Thyroid Replacement Therapy and Heart Failure

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Heart failure (HF) is a major public health and economic problem in Western countries and is one of the most common causes of hospitalization and death. Coronary artery disease is the underlying cause in more than two thirds of chronic HF patients. By 2020, the World Health Organization projects that ischemic heart disease alone will be the most important global cause of morbidity and mortality. The estimated increases in HF-related morbidity and mortality suggest that our understanding of the pathophysiological mechanisms of this syndrome is inadequate.

Interest in the role of thyroid hormones (THs) in HF has increased in recent years. The driving considerations can be summarized as follows: (1) the known effects of THs on contractile and relaxation properties of the heart; (2) experimental findings offering strong support for the hypothesis that TH signaling is critical in preserving cardiac structure and performance under normal conditions and after cardiac injury; and (3) evidence that mildly altered TH function is strongly associated with a worsening prognosis in cardiac patients in general and in HF patients in particular.

Diastolic function and systolic function are clearly influenced by THs. Ventricular contractile function is also influenced by changes in hemodynamic conditions secondary to TH effects on peripheral vascular tone. TH homeostasis preserves positive ventricular-arterial coupling, leading to a favorable balance for cardiac work. A study in rats demonstrated that chronic hypothyroidism alone can eventually lead to HF. Other studies suggest reduced cardiac tissue triiodothyronine (T3) levels after myocardial infarction (MI) or with development of hypertension by upregulating type 3 deiodinase (D3), which leads to deactivation of T3 and T4 (thyroxine). This review highlights a growing body of evidence from animal studies and small-scale clinical trials suggesting that low cellular thyroid activity at the cardiac tissue level may adversely affect HF progression and that treatment may lead to improvement.

TH Metabolism

The human thyroid gland produces and releases hormones mostly as the prohormone T4. In contrast, the thyroid gland secretes just a small amount (4 to 6 μg/d) of T3; the major portion (20 to 25 μg/d) of T4 derives from conversion of precursor T4. Thus, deiodination of T4 in peripheral tissues is the key element of TH metabolism and action because only T3 is considered the biologically active form of the TH. Three deiodinase enzymes regulate circulating and tissue concentration of THs: type 1 (D1); type 2 (D2), and type 3 (D3). D1 is considered the major peripheral source of circulating T3, whereas D2 plays a critical role in providing local conversion to T3. D3 is involved mainly in the conversion of T4 to reverse T3, which is considered an inactive form of TH, and in degrading T3 to inactive diiodothyronine (T2). Cardiac levels of active T3 are dynamically determined by a balance between availability and destruction of T3. Reduced TH function in the heart could arise from 1 or more of the following mechanisms: (1) reduced T3 production and/or increased T3 degradation resulting from inhibition of D1 and D2 activity and/or increased activity of D3, (2) reduced TH uptake and/or increased T3 degradation in the cardiac tissue, (3) changes in TH membrane transporters, and (4) altered signaling resulting from changes in TH nuclear receptors.

