Thyroid (dys)function in heart failure: is it a potential target for medical treatment?

Alessandro Pingitore
Giorgio Iervasi

Institute of Clinical Physiology, CNR, Pisa, Italy

Introduction

Currently, there is little doubt that activation of the neuroendocrine (NE) system is predominately responsible for the progressive decline of heart function in heart failure (HF). This is due to the complex action of neurotransmitters, hormonal factors, and/or immunological pathways. Evidence that supports this point of view is the clear prognostic benefit and the reduction of HF progression by using NE-guided therapeutic approaches (SOLVD investigators 1992; Eichhorn and Bristow 1996; Packer et al 1996; Opie 2004; Solomon et al 2004). However, the fact that HF represents one of the major causes of morbidity and mortality in Western countries also suggests that the current portfolio of NE antagonists fails to completely explain and possibly counteract disease progression (Guyatt and Deveraux 2004). In this context, interest in the relationship between thyroid hormones (THs) and HF is increasingly gaining prominence. The chief reason for the latter is the emerging novel actions of THs on the cardiovascular system and, more specifically, the role of TH as a prognostic biomarker of cardiac disease as well as the potential benefit of TH administration in patients with HF.

Thyroid hormones in cardiac performance and vascular tone: new evidence

Thyroid hormones and, in particular, the active form triiodothyronine (T3) regulate the synthesis and action of various cardiac proteins including α and β myosin heavy chain (α-MHC and β-MHC, respectively), sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), Na^{+}/Ca^{2+} exchanger (NCX), phospholamban, and voltage gated potassium channels (Klein and Ojamaa 2001). The fundamental actions of TH on the cardiovascular system are well documented not only by the large series of experimental data (Klein and Ojamaa 2001) but also by the more recent evidence of cardiovascular alterations in the presence of minimal changes of thyroid function in humans. We recently utilized magnetic resonance (MR) and tagging MR to evaluate cardiac morphology and function in patients with mild (subclinical) chronic hypothyroidism (SHT). We were able to demonstrate altered cardiac volumes and resting global and regional systolic performance of the left ventricle in SHT patients as compared with normal subjects. TH replacement therapy reversed the alteration to normal in SHT patients (Ripoli et al 2005). The association of reduced pre-load with increased after-load, observed in SHT in this study, is in line with the multidistrict effect of TH (Klein and Ojamaa 2001) by which central (cardiac) and peripheral (vascular) effects act synergically to improve systolic performance. The observed changes in pre- and after-load are sufficient to explain the decrease of systolic pump performance observed in SHT patients without the need to invoke a simultaneous direct impairment in myocardial inotropic function. Accordingly, for similar values of end-systolic volumes, systolic arterial pressure did not differ among patient subgroups and the control group, thus suggesting a similar degree of contractility (Ripoli et al 2005). On the basis of the above considerations, regional changes of systolic function, observed with tagging MR, might be interpreted just as the result of parallel changes in cardiac loading conditions. Future studies, however, will be helpful to define the clinical impact in terms of symptoms and outcome of these abnormalities in patients with heart failure showing abnormal peripheral TH metabolism characterized by low levels of biologically active form T3.

A close relationship between thyroid function and blood pressure physiology was also found by the use of an in vivo human model of short-term, severe hypothyroidism (Fommei and Iervasi 2002). TH withdrawal induced an increase in blood pressure levels, particularly diastolic pressure. The deprivation of TH was associated to a proportional increase in plasma noradrenaline and adrenaline, whereas the restoration of thyroid function abolished that stimulation and proportionally reduced blood pressure levels, thus indicating that TH contribute to systemic arterial blood pressure homeostasis. Accordingly, a direct relaxant effect of the TH on cultured arteriolar smooth muscle cells was also reported in recent years (Ishikawa et al 1989). Moreover, exposure to T3 of vascular smooth muscle cells isolated from rat aorta caused these

cells to relax rapidly; this effect was independent from cAMP and nitrix oxide formation (Ishikawa et al 1989; Ojamaa et al 1996).

