative clinical and
Thyroid hormones (THs) play a crucial role in cardiac development and function, acting as a negative regulator since it binds TREs on DNA but is deprived of the binding region for T3. For this peculiar characteristic, TRα2 is believed to function as suppressor of TRα1 transcription. Several important structural and functional proteins are regulated by interaction of T3 receptor complex with specific DNA sequences, either in physiological or in pathological conditions. In a different way, the non-genomic actions of TH do not require a TRE-mediated gene transcription. The mechanisms of several of these non-genomic actions of TH are now understood, at least in part, and depend upon cellular signal transduction systems and either novel cell surface receptors for TH, such as integrin αVβ3, [12], or extra-nuclear TRβ [3] or TRα [4]. These effects include several intracellular signaling pathways and might involve the transport of ions across the plasma membrane, glucose and amino acid transport, cytoskeleton and mitochondrial function. Unlike the nuclear effectors, the extra-nuclear effects may occur in a very short time and are mediated by signal-transducing pathways [5].

In the last decade, beyond the classical effects of TH on heart contractility and calcium handling, novel actions of TH have emerged opening new perspectives on physiological and therapeutic relevance of TH and their association to cardiac regeneration/regenerative process, stress response and cardiac remodeling [5,7].

**Cardiac growth & fetal gene program reactivation**

In physiological conditions, TH-activated cardiac growth and maturation require MHC gene regulation and, more specifically, a positive effect on the transcription of (MHC)α and a negative action on (MHC)β gene expression. However, in the course of cardiac remodeling following HF, several changes aiming to restore the hemodynamic compromise are observed. The reactivation of the fetal pattern of expression of contractile proteins is one of the principal biochemical manifestations of the switch to pathological hypertrophy, with a decreased expression of (MHC)α and an overexpression of (MHC)β [8]. Evidence from neonatal cardiomyocyte cultures exposed to the pro-growth factor phentylephrine (an α1-adrenergic agonist) suggested a marked cell dedifferentiation with a myosin isoform switch to a fetal pattern [9], and this response was associated to a TRα1 redistribution from cytosol to nucleus. Furthermore, TRα1 overexpression has been described in the development of pathological hypertrophy after myocardial infarction in rats, confirming its role as regulator of dedifferentiation/redifferentiation in cardiac stress [10]. Administration of T3 converts TRα1 to the liganded form and this is associated to cell reorganization and to the switch from the fetal to the adult pattern of (MHC) genes, indicating that TH signaling may promote the regeneration of damaged myocardium. To further investigate the regulatory role of TH in pathological cardiac growth and remodeling, the functions for specific miRNAs have been investigated [8]. In particular, miR-208 has been described as an important cardiac-specific regulator of (MHC)β expression and stress mediator for T3 signaling in the...
failing heart. In the absence of miR-208, the expression of \( (MHC)\beta \) is greatly reduced in adult mice in response to pressure overload or hypothyroidism, indicating a common regulatory pathway involving miR-208 to regulate \( (MHC)\beta \) transcription. It has been proposed that the \( (MHC)\beta \) gene may respond to specific TR isoforms [8] and that co-regulators, exerting positive and negative effects on transcription, may enhance the repressive activity of the TR toward \( (MHC)\beta \) expression. Therefore, it was hypothesized that co-regulators may act on specific TR isoforms or, selectively, on a subset of TR-dependent genes through interactions with promoter-specific factors and that the regulatory role of miR-208 on cardiac growth and gene expression might operate at this level (Figure 2) [11,12].

Another interesting finding is that in hyperthyroid rats, the angiotensin II receptor AT1R mediates the TH induction of cardiac miR-208a and reduction of cardiac miR-208b levels. The cardiac expression of miR-208a and miR-208b was associated with the expression of their corresponding myosin genes, \( (MHC)\alpha \) and \( (MHC)\beta \), and, like miR-208a, also \( (MHC)\alpha \) was up-regulated by T3 whereas miR-208b \( (MHC)\beta \) was down-regulated by the TH. These data strongly suggest that AT1R might have an important regulatory role in cardiac muscle strength and contractility, influencing the efficiency of the cardiac function in hyperthyroidism [13].