TH Imbalance and Heart Disease

An argument suggesting a link between heart disease and thyroid state is founded on evidence of a relationship between the presence of an altered thyroid state and the occurrence and progression of cardiac disease. Maintenance of TH homeostasis is required for proper cardiovascular function. Bioactive T3 is a powerful regulator of inotropism and lusitropism of the heart through their effects on myosin isoforms and calcium handling proteins in particular. Hyperthyroidism and hypothyroidism can lead to cardiovascular injury, including HF. Development of TH assays permitted differential diagnosis of hypothyroidism from HF in that these diseases share dyspnea, edema, pleural effusions, T-wave changes, a decrease in contractility, decreased cardiac output, and a grossly dilated, flabby heart. Hypothyroidism may lead to increased blood cholesterol levels and atherosclerosis. Hypothyroidism promotes myocardial fibrosis by stimulating fibroblasts, whereas the opposite is true of hyperthyroidism. Chronic hypothyroidism in adult rats leads to loss of coronary arterioles, impaired blood flow, a maladaptive change in myocyte shape, and development of HF. Changes in cardiac structure and function resulting from hypothyroidism depend only on the severity of TH deficiency and regress with T4 replacement treatment. Subclinical (mild)
primary thyroid hypofunction (scHypo or mild hypothyroidism) is defined by elevated values of thyrotropin (TSH) in the presence of normal free T4 (FT4) and total (TT3) or free T3 (FT3) serum concentrations.16,17 All cardiovascular alterations that have been reported in the presence of overt hypothyroidism have also been identified in scHypo, differing only in the extent of the alteration.18,24 Clinical observations suggest a strong link between scHypo and poor outcome in patients with and without heart disease.18–24 In particular, many reports suggest that scHypo is a risk factor in heart disease.18,21,25–27 In a recent prospective study of euthyroid HF patients subsequently developing scHypo, a poorer prognosis and increased hospitalization were observed in scHypo patients compared with those with persistent euthyroidism.28 In addition, in chronic HF patients, TSH levels even slightly above normal range are independently associated with a greater likelihood of HF progression.29 Epidemiological data also suggest that scHypo may be the only reversible cause of left ventricular (LV) diastolic dysfunction with slowed myocardial relaxation and impaired filling, particularly in subjects with TSH >10 µU/mL.16,30 The Health, Aging, Body Composition population-based study showed that participants with TSH >7 µU/mL had 3-times-higher HF events than euthyroid patients.31 The Cardiovascular Health Study also showed a greater incidence of HF events among participants >65 years of age with TSH >10 µU/mL.32 Reports on the prevalence of primary scHypo in the general population vary widely.23,25 The National Health and Nutrition Examination Survey III trial reported that 4.3% of the US population has scHypo, with higher rates in the elderly and women.33 In patients with cardiac diseases, however, the prevalence of primary scHypo is similar to that reported in the general population.18 scHypo is an independent risk factor for atherosclerosis and MI in women24 and is associated with coronary artery disease and increased all-cause mortality in men.25,34 Evidence indicates that patients with clinically stable heart diseases and scHypo have a greater rate of cardiac death than euthyroid patients.18 A randomized crossover trial in patients with scHypo showed beneficial effects of T4 on cardiovascular risk factors and quality of life.26 Results from the Nord-Trøndelag Health Study showed that coronary artery disease mortality in women and unfavorable serum lipids for patients increased at higher TSH levels within the normal range.27,35

