The role of thyroid hormone in the pathophysiology of heart failure: clinical evidence

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Abstract Thyroid hormone (TH) has a fundamental role in cardiovascular homeostasis in both physiological and pathological conditions, influencing cardiac contractility, heart rate (HR), diastolic function and systemic vascular resistance (SVR) through genomic and non-genomic mediated effects. In heart failure (HF) the main alteration of thyroid function is referred to as "low-triiodothyronine (T3) syndrome" (LT3S) characterized by decreased total serum T3 and free T3 (fT3) with normal levels of thyroxine (T4) and thyrotropin (TSH). Even if commonly interpreted as an adaptive factor, LT3S 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 HF patients. All these observations, together with the early evidence of the benefits of T3 administration in HF patients indicate that placebo-controlled prospective studies are now needed to better define the safety and prognostic effects of chronic treatment with synthetic TH in HF.

Keywords Heart failure · Thyroid hormones · Low-T3 syndrome

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Introduction

Heart failure and thyroid: a well-known but not yet well-understood relationship

Heart failure (HF) is a restless syndrome which represents the common final pathway of the majority of cardiac pathologies. Beginning as a single organ disease, it becomes a systemic disease during its evolution and progression. In the initial phases of HF, the decreased cardiac output, the increase in atrial pressure and/or the inadequate arterial circulating volume is compensated for by the activation of the renin–angiotensin–aldosterone system (RAS) and the sympathetic nervous system (SNS) leading to peripheral vasoconstriction to preserve blood pressure homeostasis in vital areas and regulate sodium and water retention to preserve blood volume [1, 2]. These alterations are at the basis of the two models—the so-called hemodynamic model and cardio-renal model—proposed in the past in attempt to describe the pathophysiology of the disease. These models provided the rational for the use of inotropic, vasodilatatory drugs and diuretics as therapeutical strategies in HF. Even if these therapies are effective in reducing signs and symptoms of HF, they have scarce effects in preventing progression of the disease and in improving prognosis. The recent proposed neuroendocrine model can represent a more appropriate explanation of the systemic involvement of HF because it supports the existence of a complex pattern of relationships between hormonal, immunological and proinflammatory systems like RAS, SNS, natriuretic peptides, neuropeptides, vasopressin, cytokines and endothelium mediators [1, 2]. Beginning as a compensatory mechanisms, neuroendocrine activation ultimately has toxic effects, inducing calcium overload, myocite apoptosis, myocardial fibrosis and

cardiac remodeling, leading to progressive function deterioration [3, 4]. Current treatment for HF is able to modulate the pathophysiological mechanisms that are stimulated in the disease and often requires multiple medications including β-adrenergic blocking drugs, angiotensin-converting enzyme inhibitors, aldosterone antagonists, diuretics and to a lesser extent, digitalis. Noteworthy, despite maximum medical therapy HF is still one of the major causes of morbidity, mortality, and hospitalization in Western Countries. From a European perspective, the Rotterdam Study showed that in individuals aged 55 years, 30% will develop HF during their remaining lifespan, with only 35% surviving 5 years after the first diagnosis, representing an epidemic and a great burden on health care systems [5]. This evidence suggests that something is lacking in the full interpretation of the disease progression. In this context, growing interest in the role of thyroid hormones (TH) in HF relies on many assumptions: (1) both hyper- and hypothyroidism are accompanied by relevant changes in cardiac output, cardiac contractility, vascular resistance, and blood pressure that are well explained by the cellular mechanisms of TH actions in the heart and cardiovascular system; (2) the restoration of normal thyroid function, even in patients with mild TH abnormalities, very often reverses abnormal cardiovascular hemodynamics [6–8]; (3) subclinical hypothyroidism (SHYPO) and hyperthyroidism (SHYPER) are characterized by the apparent absence of typical clinical signs or symptoms of thyroid disease, but are associated with an increased risk for cardiovascular mortality in cardiac patients [9], suggesting that restoration of euthyroidism could be beneficial; (4) 13–30% of patients with congestive HF develop a fall in serum biologically active serum triiodothyronine (T3) levels, referred to as low-T3 syndrome (LT3S) [9–15]; (5) an altered thyroid metabolism is already evident in the very early phases of left ventricular dysfunction and the decrease in serum T_3 is proportional to the severity of heart disease and symptoms, as assessed by the New York Heart Association functional classification [16].