More recently, we evaluated the role of T3 and thyroxine (T4) on the hamster cheek pouch microcirculation. The application of T3 consistently induced dose-dependent dilation of arterioles within 2.0 ± 0.5 min from administration. The application of T4 caused dilation within 16 ± 2 min. Iopanoic acid, which inhibits both 5′-type 1 deiodinase and 5′-type 2 deiodinase, abolished the dilation elicited by T4 but did not affect T3-dependent dilation. 6-propyl-2-thiouracil, which inhibits 5′-type 1 deiodinase but does not alter T3 production from T4 by 5′-type 2 deiodinase, did not affect the dilation induced by T4. Thus, local conversion of T4 to T3 represents a crucial step for the dilation of the microcirculatory system, which can be now considered a target for a TH action (Colantuoni et al 2004).

Thyroid hormone and heart failure

Changes in thyroid metabolism characterized by a reduction in biologically active T3 have been reported in HF (Klein and Ojamaa 2001) and commonly interpreted as a compensatory mechanism. The hypothesis that this alteration is an adaptive factor minimizing catabolic phenomena of illness has been recently questioned since there is evidence of a negative prognostic impact of this syndrome in patients with heart diseases and specifically in patients with HF. For example, in a cohort of 573 unselected cardiac patients, the probability of death was significantly higher in patients with low T3 syndrome; free (F)T3 resulted also in a powerful independent predictor of cardiac and cumulative death (Iervasi et al 2003). In a more recent study on patients with non-ischemic and ischemic HF, T3 levels represented an important predictor of mortality, which added prognostic power to conventional cardiac parameters (Pingitore et al 2005). Kaplan-Meyer survival curves of patients with reduced left ventricular ejection fraction (LVEF) and total (T) T3 showed the highest mortality when compared with that of patients with similar LVEF but normal total TT3, indicating thereby the power of TT3 concentration in discriminating patients at very high risk for death (Figure 1a, 1b). These results well fit with the very recent observation of a relationship between FT3/FT4 ratio, echocardiographic alterations, and mortality in patients with dilated cardiomyopathy (Kozdag et al 2005), and reinforce previous data in a smaller cohort of patients showing the potential

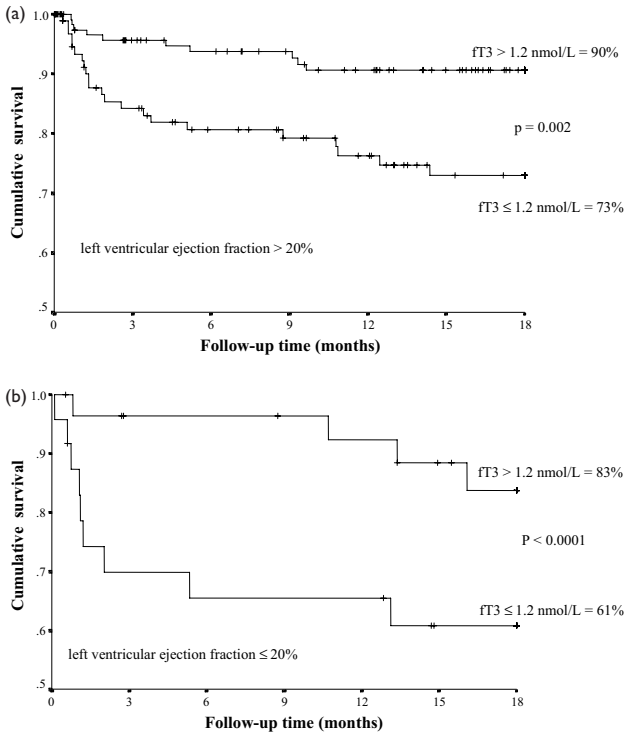

Figure 1 (a) Kaplan-Meier 18-month survival curves of the patients with left ventricular ejection fraction > 20%, divided according to the low limit of normal range of TT3 (1.2 nmol/L). (b) Kaplan-Meier 18-month survival curves of the patients with left ventricular ejection fraction ≤ 20%, divided according to the low limit of normal range of TT3 (1.2 nmol/L). Data adapted from Pingatore et al (2005).

capacity of prognostic stratification of the altered TH metabolism in HF (Hamilton et al 1990). Moreover, these results favor the experimental evidence that an altered TH metabolism may not be interpreted just as a biological risk factor of death but as a direct causal factor contributing to the progression of HF. At the same time, all the above mentioned clinical data fit well with the observation in a human model of cultured atrial cardiomyocites and myocardial tissue, that normal T3 has a critical role in maintaining morpho-structure and calcium handling (Forini et al 2001). The absence of T3 leads to disorganization of cultured myocardium and phenotypical remodeling which resembles gross and cellular structural impairment observed during HF progression (Glennon et al 1995; Mann 1999; Forini et al 2001). Following the same line of reasoning it is interesting to remark that changes in gene expression and cardiac function observed in heart disease match those seen in hypothyroidism (Brent et al 1991; Ojamaa et al 1992; Kiss et al 1994; Wickenden et al 1997; Oudit et al 2001; Yen 2001) and coincide with the so-called recapitulation of the fetal phenotype (Izumo et al 1987; Colucci 1997; Haghighi et al 2001).