Independently from the presence of primary thyroid hypofunction and differently from other organs, the heart is particularly vulnerable to reductions in biologically active T3 in plasma because cardiomyocytes have a negligible capability to generate T3 from locally converted precursor T4. Consequently, when circulating T3 is low, the myocardium may become relatively hypothyroid. In animals, a low-T3 state resulting from altered peripheral TH metabolism secondary to caloric restriction is associated with impaired cardiac contractility and changes in cardiac gene expression, similar to those observed during chronic hypothyroidism. Importantly, these alterations are reversible after restoration of normal T3 plasma levels by exogenous T3 administration.31 Low-T3 syndrome is the central finding and defines the illness in a variety of acute and chronic severe nonthyroidal illnesses with cardiac origin, including MI, HF, and surgically treated cardiac disease.1 Low circulating levels of T3 in the absence of primary thyroid hypofunction have been found in 20% to 30% of patients with dilated cardiomyopathy.18 Moreover, FT3 levels were inversely correlated to coronary artery disease, and low T3 levels conferred an adverse prognosis, even after adjustment for coronary risk factors in patients with coronary artery disease, normal LV function, and no history of MI.36 Low-T3 syndrome could be a mere marker of poor health. More intriguing, and to the contrary, is the hypothesis that a progressive T3 decrease is part of the vicious pathophysiological circle sustaining cardiac remodeling, neurohumoral activation, and systemic derangement in HF, thus leading to an increase in global and cardiac mortality. Consistent with the regulation of many structural and functional genes by T3, a low-T3 state in cardiac tissue may cause impaired diastolic and systolic function, prolongation of action potential, and increased susceptibility to arrhythmias. In addition, hypothroid hearts show poor substrate use such as glucose, lactate, and free fatty acids by mitochondria.37 Accordingly, cardiac oxygen consumption, as measured by positron emission tomography 11C acetate, was reduced in hypothyroid patients, but cardiac work was compromised more severely than oxidative metabolism. This led to decreased cardiac energetic efficiency of the hypothroid human heart.38 Because of well-known multiple and systemic actions, THs may also interact with other hormone/organ systems and with all the hemodynamic and metabolic variables involved in HF that modulate the development and progression of HF (Figure 1). At present, the concept that altered TH metabolism may contribute to human HF progression is supported mainly by several clinical observational studies showing the important role of a low-T3 state in the prognostic stratification of patients with HF (Table 1).20,22,39–41) Independently of the parameter used, all of these studies showed that impaired T4-to-T3 conversion is associated with a high incidence of fatal events consisting of cardiac or cumulative death or of heart transplantation. Impairment of T4-to-T3 conversion was also found to be proportional to the clinical severity of HF as assessed by the New York Heart Association functional classification.21,42 Furthermore, T3 levels in plasma strongly correlated with exercise capacity and oxygen consumption in HF patients.43 In summary, clinical observations seem to indicate the presence of a close pathophysiological link between primary scHypo or impaired T4 to T3 conversion and evolution of HF. It is important that clinicians and scientists evaluate the evidence fairly and objectively before making a decision on the potential for therapeutic TH treatment of heart disease. This is particularly true because there have been few promising new pharmacological treatment options for HF in recent years.

TH Metabolism During the Early Post-MI Phase

Human and animal studies suggest that low TH levels contribute to worsening outcome after MI. There is rapid decline in T3 and TSH during the first week after an acute MI in patients.44 Values for reverse T3 were increased but T4 remained normal. In-hospital and postdischarge mortality was highest among patients.
with the most pronounced T3 depression and reverse T3 elevation. Moreover, there is a worsening prognosis in post-MI patients with persistently low plasma T3. These observations, together with recent evidence that mild TSH abnormalities are associated not only with traditional coronary risk factors but also with mortality for coronary artery disease, support the hypothesis that even a mild reduction in TH levels plays an important role in the myocardial response to acute ischemia.

Induction of MI in severely hypothyroid dogs led to a dramatic increase in infarct size. Ojamaa et al demonstrated that...
strated the presence of low-T3 syndrome in rats after MI. T3 treatment improved ejection fraction and normalized some of the changes in gene expression. In another study, T4 treatment of rats with MI led to a modest improvement in heart function. Henderson et al demonstrated normal serum T4 levels but a sustained reduction in serum T3 levels 1 to 5 weeks after MI in rats. T3 treatment resulted in improved systolic function and a trend for improved diastolic function. A study by Olivares et al provided more insight into TH impairment in MI. After MI was produced in rats, there was a pronounced upregulation of D3. Serum T3 levels did not normalize for 2 months. Combined with reduced muscle D2 activity, this may provide an additional mechanism for the reduction of plasma T3 levels that is typically seen after MI. T3 treatment of rats with MI led to a decrease in DNA ladder and terminal deoxynucleotidyl transferase dUTP nick-end labeling in the border zone, suggesting a potential protective role. T3 can also prevent remodeling by reducing apoptosis at the early phase of ischemia/reperfusion. Up-regulation of D3 may be a generalized response to cardiac injury since Wassen et al have also shown D3 activation in pulmonary hypertension. The increase in D3 was specific to the overloaded right ventricle and associated with a reduction of both local T3 content and T3-dependent gene transcription. It is likely that reexpression of the fetal gene program in the overloaded ventricle, a common feature of cardiac disease, is enhanced by low tissue TH levels.