Cellular mechanisms of TH action

The thyroid gland synthesises and releases TH mostly as thyroxine (T4), while most (>80%) T3, the biological active form of the hormone, is obtained (at least in humans) by peripheral deiodination of T4 through the action of type I (D1) and type II (D2)-5′ deiodinase. Almost all circulating and intratissutal concentration of TH is the result of D1 and D2 desiodative pathway [17, 18]. Another type of deiodinase, called type III deiodinase (D3), removes iodine from the 5-(or equivalent 3-) position of the tyrosyl ring of the hormone molecule and therefore is an obligatory inactivating enzyme [19]. In normal conditions, the heart relies mainly on serum T3 because no significant myocyte intracellular deiodinase activity takes place, and it appears that T3, and not T4, is transported into the myocyte [20]. In spite of this, a mild desiodase activity is present both in atria and ventricles and is modified by pathologic conditions. In an in vitro study about the expression of iodothyronine 5′-monodeiodinase activities in normal and pathological tissues in man, Sabatino et al. observed that the right cardiac atrium basally presents a mild D1 activity, that is further reduced in ischemic conditions [21]. Likewise, Wassen et al. demonstrated that a low level of D3 activity is present in both right and left ventricles of experimental animals, and increases in conditions of induced HF [22]. Recently, Simonides et al. have shown that hypoxia induced the expression of the D3 gene DIO3 by an hypoxia-inducible factor-dependent (HIF-dependent) pathway in diverse cell types including neurons, hepatocytes, and even cardiomyocytes. In particular, using a rat model of cardiac failure due to right ventricular hypertrophy, they found that D3 proteins were specifically induced in the hypertrophic and hypoxic myocardium of the right ventricle, associated with a local anatomically precise decrease in T3 as well as T3-dependent transcriptional activity [23]. All these observations suggest the hypothesis that desiodase activities could have a key role in modulating cardiac levels of available biologically active T3, thus contributing to the local hypothyroid state in the failing heart [22, 23]. T3 cellular actions are mediated by non-nuclear and genomic, nuclear mechanisms. Thyroid non-genomic actions are rapid in onset and are localized at the level of the plasma membrane, cytoplasm and cellular organelles of various tissues including the myocardium, and modulate cellular metabolic activities such as sugar and amino acid transport, ion fluxes at the level of the plasma membrane [24, 25] and mitochondrial gene expression and function [26], even modulating the generation of intracellular secondary messengers and induction of Calcium-dependent, cyclic AMP or protein kinase signaling cascades [27]. T3 exerts its nuclear action through binding TH nuclear receptors (TRs), which belong to the superfamily of steroid hormone receptors. These receptor proteins mediate the induction of transcription by binding to thyroid hormone response elements (TREs), that are specific DNA sequences in the promoter regions of positively regulated genes. TRs bind to TREs in the absence as well as in the presence of ligand. TRs bind to TREs as homodimers or, more commonly, as heterodimers with one of three isoforms of retinoid X receptor [24]. All TRs are splicing variants of the product of two main genes, α and β. TRα1, TRα2, and TRβ1 are widely expressed; TRβ2 is present mainly in pituitary cells and represents a small

fraction of T3-binding TRs in the heart, while TRβ3 represents a minor variant. TRα2 binds TREs on DNA, but does not bind T3 and can function as a dominant negative, also suppressing TRα1 trascription and producing a hypothyroid-like effect and actively modulating TH signaling [28]. On a TRE-containing target gene, TH binding acts as a switch between repressed and activated states. However, while positive regulation of gene expression by TH is nicely explained by this model, TH also downregulates numerous genes [24, 29]. The mechanism of negative regulation is not well understood: in one model, the TR binds directly, via its DNA-binding domain, to a "negative" TRE in a negatively regulated gene [30], but it is possible that another mechanism for negative regulation is a squelching model, whereby TR acts in the nucleus to steal co-activators and co-repressors from other nuclear receptors as well as additional transcription factors that utilize the same coactivators or corepressors [31]. Notably, non-genomic and genomic actions of TH may interface because TR can also exert effects through non-classical mechanisms involving activation of signal transduction pathways leading to activation of kinase cascades that ultimately impact on nuclear transcription factor function [32].

Thyroid hormones and the cardiovascular system

Beginning during the development and extending to adult physiology, a close relationship exists between the thyroid gland and the cardiovascular system. This intimacy is affirmed by the predictable changes in cardiovascular function that occur across the entire range of thyroid disease states. TH effects on the cardiac myocyte are intimately associated with cardiac function via regulation of the expression of key structural and regulatory genes of several enzymes, functional and structural proteins such as myosin heavy chain (MHC) α and β, the sarcoplasmic reticulum Ca^{++}-ATPase (SERCA2) and its inhibitor phospholamban, voltage-gated K$^+$ channels, β1-adrenergic receptor, guanine nucleotide regulatory proteins, adenylate cyclase, NA$^+$/K$^+$-ATPase, and Na/Ca exchanger [6–8]. The net effect of all these activities is that TH influences diastolic and systolic function both directly and indirectly. The increased left ventricular relaxation is mediated through the activation of the SERCA2, which reduces cytosolic calcium from the high systolic to low resting levels in diastole [33], and the concomitant inhibition of phospholamban, which inhibits SERCA through a decrease in the affinity of the enzyme for Ca^{++} [34]. The TH direct effects on contractility are mediated by increasing the α-MHC content, which have a high contractility state and decreasing β-MHC expression, which is associated with a