**Cardiac disease & TH-receptor axis impairment**

TH affects cardiac growth and phenotype; however, the intracellular mechanisms underlying this response remain poorly understood since they are diverse and complex, cell type specific and involve multiple regulatory mechanisms.

Many evidences show that an impaired TH–TR axis is a characteristic mark of the failing heart and is associated with impaired cardiac function and increased mortality [14]. Even though most of the effects of TH on cardiac function are mediated by binding of the hormones to nuclear TRs, recent studies supported the hypothesis that TRs could also mediate T3 biological activities beyond TRE-mediated gene transcription by a non-genomic action mediated by the TR cytosolic counterpart [15,16]. In this matter, several studies focused on the characterization of TR\( \alpha \)1 isoform, which is most expressed in the myocardium and is believed to play a crucial role in the mediation of T3 effects on the recovery of cardiac function and prevention of pathological hypertrophy after myocardial infarction. In neonatal rat, cardiomyocytes treated with phenylephrine showed an increased nuclear TR\( \alpha \)1 content associated to cardiac pathologic growth only in the absence of T3 in the culture medium, whereas a cardiac physiologic growth was detected if T3 was present [16]. This finding strongly supports the hypothesis that TR\( \alpha \)1, depending on its liganded state, may act as a molecular switch to convert pathologic to physiologic growth and that adrenergic system may play a role in the mechanisms involved in the pathophysiologic of cardiac remodeling. The mechanisms involved in the TR\( \alpha \)1 induction after prolonged exposure of cardiomyocytes to phenylephrine remain mostly unknown; however, most of them seem to be mediated by ERK signaling pathway. It was observed that, in the absence of T3, a redistribution of the TR\( \alpha \)1 from nucleus to cytosol was induced with a significant prevalence of \( (MHC)\beta \) expression, leading to the fetal phenotype and pathologic growth. These findings are relevant in the context of HF where a prolonged adrenergic stimulation occurs (Figure 3) [17]. Analogously, in another report, it was observed that TH induced hypertrophy on rat neonatal cardiomyocytes as a direct result of binding to the TR\( \alpha \)1 isoform. It was shown that the mechanism of TH and TR\( \alpha \)1-specific hypertrophy involved the p38, the arm of the mitogen-activated protein kinase (MAPK) family most frequently associated with pathologic hypertrophy. T3-induced p38 activity and myocyte growth was due to the action of the TR\( \alpha \)1 on the upstream kinase, TAK1 (Figure 3) [9]. On the other hand, Kenessey et al. showed that T3-physiologic cardiac growth is mediated by PI3K/Akt/mTOR (mammalian target of rapamycin) signaling throughout a direct interaction with cytosol-localized TR\( \alpha \)1 [17]. Furthermore, protein–protein interactions between cytosolic TH receptors and the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K) have been recently reported in co-precipitation studies in human endothelial cells, leading to the phosphorylation and activation of Akt and endothelial nitric oxide synthase [18]. The TR-mediated PI3K activation has also been found in other cell types such as human fibroblasts [19] and rat neonatal cardiomyocytes [17]. Interestingly, the activation of PI3K and Akt appears to be a common pathway to various cardioprotective mechanisms involving numerous peptide hormones other than TH, including IGF-1, insulin, adrenomedulin and estrogen [20,21].

All these data support the hypothesis that TR\( \alpha \)1 isoform and its signaling partners are likely to be involved in myocardial growth and gene expression in diseased heart. This is of clinical relevance since TH–TR axis may represent a new target in possible therapeutic approach to HF.
HF: a paradigm model of systemic disease with thyroid system as a new player

The systemic hypothesis of HF

In recent times, the classic hypothesis of HF interpreted as the result of the unbalancing of cardio-hemodynamic system has been greatly revisited and enriched by the new concept, whereby HF is the inevitable consequence of a systemic multifactorial derangement at different levels in the whole body. Therefore, on the basis of the original understanding, HF progression was the result of increased cardiac loading conditions and reduced cardiac contractility (hemodynamic hypothesis) or the obvious consequence of a prolonged sodium retention (cardiorenal hypothesis).