Pantos and colleagues have published numerous animal studies on the effects of THs on the heart, particularly during ischemia or MI. They have shown that short- and long-term T3+T4 treatment of rats with MI leads to improved LV function and remodeling. However, remodeling data were limited to echocardiographs and measurement of infarct size with no tissue structure analyses of spared myocardium. Importantly, the Pantos group has not observed any TH treatment–related changes in infarct scar remodeling. Because interventions affecting post-MI scar remodeling may lead to cardiac aneurism or rupture and THs are known to have antifibrotic effects, it is reassuring to know that TH treatment is not likely to promote such changes. It is interesting to note that T3 and/or T4 replacement therapy has never been tested in humans after MI despite a clear association between low thyroid function and poor prognosis after MI and many animal studies showing similar changes and improvement with TH treatment. At present, the issue of using T3, T4, or their combination has not been completely resolved but may depend on specific clinical situations. For instance, it seems logical that T4 treatment may work better in the presence of primary hypothyroidism but not in the presence of impaired peripheral conversion of T4 to T3, when T3 seems to be more useful.

When considering the large number of patients with primary scHypo and the number of patients with heart disease, it is remarkable that only a few animal studies have investigated the combined effects of these conditions. We confirmed the presence of scHypo (increased TSH, normal T3 and T4) in BIO-T02 cardiomyopathic hamsters. Treatment of T02 hamsters with a therapeutic dose of T3+T4 from 4 to 6 months of age prevented progression of fibronecrosis and further loss of cardiac myocytes and attenuated progressive LV dilatation and dysfunction. Resting and maximum (adenosine) coronary blood flow was significantly reduced in both 4- and 6-month-old T02 hamsters. T3+T4 treatment of T02 hamsters normalized resting and maximum blood flow. This was the first study to demonstrate potential benefits of TH treatment of scHypo in an animal model of HF. It is not known at present if long-term TH treatment of T02 hamsters will reduce mortality. Our studies with T02 hamsters raise the possibility that patients with similar cardiac conditions may benefit from TH treatment. A recent rat study also demonstrated that serum TH levels may be normal when cardiac tissue levels are significantly depressed. Cardiac tissue TH levels were a more reliable indicator of LV function than serum hormone levels. This raises an important question: How much ventricular dysfunction in cardiac patients who are diagnosed as “euthyroid” is actually due to low tissue hormone levels? Thyroid dysfunction at the tissue level may be exacerbated by downregulation of thyroid nuclear receptors, known to occur in HF.

**Cardiac Remodeling and the Effect of THs**

Although much of the work on HF has focused largely on improving contractility and relaxation without inducing an increase in heart rate, new evidence suggests that beneficial effects on myocardial tissue remodeling could be a more important target. To understand and fully appreciate the effects of THs on myocyte remodeling, a brief overview of myocyte remodeling is helpful. Because changes in wall stress are directly proportional to chamber diameter and inversely proportional to wall thickness, it seems plausible that changes in myocyte length and width are likely to play a key role in pathological alterations in chamber diameter and wall thickness, respectively. After extensively characterizing and implementing a precise method to measure myocyte size, we subsequently documented patterns of myocyte remodeling in many mammalian species during physiological and pathological cardiac growth (see reviews). We demonstrated that pressure overload leads to an increase in myocyte cross-sectional area (CSA) and volume overload leads to proportional growth of myocyte length and width (Figure 2). Regardless of the starting point (normal CSA or increased CSA with the presence of hypertension), progression to dilated failure is associated with only cell lengthening from series addition of sarcomeres. This is the case in dilution of the noninfarcted myocardium after MI, idiopathic dilated cardiomyopathy, and hypertension associated with dilated failure (Figure 2). Cumulatively, our remodeling data suggest that the cellular defect in progression to dilated failure is related to the inability of the myocytes to properly regulate CSA. The absence of an increase in CSA as myocytes lengthen leads to a vicious cycle of progressively increasing wall stress, impaired coronary blood flow, and increased stiffness from collagen accumulation in HF.