better energetic efficiency and economy of force maintenance [35]. As shown in experimental models, TH are active also at the vascular level [36]. In primary cultures of vascular endothelial cells, exposure to T3 induced vascular relaxation that was not associated with nitric oxide production as measured by cellular cGMP content and nitrite release. These observations suggest that T3 acts directly on the vasculature, in a manner that is non-genomic and endothelium independent [37]. On the contrary, in an in vivo model of hamster cheek pouch microcirculation, Colantuoni et al. showed that T3 administration caused a dose-dependent vasodilatation of the arterioles within few minutes of its application, which was abolished by nitric oxide synthase (NOS) inhibition, indicating a correlation between T3-induced dilatation and NOS activation [38]. These discrepancies with previous in vitro findings may be ascribed to differences in the experimental procedure and it is reasonable to suppose that in vitro conditions do not allow one to observe the integrated response of the peripheral microcirculation that are evident in vivo. In the same hamster cheek pouch microcirculation model, T4 application on vascular smooth muscle cells (VSMCs) determines dilatation that is delayed in onset, requiring local conversion to T3 by the activity of 5′-deiodinase. Interestingly, the effect of T4 is abolished by unselective deiodinase inhibition by iopanoic acid (IPA), while 6-Propyl-2-Thiouracil (PTU), a selective inhibitor of D1 does not interfere with the dilatation induced by T4 and confirms the hypothesis of the presence of D2 in VSMCs, as previously observed by Mizuma et al. in cultured human VSMCs [38, 39]. Furthermore, TH may have also some genomic effects, modulating the expression of genes that are fundamental in maintaining endothelial homeostasis such as angiotensin receptors in VSMCs [40] and reinforcing the hypothesis that vasculature is a principal target for TH action. This appears to be confirmed by the characteristically high systemic vascular resistance (SVR) observed in patients and experimental animals with hypothyroidism, which is rapidly reversed with TH treatment [41, 42]. On the contrary, hyperthyroidism produces a marked decrease in SVR, which in turn facilitates an increase in cardiac output and augments peripheral blood flow [43].

The vasodilatory response induced by TH is not uniform. Administration of T3 in vivo in the circulation of major organs of anesthetized rabbits is associated with a vasodilatory response that occurs preferentially in the ventricles and kidneys, but not in the atria or skeletal muscle [44]. The observation of a vasodilatory response induced by TH in coronary arteries is in line with previous reports by Yoneda et al. that showed that a bolus injection of T3 or T4 in rat coronary arteries elicited a transient, dose-dependent decrease in coronary perfusion pressure, as

well as an increase in arterial vasodilation [45]. The documented expression of D2 by coronary VSMCs suggests that intracellular TH activation may be involved in the modulation of DNA synthesis and probably in migration activity of human coronary VSMCs [46]. These results, together with the observation that coronary flow reserve is impaired in patients with SHYPO [47] support the hypothesis that THs may play a role in preventing myocardial ischemia and ameliorating cardiac function. Considering overall genomic and non-genomic cellular effects of TH on the heart and vascular system, it is not surprising that these hormones play a pivotal role in cardiovascular homeostasis. TH act first to lower SVR through the above-mentioned pathways, which cause mean arterial pressure to decrease. This is sensed by the juxtaglomerular apparatus, which leads to increased renin synthesis and secretion and to an increase in blood volume and preload enhancing both cardiac output [6–8, 43, 48]. The final hemodynamic result is that TH homeostasis preserves a positive ventricle-arterial coupling, thus leading to a more favorable balance for the heart to work without increment in left ventricular oxygen consumption [49]. The importance of TH in maintaining cardiovascular homeostasis is also deducible from data showing that mild forms of TH abnormalities, i.e., SHYPO and SHYPER, significantly alter cardiovascular function. In particular, SHYPO is associated with left ventricular diastolic dysfunction evidenced by delayed relaxation, impaired systolic function on effort that results in poor exercise capacity, decreased cardiac preload and increased afterload with a consequent reduction in stroke volume (SV) [50]. As shown in a study in which cardiac function was studied in patient with SHYPO using cardiac magnetic resonance (CMR) before and after TH replacement therapy, patients with SHYPO showed reduced end diastolic volume and increased SVR, leading to a reduction in SV [51]. Since in these patients heart rate (HR) was unaffected by TH abnormalities, the reduction in the so-called double product (the product of HR and systolic blood pressure which represent an estimate of systolic function) seen in SHYPO was attributable only to the decreased SV and increased SVR. All hemodynamic alterations described typically reversed to normal after TH replacement therapy and are sufficient to explain the decrease in systolic pump performance observed in SHYPO patients, without the need to invoke simultaneous impairment in myocardial inotropic function [52] (Fig. 1).

Fig. 1 Scatterplots showing the relationship between thyroid-stimulating hormone (TSH) and end- diastolic volume (EDV), stroke volume (SV), cardiac index (CI) and systemic vascular resistences (SVR). *Open circles*: subclinical hypothyroidism (SHYPO) patients before thyroid replacement therapy; *filled circles*: SHYPO patients after thyroid replacement therapy; *open triangles*: control group Modified from Ripoli et al. [51]

In this study, a relative good correlation was found between thyrotropin (TSH), the best biochemical marker of whole-body thyroid hypofunction and the parameters of systolic left ventricular performances. This finding fits well with the results from a population-based survey by Rodondi et al., in which SHYPO was associated with a higher rate of incident and recurrent congestive HF in a manner that is correlated with TSH level; notably this association persisted after adjustment for traditional cardiovascular risk factors [52]. SHYPO is also characterized by an altered lipid metabolism, with elevated total and LDL cholesterol levels and low HDL [53], by endothelial dysfunction resulting from a reduction in nitric oxide availability as seen in the impairment in the endothelium-dependent vasodilatation [54] and by an increase in intima-media thickness [55] that could be reversed by hormone replacement therapy [56]. Furthermore SHYPO has been identified as a strong predictor of mortality in chronic dialysis patients and a risk factor for nephropathy and cardiovascular events in type II diabetic patients [57]. A recent survey by Chonchol et al. [58] revealed that SHYPO is also associated with a significant decrease in glomerular filtration rate (GFR) in general population, with a prevalence that increase at lower GFR. All the described aspects are probably responsible for the increased risk of atherosclerosis and probably of coronary artery disease (CAD) seen in patients with SHYPO [59, 60]. As SHYPO, SHYPER is associated with many cardiovascular effects. Increased HR and increased risk for atrial arrhythmias, particularly atrial fibrillation [61], are attributable to the effects of T3 on systolic depolarization and diastolic repolarization, with a decrease in the action potential and refractory period duration in atrial and ventricular myocardium [62]. Holter ECG recordings show a decreased cardiac vagal control that may have important clinical implication, since reduced HR variability may predict an increased risk for subsequent cardiac events in the general population [63]. SHYPER is also associated with an increased left ventricular mass at Doppler echocardiography [64], which significantly correlates with late diastolic dysfunction [65] and with decreased exercise tolerance, maximal VO_2 achieved at the peak exercise and anaerobic threshold with severe impairment of quality of life [66].