The neuroendocrine hypothesis gathers the activation of the sympathetic autonomic nervous, renin–angiotensin–aldosterone and natriuretic peptides atrial and brain natriuretic peptides (ANP and BNP) systems that participate in the systemic involvement of HF. Initially, their action is protective and adaptive to hemodynamic changes induced by reduced cardiac output. However, due to their continuous activation, their protective mechanisms become less effective first and then maladaptive and dangerous for the entire body and heart, contributing to progression of the disease [25]. At the cardiac level, the result of the toxic action induced by continuous neuroendocrine activation is the ventricular remodeling process that results in progressive enlargement and systo-diastolic dysfunction of the left ventricle. This is characterized by increased myocardial mass, ventricular volume, change in ventricular shape and interstitial growth. In particular, chamber dilatation in progression to HF is largely due to myocyte lengthening from series addition of new sarcomeres [26,27]. The prolonged β- and angiotensin-receptor activation leads to an apoptotic process [28,29], associated to left ventricular remodeling, progressive dysfunction and thus HF progression [30].

Inflammatory system is also activated in HF initially with an adaptive and protective function, producing several proteins in the heart (free radical scavengers and heat shock proteins), conferring resistance to myocardial hypoxic injury and providing a stimulus for myocardial growth by promoting extracellular matrix remodeling and cell proliferation [31,32]. However, the result of continuous activation of this system is dangerous for the heart, with the induction of apoptosis in myocytes and endothelial cells, worsening the left ventricular function [33].

The systemic involvement and derangement in HF, highlighted by the above-mentioned hypothesis, has relevant clinical impact, considering that the clinical condition of HF patients is frequently characterized by several co-morbidities [34–36]. In the study of Lee CS et al., three main ‘co-morbidity patterns’ were identified: the renal pattern with high incidence of renal failure, complicated diabetes and fluid and electrolyte imbalance; the neurovascular pattern characterized by prevalence of cerebrovascular disease; the lifestyle pattern characterized by uncomplicated diabetes, hypertension and pulmonary disorders. All these patterns were associated with higher incidence of death, longer hospital stay and greater health costs [37–40].

Low T3 syndrome, the more frequent TH alteration in HF

Subclinical hypothyroidism and low T3 syndrome are the more frequent alterations of TH and metabolism [41]. In particular, low T3 syndrome, which mimics hypothyroid state, sharing similar cardiovascular and systemic alterations, is present in about 30% of HF patients [42]. In the past, this was judged as an adaptive mechanism inducing the reduction in metabolic demand, and thus not suitable for medical treatment. However,
experimental evidences suggest the hypothesis of a direct involvement of TH abnormalities, and thus of low T3 syndrome, in the HF progression [39]. In the clinical setting, low T3 syndrome has been associated with a worse prognosis in HF patients, independent of conventional clinical and cardiac variables. In particular, Kaplan–Meier survival curves of patients with reduced left ventricular ejection fraction and total T3 showed the highest mortality when compared with that of patients with similar left ventricular ejection fraction but normal total T3. This finding indicates an independent prognostic power of T3 in discriminating patients at high risk for death. Further, the negative prognostic power is enhanced in those patients with higher BNP concentration both in acute decompensated and in chronic compensated HF [42,40]. In the Passino study, both free T3 and BNP, together with NYHA classification, were independent predictors of cardiac mortality among a wide panel of clinical variables. Their additive prognostic power was highlighted by the analysis of the survival curve of those patients with combined high BNP/low free T3, who showed the highest mortality rate and those with combined low BNP/normal free T3. More recently, several studies enrolling large cohort of patients showed that increasing thyroid stimulating hormone (TSH) levels above normal were independently associated with an increased risk of HF in elderly population with known cardiovascular risk factors or previous cardiovascular disease and in HF patients with clinical HF progression and increased mortality. Furthermore, the studies showed that the prognostic impact was maintained, even after adjusting for other known predictors of outcome [43–47]. However, in one article published in the same period of the above-mentioned studies, TSH was weakly associated with cardiac mortality and this association disappeared after adding proBNP values in the statistical analysis [48]. These contrasting data could be explained by the distribution of TSH values within the population enrolled, if we consider that in the population subclinical hypothyroidism is associated with an increased risk of cardiovascular events and mortality in those with a TSH concentration of 10 mIU/l or greater [49]. In fact, in the Chen Study, the highest TSH quartile was associated with increased mortality compared with those with the lowest mortality [50]. Moreover, it is important to emphasize that the accurate definition of the TH metabolism cannot disregard the assessment of the two THs, T3 and T4, considering the high incidence of low T3 syndrome in HF characterized by a reduction in serum total and free T3 concentrations in the presence of normal levels of T4 and TSH [51].