Induction of hyperthyroidism in normal rats leads to balanced growth of myocyte length and width, a pattern similar to that of normal physiological growth. Hypothyroidism induced by propylthiouracil in rats leads to cardiac atrophy caused by a reduction in myocyte CSA initially.
However, long-term hypothyroidism leads to induction of cell lengthening from series sarcomere formation. Series addition of sarcomeres is a unique feature of dilated HF and is reversed in myocytes from HF patients after unloading as a result of implantation of a LV assist device. So, LV unloading caused by hypothyroidism leads to an unexpected change in myocyte shape typical of HF rather than mechanical unloading.

We investigated the effects of T3+T4 on LV chamber and myocyte remodeling in aging spontaneously hypertensive heart failure rats approaching dilated HF. There was a dose-related improvement in the ratio of chamber diameter to wall thickness that normalized systolic wall stress despite the presence of sustained hypertension. This alteration in chamber anatomy resulted from a specific change in myocyte shape, namely a reduction in myocyte major diameter (axis runs in a circumferential direction correlating with chamber shape, namely a reduction in myocyte major diameter (axis runs in a circumferential direction correlating with chamber dimension) and an increase in myocyte minor diameter (axis runs in a transmural or wall thickening dimension). Preliminary results from T3-treated rats after MI also suggest beneficial changes in myocyte shape (A.M.G., unpublished observation, 2010). Cumulatively, our studies showing improved myocyte shape with TH treatment of various animal models of HF suggest that TH plays an important role in the regulation of myocyte shape in heart disease. In particular, THs appear to play a key role in the proper regulation of myocyte transverse growth in myocardium. It is possible that impaired transverse growth during progression to dilated HF is due to low thyroid function at the tissue level.

Our knowledge of the molecular regulation of cardiac myocyte shape is slowly evolving. Of note, a vast array of complex protein interactions in mechanical stress sensors has been found in many regions of cardiac myocytes, including costameres, intercalated disks, and caveolae-like domains. To the best of our knowledge, insertion of series sarcomeres has never been observed in adult heart. In vitro work by Yu and Russell, however, suggests that new series sarcomeres are formed throughout the cell length. Very little is known about the regulation of myocyte CSA. Of interest is the transmission of lateral force during myocyte contraction via cytoskeletal linkage from the sarcolemma to the nucleus. A complex array of structural and signaling proteins is located in this transverse network involving the sarcolemma, costameres, and Z disks. It is possible that this lateral network is a key regulator of myocyte CSA. This was suggested by studies showing a critical role for the cytoskeletal protein melusin, which interacts with the β1-integrin in the costameric region of cardiac myocytes. Melusin is upregulated in early hypertension (CSA growth period) and downregulated with progression to dilated HF (cell-lengthening phase). Melusin knockout mice showed excessive dilatation and impaired growth of myocyte CSA after aortic constriction, whereas melusin overexpression promoted wall thickening and prevented dilated HF after aortic constriction. Like THs, melusin protects from fibrosis and apoptosis and stimulates Akt signaling. THs increase NO expression, and NO is known to increase expression of costameric proteins. T3 has also been shown to trigger Akt-dependent changes in titin isoform transitions. These examples are given simply to show how THs could affect mechanosensors and myocyte shape. Clearly, more work is needed to demonstrate specific mechanisms and causality.