Whether subclinical thyroid dysfunction per se contributes to an increase in cardiovascular and overall mortality in general population is still a matter of debate. In the last few years, many population-based studies have attempted to answer this question but the results are somewhat contradictory [9, 52, 60, 67–73]. In any case, given the relevant unfavorable effect of subclinical thyroid dysfunction on cardiac morphologic features and function, blood pressure and HR and renal function (Table 1), the observation made by Iervasi et al. of a significant increase

Table 1 Effects of thyroid hormone on heart failure physiology

	Main findings in HF	Effects of low thyroid state/ function	Effects of T3 treatment
Cardiovascular system			
LV systolic function	↓	↓	↑
LV diastolic function	↓	↓	↑
Systemic vascular resistances	↑	↑	↓
Renal function			
Glomerular filtration rate	↓	↓	↑
Neuroendocrine system			
Norepinephrine	↑	↑	↓
Aldosterone	↑	No effect or ↑	↓
Natriuretic peptides			
Synthesis	↑	↓	↑
Resistance	↑	No effect	No effect

LV left ventricle

in cardiac and overall mortality in cardiac patients with subclinical thyroid disease [9] should not be considered a surprising finding but simply the confirmation of the close relationship between cardiovascular homeostasis and TH axis.

Pathophysiological effects of an altered TH state in heart failure

LT3S is the most common alteration of TH metabolism in patients with HF. It could be more properly but generically defined as "Non-thyroidal illness syndrome" since it appears in patients without previous thyroid disorders, but who suffer from severe clinical conditions such as starvation [74], HF [9–14], acute myocardial infarction [75, 76], heart (or other organ) surgery [77–80] or in intensive care patients [81]. These patients have low serum T3 levels—which are inversely related to the severity of their illness—associated with normal or mildly reduced serum T4 and TSH concentrations and increased reverse-T3 (rT3) plasma levels [81]. The physiological bases for the development of a low T3 state in patients with severe illness and, in particular, with HF, are not been clearly understood, but central and peripheral mechanisms have been called in cause. There are at least three potential mechanisms that may explain the development of the LT3S in severely ill patients: (1) a decreased extrathyroidal conversion of T4 attributable to a diminished activity of peripheral deiodinase, associated with a decreased transport of T4 into tissues [81, 82]; (2) increased peripheral TH catabolism due to an ectopic induction of D3 activity in peripheral

tissues [83] and to increased sulfation, as shown by the elevated plasma levels of T4 sulfate in patients who died in intensive care units [84]; (3) the development of central hypothyroidism as shown by the decreased plasma levels of TSH and by the concomitant abnormalities in thyrotropin releasing hormone (TRH) plasma concentration, clearance, half-time, and effects [85]. While these mechanisms are able to explain the low T3 levels observed in the syndrome, the elevation in serum rT3 levels is attributable to both a diminished renal clearance and a reduced peripheral catabolism [81].

Although a comprehensive theory explaining the etio-pathogenesis of LT3S in severely ill patients is still lacking, there is evidence that the increased levels of interleukins and cytokines (i.e., Interleukin-6, Tumor Necrosis Factor) seen in patients with severe illness are associated (in clinical and experimental settings) with a TH pattern similar to low T3 state [86–89]. This observation is particularly interesting because supports the hypothesis of a close integration between neuroendocrine and proin-flammatory/immunitary systems, which also have a pivotal role in explaining the progression of HF toward cachexia [90]. Moreover, the abnormalities in TRs expression observed in patients with HF [91–93] could contribute, along with reduced plasma T3 levels and decreased desiodase activities, to the development of tissue hypo-thyroidism. As highlighted by Liu et al. in a rat model of thyroidectomy-induced hypothyroidism, T4 replacement therapy was able to normalize TH plasma levels, but not to reverse cardiac atrophy and arteriolar rarefaction, sug-gesting that serum TH levels may not accurately reflect TH tissue levels [93]. From this point of view, a full expla-nation of TH cellular action in patients with HF is necessarily associated with understanding the TR system. In human hearts, two TR genes are expressed and each gene generates two isoforms: TRα1, TRα2 and TRβ1, TRβ2. All types of TRs are homogeneously expressed in human atria and ventricles from euthyroid patients with normal cardiac function when TR-mRNA is measured with an accurate quantitative approach such as real time PCR [94]. On the contrary, various data in literature show that cardiac dysfunction is associated with abnormalities in TR gene expression. A study from Sylven et al. described a decrease in TRα1 levels in the failing myocardium and an increase of TRβ1, while TRα2 levels remained unchanged [91]. In an analogous report, Kinugawa et al. showed no significant differences in total TRα gene expression, with an increase in TRα2 levels and a concomitant decrease in TRα1 [92]. Most of the reported data seem to indicate that the actual number of TH receptors, and in particular TRα1, are fewer in presence of HF, possibly contributing to making cardiac tissue less responsive to TH signaling and representing a potential therapeutical target [95].