The vicious circle among thyroid, the comorbidities & the systems activated in HF

TH abnormalities occur frequently in co-morbidities independent from HF, worsening the clinical status and prognosis (Figure 4). Therefore, although there are no relevant data on the potential association among TH abnormalities, HF co-morbidities and HF, it is conceivable that these associations could result in a vicious cycle, leading to additive and detrimental effect on clinical conditions and prognosis of HF patients. In particular, in HF subjects with hypothyroidism, renal insufficiency was significantly worse than in patients with normal thyroid function [52,53]. Similarly, in hemodialysis patients, low T3 syndrome was strongly associated with cardiac death and TH replacement therapy attenuated the rate of decline in renal function in chronic renal failure patients with subclinical hypothyroidism [54,55]. Thus, alterations in the levels and function of TH could be considered to be cardiorenal connectors as both renal failure and HF progress with the development of non-thyroidal illness [56].

In diabetic patients, the prevalence of thyroid dysfunction is greater than in the general population and is associated with higher prevalence of microalbuminuria, also in pre-diabetic subjects [57,58]. In the cross-talk among human body systems, the increased HbA1C in hypothyroid non-diabetic patients is intriguing, suggesting that anemia may be the connecting link [59]. In fact, anemia can be a non-diabetic cause of increased HbA1C circulating levels. Furthermore, anemia is frequently diagnosed in hypothyroid patients as a result of iron deficiency or depressed erythrocyte production by bone marrow affecting the erythrocyte life span.

Figure 4. Cardiovascular and systemic effect of hypothyroidism.
Despite a recent paper concluding that the relationship between thyroid function and depression remains poorly defined [60], it has been observed that in subjects with major depression, a blunted TSH response to TRH stimulation associated with increased concentration of reverse T3 and decreased concentration of T3 can induce low T3 syndrome [61,62]. Interestingly, Bunevicius et al. showed that patients with coronary artery disease and depressive symptoms had a higher prevalence of HF, higher NT-proBNP concentrations and lower T3 than patients with coronary artery disease without depressive symptoms. Further higher NT-proBNP concentrations were inversely related to lower total T3 and to higher reverse T3 serum levels [63]. Taken as whole, these results suggest that symptoms of depression in patients with coronary artery disease are associated with thyroid axis and cardiac impairment.

The bidirectional cross-talk between TH and inflammatory and neuroendocrine system can also influence HF progression. Experimental studies showed that TH modulates the sympathetic and plasma renin–angiotensin–aldosterone system activating natriuretic peptide transcription and synthesis. In hypothyroid patients, sympathetic activity is enhanced, contributing to vasoconstriction and down-regulation of adrenoreceptors [64]. Cytokines, in particular tumor necrosis factor and IL-1 and IL-6, have been implicated in the pathogenesis of low-T3 syndrome in HF patients through reduced peripheral conversion of T4 into T3 and by inhibiting 5’-deiodinase activity [65]. It is noteworthy that in HF patients with low T3 syndrome, T3 treatment induced blunting of inflammatory and neuroendocrine activation, with a reduction in plasma levels of norepinephrine, NT-proBNP, aldosterone and cortisol levels and IL-6 along with improvement in cardiac performance [66].

**Implications of substitutive TH treatment in HF**

Table 1 summarizes the studies in which short-term and long-term TH replacement therapy has been applied in patients with ischemic and non-ischemic HF [66–73]. A beneficial effect on cardiac function and performance and reduction in systemic cardiovascular resistance was shown. Also TH treatment induced the resetting of neuroendocrine system, with a significant reduction of circulating levels of catecholamines, aldosterone and NT-proBNP after T3 treatment. These effects can be directly mediated by the reciprocal interference among TH and

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**Table 1. Criteria for diagnosis of polycystic ovary syndrome.**