**TH Treatment in HF**

A prolonged controversy has developed over the issue of TH treatment in cardiac patients, with data limited to only a few studies. A strong argument in favor of TH treatment in HF is that the failing heart has alterations in gene expression similar to that found in hypothyroidism, with all abnormalities being reversible with TH substitutive treatment. An unresolved question, however, is related to the meaning of low FT3 in the background of normal levels of TSH and FT4, which is observed in the majority of nonthyroidal illness patients. Under these circumstances, TH action in peripheral target tissues such as the heart is poorly understood. A major limitation involves the assessment of tissue TH status in peripheral tissues based on hormonal blood-borne data only. Aside from the central issue of dosage, timing for initiating and discontinuing TH treatment in scHypo patients with HF is not clear. A good biomarker of intracardiac TH signaling would be helpful but has not been identified. In the absence of such a marker, a rational, cautious therapeutic approach might be to restore and maintain over time biochemical euthyroidism as documented by normal circulating levels of TSH, FT4, and FT3.
Table 2. TH and TH Analog DITPA Treatment in Patients With HF

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design</th>
<th>Population</th>
<th>Patients, n</th>
<th>Age*, y</th>
<th>NYHA</th>
<th>LVEF, %</th>
<th>Intervention</th>
<th>Main Findings</th>
<th>Heart Rate</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moruzzi et al, 1994</td>
<td>Randomized (1:1), placebo controlled</td>
<td>Nonischemic HF</td>
<td>10</td>
<td>47–78</td>
<td>8–III</td>
<td>27±8</td>
<td>T4 100 μg/d for 1 wk OS</td>
<td>↓ SVR (dobutamine test), ↑ CO (dobutamine test), ↑ O2 consumption, ↑ exercise tolerance, ↑ resting LVEDV, ↓ SVR</td>
<td>Unchanged</td>
<td>No</td>
</tr>
<tr>
<td>Moruzzi et al, 1996</td>
<td>Randomized (1:1), placebo controlled</td>
<td>Nonischemic HF</td>
<td>10</td>
<td>51–70</td>
<td>II–IV</td>
<td>29±6</td>
<td>T4 100 μg/d for 3 mo OS</td>
<td>↑ Cardiac performance at rest, exercise, and dobutamine test, ↓ LVEDD, ↓ SVR</td>
<td>Unchanged</td>
<td>No</td>
</tr>
<tr>
<td>Hamilton et al, 1998</td>
<td>Uncontrolled</td>
<td>Ischemic, nonischemic HF</td>
<td>23</td>
<td>50</td>
<td>III–IV</td>
<td>22±1</td>
<td>T3 cumulative dose 0.15–2.7 μg/kg bolus + continuous infusion (6–12 h)</td>
<td>↑ CI, ↑ PCWP and MAP</td>
<td>Unchanged</td>
<td>No</td>
</tr>
<tr>
<td>Malik et al, 1999</td>
<td>Uncontrolled</td>
<td>Systolic HF (cardiogenic shock)</td>
<td>10</td>
<td>37–65</td>
<td>Not available</td>
<td>T4 20 μg/h bolus + continuous infusion (36 h)</td>
<td>↑ SVR, ↑ CO, ↑ UO</td>
<td>Unchanged</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Iervasi et al, 2001</td>
<td>Uncontrolled</td>
<td>Ischemic, nonischemic HF</td>
<td>6</td>
<td>64±8</td>
<td>III–IV</td>
<td>24±3</td>
<td>T3 initial dose 20 μg/m2bs per d, continuous infusion (4 d)</td>
<td>↑ LFSV, ↑ LVEDV, ↓ NT-proBNP, ↓ noradrenaline, ↓ aldosterone</td>
<td>Reduced</td>
<td>No</td>
</tr>
<tr>
<td>Pingenitore et al, 2008</td>
<td>Randomized (1:1), placebo controlled</td>
<td>Ischemic, nonischemic HF</td>
<td>20</td>
<td>64–77</td>
<td>I–III</td>
<td>25±18–32</td>
<td>T3 initial dose 20 μg/m2bs per d, continuous infusion (3 d)</td>
<td>↑ CI, ↓ SVR, ↓ lipoproteins and cholesterol</td>
<td>Increased</td>
<td>Poorly tolerated, weight loss, fatigue, GI complaints</td>
</tr>
<tr>
<td>Goldman et al, 2009</td>
<td>Randomized (2:1), placebo-controlled</td>
<td>Ischemic, nonischemic HF</td>
<td>86</td>
<td>65.6±11 (T)</td>
<td>II–IV</td>
<td>28±6.8 (T)</td>
<td>DITPA twice daily, 90-mg increments (every 2 wk) to maximum 360 mg</td>
<td>↑ CI, ↓ SVR, ↓ lipoproteins and cholesterol</td>
<td>Increased</td>
<td>Poorly tolerated, weight loss, fatigue, GI complaints</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; DCM, dilated cardiomyopathy; LVEF, LV ejection fraction; SVR, systemic vascular resistances; CO, cardiac output; CI, cardiac index; UO, urinary output; LVEDD, LV end-diastolic diameter; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial pressure; LVSV, LV stroke volume; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; T, Treated; P, Placebo; GI, gastrointestinal; m2bs, m2 body surface; and OS, oral administration.