Moreover, abnormalities in TR may aid in understanding the possible close interrelationships between an altered thyroid state observed during progression of HF and remodeling of the myocardium. During fetal life, low-cir-culating TH levels are associated with a specific pattern of TR activity: the unliganded receptors, particularly TRα, bind DNA and repress the transcription of target genes such as TRβ and several genes encoding ion channels involved in cardiac contractile activity. When T3 concen-tration increases after birth, inactivation of TRα turns on the expression of previously inhibited genes, becoming a molecular switch of cardiac function between fetal and postanatal life [96]. TH deficiency, as seen in the LT3S, and the concomitant alteration in TR expression resulting in tissue-specific hypothyroidism seen in failing hearts [97], could contribute to explaining the molecular mecha-nism that induces fetal gene expression in the failing human ventricle and the so-called activation of the fetal gene program, otherwise indicated as "recapitulation of fetal phenotype", typical of cardiac dysfunction [98–101].

Effects of TH on myocardial protein gene expression

In a rat model of starvation-induced LT3S, the mRNA content of cardiac α-MHC gene was reduced by 46% when compared with controls; importantly, the decline was lin-early related to the decrease in serum T3 [102]. A similar result was observed on SERCA2 mRNA content. Systolic and diastolic left ventricular function were also affected, with a reduction in left ventricular contractility, as reflected by the 13% reduction in +DP/dt, and worsened diastolic function as clearly expressed by the 21% increase in mean left ventricular relaxation time. Importantly, supplementa-tion with synthetic T3 normalized the α-MHC isoform and SERCA2 contents despite persistence of food restriction, as well as improved systolic and diastolic heart performance [102]. These results are similar to those obtained by Ladenson et al. in a patient with dilated cardiomyopathy and hypothyroidism. Also in this case restoration of euthyroidism was associated with an 11-fold increase in ventricular α-MHC mRNA levels and substantial reduction of ANF mRNA and with a gradual and substantial improvement in the patient's ventricular ejection fraction and functional capacity [103].

Effects of low T3 on cardiac histology and cardiomyocyte morphology

As shown by Forini et al. in human atrial myocardial tissue in vitro, long-term T3 deprivation has detrimental effects on myocardial histology and morphology, leading to cel-lular disorganization, fibrosis and phenotypical remodeling which resemble cellular and structural impairment

observed during HF progression [104]. At the molecular level, these alterations are the result of a decreased expression and activity of SERCA2, leading to poor calcium cycling, which in turn has been found to be associated with reduced frequency and potentiation of contractile force, an important marker of HF [105]. The concomitant significant reduction in α-sarcomeric-actinin, a cytoskeletal molecule which is essential in the maintenance of sarcomeric organization, leads to abnormalities in myocyte shape and geometry [104]. If we consider that the cytoskeleton is a complex network of filaments and tubules which transmit mechanical and chemical stimuli within and between cells and contributes substantially to cell stability by anchoring subcellular structures, such as mitochondria, Golgi apparatus, nuclei, and myofibrils [106], it is not surprising that cytoskeletal abnormalities induced by TH deprivation could represent a morphological basis for reduced contractile function. Moreover, cytoskeletal abnormalities narrow the gap between changes within cardiac myocytes and the extracellular matrix, contributing to alterations in myocardial shape and geometry. The influence of TH on determining myocardial shape is further reinforced by the observations made by Pantos et al. on culture of rat neonatal cardiomyocytes supplemented with T3 [107]. In this in vitro study, supplementation with T3 was associated with an increased ratio of the major to minor cell axis and with a change in myocyte shape from an almost circular to an elongated form with respect to untreated cultured cells. These morphological alterations were associated with an increase in protein synthesis, since T3-treated cells expressed 51% α-MHC and 49% β-MHC as compared to 100% β-MHC expression in non-treated cells. This response was accompanied by a concomitant increase in phospho-ERK. Administration of PD98059 (an inhibitor of ERK signaling) prevented the TH-induced changes in cardiomyocyte geometry and shape without a significant reduction in cell area and protein synthesis, showing that T3-induced changes in cardiomyocyte shape and geometry involve specific patterns of intracellular messenger such as ERK kinase signaling.

The observation made by Lee et al. that hyperthyroidism-induced myocardial hypertrophy is not associated with myocardial fibrosis supports the hypothesis that TH are able to regulate extracellular matrix synthesis [108]. Actually, TH downregulates collagen type I biosynthesis in the heart and fibroblasts through a genomic mechanism that require an interaction between AP-1 and TR [108]. Moreover, TH administration can normalize collagen type I expression in ventricular issues in a genetic model of cardiac fibrosis [109] and prevent fibrosis in aortic banded animals [110]. The observation that TH administration can prevent myocardial fibrosis, even in pathologic conditions, seems particularly interesting if we consider the role of fibrosis in determining morphological alteration, systolic and diastolic dysfunction in HF [111].