<table>
<thead>
<tr>
<th>Patients (N)</th>
<th>Study design</th>
<th>LVEF (%)</th>
<th>TH dose treatment</th>
<th>Main findings</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 pts with non-ischemic HF</td>
<td>Randomized (1:1) placebo controlled</td>
<td>27 ± 8</td>
<td>T4 100 µg/d OS for 1 week</td>
<td>Improvement in cardiovascular performance at rest, exercise and dobutamine stress test</td>
<td>[6]</td>
</tr>
<tr>
<td>10 pts with non-ischemic HF</td>
<td>Randomized (1:1) placebo controlled</td>
<td>29 ± 6</td>
<td>T4 100 µg/d OS for 3 months</td>
<td>Improvement in cardiovascular performance at rest, exercise and dobutamine stress test</td>
<td>[68]</td>
</tr>
<tr>
<td>23 pts with ischemic and non-ischemic HF</td>
<td>Uncontrolled</td>
<td>22 ± 1</td>
<td>T3 cumulative dose 0.15-2.7 µg/kg bolus + continuous infusion (6-12 h)</td>
<td>↓ SVR</td>
<td>[69]</td>
</tr>
<tr>
<td>10 pts with cardiogenic shock</td>
<td>Uncontrolled</td>
<td>Not available</td>
<td>T4 20 µg/h bolus + continuous infusion (36h)</td>
<td>↑ CI, PCWP and MAP</td>
<td>[70]</td>
</tr>
<tr>
<td>6 pts with ischemic and non-ischemic HF</td>
<td>Uncontrolled</td>
<td>24 ± 3</td>
<td>T3 initial dose 20 µg/m2bs/d Continuous infusion (4 d)</td>
<td>↓ SVR</td>
<td>[71]</td>
</tr>
<tr>
<td>20 pts with ischemic and non-ischemic HF</td>
<td>Randomized (1:1) placebo controlled</td>
<td>25 (18-32)</td>
<td>T3 initial dose 20 µg/m2bs/d Continuous infusion (3 d)</td>
<td>↑ LVSV, LVEDV</td>
<td>[70]</td>
</tr>
<tr>
<td>86 pts with ischemic and non-ischemic HF</td>
<td>Randomized (2:1) placebo controlled</td>
<td>28 ± 6</td>
<td>DTPA twice daily 90 mg increments (every 2 wks to maximum 360 mg)</td>
<td>↑ CI</td>
<td>[72]</td>
</tr>
<tr>
<td>163 pts with ischemic and non-ischemic HF and subclinical hypothyroidism</td>
<td>Uncontrolled</td>
<td>T4 dose necessary to normalize TSH</td>
<td>↑ Physical performance at 6-minute walking test</td>
<td>[73]</td>
<td></td>
</tr>
</tbody>
</table>

CI: Cardiac index; CO: Cardiac output; DTPA: 3,5-Diiodothyropropionic acid; HF: Heart failure; LVEF: Left ventricular ejection fraction; LVEDV: Left ventricular end diastolic volume; LVSV: Left ventricular stroke volume; MAP: Mean arterial pressure; NT-proBNP: N-terminal pro-Brain natriuretic peptide; PCWP: Pulmonary capillary wedge pressure; T3: Triiodothyronine; T4: Thyroxine; SVR: Systemic vascular resistance; UO: Urinary output.
sympathetic and neuroendocrine pathways, but also indirectly mediated by the improvement of hemodynamics, as documented by increased left ventricular stroke volume. Deactivation of the neuroendocrine system is a crucial goal in the therapeutic management of HF. The potential clinical relevance of T3-induced neuroendocrine deactivation is clearly deducible from a study showing highly beneficial effects of aldosterone and adrenergic antagonists in terms of survival, rate of hospitalization, symptoms, cardiac remodeling and performance [74]. Regarding side effects, all the studies showed no occurrence of major or minor side effects and good tolerance without the increase in heart rate, when T3 or T4 were used. On the contrary, the study of Goldman, in which 3,5-diiodothyropropionic acid, a TH analog, has been used, was interrupted prematurely due to the occurrence of side effects consisting of weight loss, increased heart rate, fatigue, suppression of TSH and also a trend toward increased mortality. However, all the referred signs and symptoms suggest an excess in DITPA administration as the main cause of thyrotoxicosis. This highlights an important endpoint of TH treatment that is to restore TH deficiencies and maintain levels of circulating TSH, T3 and T4 within normal ranges [75]. Moreover, the restoration of normal TH metabolism is also an endpoint of TH treatment of chronic kidney disease. Several studies showed the potential benefits of a delay in progression of disease and obtaining clinical and biohumoral improvements [56]. However, the absence of sufficient data derived from multicentric and long-term prognostic studies and the uncertainty on timing and hormone administration modalities (intravenous or orally) do not allow TH treatment in HF patient at this moment.