*Age reported as range, mean, or mean ± SD.

TH-based novel therapeutic options could find suitable application not only at early but also at end stages of HF. Treatment with physiological doses of T3 is able to restore the expression of Ca(2+) cycling and handling proteins and contractile function of cardiac myocytes in an animal model of chronic cardiac unloading (a condition similar to that in patients with end-stage HF after LV assist device implantation).89 Tissue-engineered heart muscle (also called cardioids) is a fascinating alternative treatment modality for end-stage HF. T3 stimulation is able to promote the self-organization of primary neonatal cardiac cells into a contractile tissue construct. An increased rate of contraction and relaxation in response to T3 stimulation is observed with parallel changes in the gene expression of SERCA2, phospholamban, and myosin heavy chains.90

A number of preclinical studies have tested L-T4, L-T3, or TH analog diiodothyropropionic acid (DITPA) replacement therapy in patients with HF (Table 294–306,91–94). Synthetic L-T3 or L-T4 improved LV function consisting of enhanced resting cardiac output and exercise capacity and reduced systemic vascular resistance. However, the protocols used for T3 administration in HF patients were much different. Independently of the adopted L-T3 regimen and different from DITPA, T3 was well tolerated, and undesirable effects consisting of arrhythmias, myocardial ischemia, or hemodynamic instability were not documented. In a clinical study from our group, improvement in cardiac performance induced by T3 did not correspond to increased myocardial oxygen consumption as indirectly estimated by calculation of the rate-pressure product and total cardiac work.93 Importantly, the benefit of T3 infusion on cardiac function paralleled the benefit of T3 infusion on cardiac function paralleled deactivation of the neuroendocrine profile. In the abovementioned study,93,95 the effects of TH replacement therapy on cardiac function and morphology were assessed by cardiac magnetic resonance, a noninvasive and nonionizing technique currently considered the gold standard approach to assess LV volumes and regional global function. The high quality of imaging and the 3-dimensional approach of cardiac magnetic resonance allow assessment of LV postschematic remodeling accurately with high reproducibility, enabling smaller sample sizes to reach statistical significance.96,97

It is worth noting here that a phase II, randomized, double-blind, placebo-controlled clinical trial investigating the effects of T3 treatment in patients with MI was recently initiated by Dr Iervasi (Thyroid Hormone Replacement Therapy in ST Elevation MI [THiRST]).

Conclusions

A growing body of evidence suggests that TH dysfunction may play an important role in the progression to dilated HF.
Therapeutic use of THs in HF has not been adequately studied. Until now, most studies have targeted improvement in LV function. THs also produce remarkable improvements in LV function. THs also produce remarkable improvements in LV function.

Disclosures

None.

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