Effects of THs on myocardial blood flow

Associated with the previously described abnormalities in diastolic and systolic function, TH deficiency is characterized by severe impairment in coronary blood flow, a rarefaction in myocardial arterioles, myocyte loss and a greater extent of fibronecrosis, as can be seen in a model of cardiomyopathic hamster that develops SHYPO [112]. This evidence is in accordance with previous observations made in the same animal model by Ryoke et al., who concluded that ischemic myocyte loss (oncosis), rather than apoptosis, was the likely explanation for pathological changes found in cardiomyophatic hamsters [113] and could be attributed to the reduced availability of endothelial NOS synthesis that has been shown to be reduced in SHYPO [54]. Interestingly, treatment of cardiomyopathic hamsters with a replacement dose of TH partially reversed these abnormalities. This observation is in line with the well-known effects of TH on microvasculature [112]. A marked angiogenetic response within the myocardium of rats chronically treated with TH has been recently documented [114] and is probably dependent on the up-regulation of pro-angiogenetic factors such as FGF, VEGF, angiopoietin and Tie-2 [115, 116] through a MAP kinase-dependent pathway [117]. This experimental evidence has important clinical impact since about 80% of HF can be attributed to CAD. Furthermore, an abnormal coronary microcirculatory flow, potentially causing impairment of myocardial perfusion and regional metabolic changes compatible with myocardial ischemia, has been shown in patients with dilated cardiomyopathy [118]. The severity of flow abnormalities and hence microvascular dysfunction, is able to predict the evolution of the disease towards progressive ventricular dysfunction and HF, and is a predictor of poor prognosis in patients with idiopathic left ventricular dysfunction independently of the degree of left ventricular functional impairment and of the presence of overt HF [119]. Although TH are currently being evaluated as an inotrope and vasodilator in various clinical settings, new information has been gathered recently in an experimental setting regarding the protective role of TH in the response of the heart to ischemic stress [120]. The physiological basis of these observations rests on the substantial anti-oxidant effects of TH. During reperfusion of the post-ischemic rat heart, TH administration leads to improved coupling of glycolysis to glucose oxidation, thereby decreasing H+ production and increasing cardiac efficiency as well as contractile function [121]. Moreover, Chen et al. have studied the effect of 3 days of T3 treatment on left ventricular function and myocyte

apoptosis after coronary ligation induced myocardial infarction in rat. Compared with sham-operated animals, rats with myocardial infarction showed significantly increased cardiac chamber dimension, decreased left ventricular function and significantly increased myocyte apoptosis in the border area of the infarct, as assessed by DNA laddering and TUNEL assay. Interestingly, T3 treatment was associated with a decrease in myocyte ischemia-induced apoptosis, through the non-genomic activation of Akt signaling pathway, which has been shown to play a role in regulating cardiomyocyte growth and survival [122]. Another potential mechanism of TH-induced cardioprotection is the increased expression of heat shock proteins such as HSP-27 and HSP-70, two redox-regulated molecular chaperones that enhance cell survival under stress [123, 124]. This TH effect seems particularly interesting since in patients with left ventricular dysfunction due to non-atherosclerotic cardiac disease, serum levels of heat shock proteins, IL-6 and CRP are elevated and the entity of this elevation is associated with a more severe disease as evidenced by a more depressed myocardial blood flow at rest and during dypiridamole, indicative of microvascular impairment [125].

Thyroid hormones and heart failure: clinical evidence

The hypothesis that an altered TH metabolism may play a direct role in the complex pathophysiology of HF progression is strongly suggested by the above-mentioned experimental evidence and reinforced by clinical and prognostic findings. Among all the potentially altered thyroid metabolism forms, LT3S has been extensively studied in patients with both early and overt HF. The prevalence of LT3S changes with the severity of disease, being approximately 20–30% in patients with overt HF and

Fig. 2 Prevalence of Low T3 Syndrome through clinical evolution of chronic heart failure * Opasich et al. [14]; ** Ascheim et al. [11]; *** Iervasi et al. [12]

less than 10% in those with early HF [9–16, 126]. T3 reduction is more frequent in patients in NYHA classes III–IV [11, 12, 14] (Fig. 2) and is frequently associated with a catabolic pattern characterized by lower insulin levels, higher cortisol levels [14], lower plasma lipid levels [12, 13], lower body weight and lower albumin levels [10, 12, 14]. From a hemodynamic point of view, a low cardiac index with increased left ventricular end diastolic pressure, increased right atrial filling pressure and a greater functional impairment assessed by VO_2 peak has been observed in low-T3 patients [10, 14]. Furthermore, in asymptomatic and mildly symptomatic patients with non-ischemic left ventricular dysfunction, T3 values and T3/T4 ratio are linked to both severity of left ventricular dysfunction and clinical status, being progressively lower in patients with more depressed ventricular dysfunction (and higher BNP values) and early symptoms of HF as expressed by NYHA class [16]. In this study, T3 was an independent predictor of left ventricular dysfunction at univariate regression analysis and the only independent predictor of NYHA class at multivariate analysis, whereas BNP was the most important predictor of left ventricular dysfunction only. A possible explanation for these findings is that at early phases of left ventricular dysfunction, when HF is still a organ (cardiac) disease without systemic involvement and full activation of the neuroendocrine system, T3 is a marker of cardiac impairment. Conversely, when cardiac disease progresses towards overt HF, the prevalence of LT3S increases and T3 concentration is not yet related to cardiac dysfunction, but represents a marker of multi-system involvement and thus an important prognostic marker of death. This hypothesis is reinforced by the evidence of the prognostic stratification of LT3S syndrome in patients with cardiac diseases and in particular, in HF patients. In an unselected sample of 573 patients with cardiac disease, cumulative and cardiovascular mortality were significantly higher in patients with than in those without LT3S (14.4% vs. 3%, and 7.5% vs. 1.5%, respectively) with a good correlation between free T3 (fT3) values and survival time ($r = 0.60$, $P < 0.001$) [12]. More recently, in a cohort of 3308 cardiac patients, survival rate for cardiac death was lower in patients with SHYPO, or LT3S with respect to euthyroid patients, suggesting that, independently on any form of mild thyroid dysfunction—either primary or secondary (low T3)—a normal thyroid status is essential for maintaining systemic and cardiovascular homeostasis; when euthyroidism is persistently lost, an increased whole-body and cardiovascular vulnerability is observed [9].