Expert commentary

In the pathophysiology of chronic stress stimuli, HF should be seen in a unique scenario of altered systemic homeostasis in which heart dysfunction, peripheral organ dysfunction and derangement of the neuroendocrine, immune and inflammatory systems represent chronic stress stimuli, with continuous activation of the stress response. This, in turn, predisposes to allostatic load, defined by McEwan as ‘the cumulative strain on the body produced by repeated ups and downs of physiologic systems; as well as by the elevated activity of physiologic systems under challenge and the changes in metabolism and the impact of wear and tear on a number of organs and tissue’, which ‘can predispose the organism to disease’. In other words, allostatic load is the price the body pays for being continuously forced to adapt to adverse physical and pathophysiological situations. In the case of HF, this refers to the continuous up-regulation that occurs when neuroendocrine and immuno-inflammatory systems shift their effects from compensatory to unfavorable and, finally, to toxic, inducing left ventricle remodeling at the level of the heart and the high incidence of co-morbidities as expression of systemic derangement. In this milieu of systemic dyshomeostasis, TH system can be included because of the following reasons:

- The relevant role in the cardiovascular and systemic homeostasis regulation and maintenance;
- The new evidences on cardiac protection and regeneration;
- The fine tuning between TH, neuroendocrine and inflammatory systems;
- The frequent alteration of TH metabolism, consisting, in particular, of the appearance of low T3 syndrome;
- The experimental and clinical evidences of the dangerous effect of mild alteration of TH metabolism on cardiac function, structure and morphology and on the other organs affected by HF syndrome;
- The initial and encouraging therapeutic approach with replacement TH therapy.

Five-year view

HF syndrome may be considered a stress-induced disease, mainly triggered by complex and concatenate systemic dysfunctions. Therefore, a multifactorial approach may be more suitable in order to accurately identify patterns of disease progression, prognostic risk stratification and innovative therapeutic approaches. In this context, TH system can play a pivotal role, particularly in light of the new evidences of TH effects on cardiac protection and regeneration, systemic homeostatic effects, reversibility of genomic, structural and functional abnormalities after restoring a normal TH metabolic pattern. Original molecular actions of TH have recently emerged, opening new perspectives on physiologic and therapeutic relevance of TH and their association to cardiac regeneration/reparative process, stress response and cardiac remodeling. In particular, the miRNA regulatory role and the recently unveiled TH–TR axis potential in the regulation of cardiac regeneration/reparative process are surprisingly innovative and open new innovative therapeutic approaches. Thus, T3, T4 and TSH are currently sampled in the daily clinical practice to define more accurately clinical and prognostic stratification of HF patients. The next challenge will be to ascertain the benefit of TH replacement therapy in HF patients, taking into consideration type of hormone to administer, T3 or T4, and dosage and treatment schedule.

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**Key issues**

- Heart failure (HF) is an intriguing model of chronic disease, in which systemic pathways, continuously activated, play a central role in the progression of the disease, switching their effect from protective to harmful.
- An impaired thyroid hormone (TH)–TH receptor axis is a characteristic mark of the failing heart. TRα1, depending on its liganded state, may act as a molecular switch of cellular pathways regulating cardiac regeneration/repairative process, stress response and cardiac remodeling.
- TH non-genomic action depends, at least in part, on interaction of the hormones with specific cell surface or extra-nuclear receptors. Particularly, integrin αVβ3 is present in virtually all cells and mediates a large number of cell signals.
- TH plays a fine cardiovascular and systemic homeostatic role, if we consider the negative impact of mild or overt TH abnormalities in the molecular and cellular processes as experimentally documented, and the negative clinical and prognostic impact in the clinical setting.
- Several questions arising from the clinical scenario support the experimental evidences showing a critical role of TH in HF. These questions include the incidence and prognostic weight of TH abnormalities in HF, the effects of TH abnormalities on the same organs and systems altered in HF and the potential benefits of restoring a normal TH profile by medical replacement therapy.

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