The prognostic impact of LT3S has been documented in several studies of patients with both ischemic and non-ischemic HF and different degrees of disease severity. In 58% of patients hospitalized for chronic advanced HF, Hamilton et al. observed a reduction in fT3 index and an

elevation in rT3, with the consequent reduction in fT3 index/rT3 ratio. The 1-year survival rate was 100% for patients with a normal and only 37% for those with a low fT3 index/rT3 ratio [10]. These data were more recently confirmed by Kozdag et al. in a group of 111 patients with ischemic and non-ischemic dilated cardiomyopathy and advanced NYHA class (III-IV). In this study patients with fT3/fT4 < 1.7 had a significantly less favorable outcome compared with those having higher fT3/fT4 ratio with a sensivity, specificity, positive and negative predictivity of 100, 71, 36, and 100, respectively [15]. In a group of 281 patients with post-ischemic and non-ischemic dilated cardiomyopathy, T3 levels and ejection fraction were the only independent predictors of cardiovascular and total mortality at univariate and multivariate regression analysis [13]. When evaluating the prognostic power of these two predictors by receiving operating characteristics (ROC) curve, the area under ROC curves (AUC: Area Under the Curve) showed a slightly higher prognostic accuracy for left ventricular ejection fraction (AUC = 0.659, $P < 0.0001$) as compared to total T3 (AUC = 0.610, $P < 0.0001$), although the difference between the two areas was not statistically significant ($P = 0.733$) [127]. Based on the above considerations a new integrated prognostic index was extracted from the multiple logistic regression model, and the AUC curve of this integrated index was obtained. The final result was that the AUC curve for this integrated index (0.759, $P < 0.0001$) was significantly higher than that of T3 and left ventricular ejection fraction alone in comparison to the AUC for both individual left ventricular ejection fraction and total T3 curves, resulting that the difference between the areas was statistically significant ($P = 0.008$ vs. left ventricular ejection fraction AUC, $P = 0.003$ vs. total T3 AUC). The analysis of the ROC curves indicates that the sensitivity of total T3 was higher than that of left ventricular ejection fraction in the higher specificity region of the ROC, indicating that the

prognostic incremental value of total T3 was particularly evident in patients with severely reduced left ventricular ejection fraction, i.e., <0.20. According to the best cut off value of 0.20 for left ventricular ejection fraction, as assessed by ROC curve (sensitivity = 31%, specificity = 84%) in combination with the low limit of normal range of total T3 (1.2 mmol/l), four groups were identified [13]. As showed in Kaplan–Meyer survival curves (Fig. 3), the estimated survival of patients with an ejection fraction <20% and a total T3 level ≤1.2 mmol/l was significantly reduced with respect to the others, and particularly with respect of patients with ejection fraction <20% and T3 levels ≥1.2 mmol/l revealing that the measurements of T3 levels adds prognostic information to conventional clinical and functional parameters, even among patients with low ejection fraction. These observations well fit with the common clinical observation that patients with the same ejection fraction may have different functional status, as expressed by NYHA class, and different prognosis and clearly indicate that T3 state does not represent a mere surrogate of other more powerful and frequently-used indicators of bad outcome.

Low T3 syndrome and heart failure: an adaptative mechanism, a maladaptative mechanism or both?

The link between T3 and HF is well documented. However this does not imply a causal association. Several doubts remain whether the T3/HF link is adaptative, and thus beneficial, or maladaptative. In accordance with the experimental and clinical findings LT3S can be even more considered directly and unfavorably involved in the HF progression process. This hypothesis is sustained by the evidences showing that: (1) in in vitro and ex vivo experimental studies an altered TH metabolism modifies cardiovascular homeostasis with regard to cardiac protein

Fig. 3 Kaplan–Meyer 18 month cumulative death in four subgroups identified according to the cut-off values of 0.20 for left ventricular ejection fraction and 1.2 nmol/l for triiodothyronine (T3) levels. Modified from Pingitore et al. [13]

gene expression, diastolic and systolic myocardial function, cardiac histology, cardiomyocyte morphology, and myocardial blood flow [102–125]; (2) TH replacement therapy reverses all these alterations; (3) LT3S is associated with different clinical parameters of disease severity in HF [9–16]; (4) LT3S is just associated with a worse prognosis in HF patients [9, 12, 13]. This new hypothesis contrasts with the previous one indicating that decreased T3 concentration is the result of an adaptative process finalized to reduce catabolic processes and thus energy expenditure [128, 129]. This interpretation is mainly founded on the apparently lack of symptoms and signs compatible with hypothyroidism in patients with LT3S. However taking into account all the experimental and clinical evidences and also the neuroendocrine interpretative model of HF in which neuroendocrine activation is initially compensatory and finally toxic, the two hypothesis of the LT3S role in HF can be enclosed in a unique scenario. At early phase of HF LT3S appearance may be an adaptative mechanism due to reduced cardiac output, having a potential beneficial effect through reducing metabolic demand [128]. This accounts for the correlation between severity of left ventricular dysfunction and T3 circulating levels [16]. Thereafter when persistently activated, a LT3 state may represent a maladaptive mechanism favouring cellular, morphostructural and functional cardiac (and vascular) remodeling and thus HF progression.

Is it time for TH-system based therapy in patients with heart failure?

All the above-mentioned experimental and clinical evidences portend the observation of increased cardiac risk in patients with HF and LT3S and offer a mechanistic basis for a TH-system based therapy in patients with left ventricular dysfunction and low/borderline levels of T3 [130]. In this subset of patients, the restoration of a normal TH profile might counteract progression of heart disease by (1) a positive remodeling through the modulation of myocardial gene expression; (2) improving cardiac systo-diastolic function and reducing vascular resistance with a consequent improvement in hemodynamics; (3) improving myocardial perfusion, known to be impaired in the early stage of dilated cardiomyopathy and leading to progression towards HF and death. Until now, experimental evidences have shown the benefit of T3 treatment in acute myocardial infarction [122, 131], and clinical reports have demonstrated the potential benefit of T3 replacement therapy in patients with myocarditis [132], cardiogenic shock [133] and cardiopulmonary bypass [134, 135]. As far as human HF is concerned, Moruzzi et al. demonstrated that short and medium term L-T4 treatment in patients with

idiopathic dilated cardiomyopathy improves cardiac contractility, resting circulatory parameters and exercise performance, without significant side effects [136, 137]. In a group of 23 patients hospitalized for advanced HF (NYHA class III-IV) and subjected to short-term intravenous T3 administration at supraphysiological doses (bolus only or bolus plus infusion) Hamilton et al. showed an increase in cardiac output and a reduction in SVR, without change in blood pressure or HR in patients who received the larger T3 doses [138]. In all these clinical studies, TH treatment does not produce side effects when administered in either physiological or short-term pharmacological doses. On the basis of these previous findings, our group studied 20 patients with HF and low T3 levels and randomized them to treatment with T3 infusion for 3 days at physiological dosage or to placebo [139]. Interestingly, the restoration of normal T3 plasma levels was associated with an increase in SV and left ventricular end diastolic volume when compared with pre-treatment levels and with placebo. These beneficial effects on functional parameters were further reinforced by the evidence of a positive neuroendocrine reset, with a significant decrease in norepinephrine, aldosterone and NT-pro BNP plasma levels. An example of this T3-induced neuroendocrine reset is shown in Fig. 4. The potential clinical relevance of T3-induced neuroendocrine deactivation in patients with left ventricular dysfunction is clearly deducible from 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 and cardiac performance [1–4]. In spite of these observations, it is clear that the small cohort of patients enrolled in all the studies cited above, the absence of a sufficient period of observation and the lack of control and randomization, i.e., Hamilton's study, largely affect the correct interpretation of results, particularly in view of possible long-term administration of synthetic TH is concerned. In this context, other therapeutical strategies useful for restoring a normal TH axis could be represented not only by the use of synthtetic T3 and T4, but also by the use of TH analogs [140] like 3,5-diiodothyropropionic acid (DITPA), which has shown to have cardiac inotropic selectivity and minimal effects on HR and metabolic activity [141–143]. Another potential new frontier could be represented by gene therapy able to modify TR expression or deiodinase activity, both involved in determining tissue hypothyroidism as observed in patients with HF. As far as TRs expression is concerned, Belke et al. [95] have shown that in mice subjected to aortic constriction to generate pressure overload-induced hypertrophy and to gene therapy using adeno-associated virus expressing either TRα1 or TRβ1, treatment with T3 was associated with an improvement in contractile function and SERCA

Fig. 4 A typical example of T3 circulating levels during T3-infusion and T3-induced neuroendocrine reset in a patient with dilated cardiomyopathy. T3 circulating levels before and during L-T3 treatment (left panel) and noradrenaline, aldosterone, NT proBNP levels before and after L-T3 treatment (right panels) Modified from Pingitore et al. [139]

expression. Similar results were obtained by Trivieri et al. [144] in transgenic mice overespressing D2 in the heart. These had enhanced contractile function in association with changes in the expression of calcium handling proteins and were particularly resistant to pressure-induced impairment of calcium cycling and contractility.

Conclusions and perspectives

More and more emerging experimental and clinical findings strongly support the concept that TH plays a fundamental role in cardiovascular homeostasis in both physiological and pathological conditions. However, additional pathophysiological studies in animals and humans are needed to better define the potential positive and/or negative effects of an altered thyroid metabolism as observed throughout evolution of HF. Large multicenter, placebo-controlled prospective studies could provide safety and prognostic effects of chronic treatment with thyroid hormone replacement therapy with L-T3 and/or L-T4. Important issues should be a clear definition of primary and secondary end points (i.e., mortality, hospitalization, quality of life, side effects, etc.) as well as type, dosage and schedule of

treatment. Other interesting therapeutic strategies are the use of TH analogs or specific modulation of TR or desiodase expression in the heart and/or peripheral tissues. The latter options seem particularly interesting if we consider that the finding of a D2 (and D3) gene expression in the cardiovascular system open the way to potentially interesting therapeutic perspectives involving novel molecular and pharmacological strategies in the field of HF.

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