Treatment of heart failure with synthetic thyroid hormone

A strong argument in favor of the hypothesis that a low T3 state may contribute to the poor prognosis of HF patients comes from data showing the benefit gained from treating patients with synthetic TH. Unfortunately, only a few studies have tested the synthetic T4 or T3 as a potentially beneficial treatment of cardiac dysfunction (Klemperer et al 1995; Hamilton et al 1998). From the first observation (Gay et al 1988), it was clear that one of the major limitations of the hypothesis would have been the plethora of noncardiac collateral effects induced by the hormone such as the increase in oxygen consumption and heart rate as well as negative effects on protein and fat metabolism. Interestingly, in humans, three studies evaluated the possibility of using T3 and T4 therapeutically with the purpose of improving cardiac function of HF avoiding the unwanted detrimental effects (Moruzzi et al 1996; Hamilton et al 1998; Iervasi et al 2001). In the first two studies (whether intravenous infusion [IV] of supraphysiological doses of T3 for 6 hours was used or treatment with 0.1 mg of T4 was given daily for 12 weeks, respectively), there was an increase in cardiac output associated with a decrease in systemic vascular resistance (Moruzzi et al 1996; Hamilton et al 1998). The more recent pilot study from our laboratory (Iervasi et al 2001) also provided data on the safety and efficacy of long-term (96 hours) IV T3 replacement (ie, 20 $\mu g \cdot die \cdot m^2$) therapy in patients with low T3 syndrome and severe chronic HF. A significant increase in cardiac output with unchanged heart rate was already observed after 24 hours of T3 infusion together with a progressive increase in LVEF and a reduction in systemic vascular resistance. Most importantly, the improvement in the cardiovascular (and renal) hemodynamics was also associated with a progressive increase in 24-hour urinary output and a reduction in noradrenaline plasma levels. The interpretation of the results is, however, largely affected by the small cohort of patients enrolled in all studies (Moruzzi et al 1996; Hamilton et al 1998; Iervasi et al 2001), the absence of a sufficiently long period of observation and, with the exception of the Moruzzi's study, the lack of randomization.

An alternative approach to the problem could be the use of TH analogs with fewer side effects, and among these, the more emerging 3,5-diiodothyropropionic acid (DITPA) (Pennock et al 1992; Morkin et al 2004), which has shown to have cardiac inotropic selectivity and minimal effects on heart rate and metabolic activity. Several studies (Pennock et al 1993; Mahaffey et al 1995; Wickenden et al 2000) confirmed in various animal models the beneficial effects of the drug on HF and peripheral resistance, and they have formed the basis for a large clinical trial in HF patients with low T3, which is currently in progress (Morkin et al 2004).

Perspectives and conclusions

There are increasing experimental and clinical findings that strongly support the fundamental role of TH in the cardiovascular homeostasis both in physiological and pathological conditions. In particular, clinical data (Kozdag et al 2005; Pingitore et al 2005) seem to suggest that an altered TH metabolism characterized by a reduced level of biologically active T3 or FT3/FT4 ratio may contribute to poor prognosis. An important issue that needs further exploration is the relationship between TH and the other NE systems activated in HF. Additional pathophysiological studies in animal models and in humans are needed to improve our knowledge on the positive and/or negative effects of an altered thyroid metabolism in HF. Moreover, large, multicenter, placebo controlled prospective studies could provide fundamental data on safety and prognostic effects of the chronic treatment with TH replacement therapy using T3 and/or T4 or TH analogs. Important issues include a clear definition of primary and secondary, clinically relevant end points (ie, mortality, hospitalization, quality of life, side effects etc) as well as type, dosage, and schedule of treatment.

At the same time, the more recent finding of a consistent 5′-type 2 deiodinase gene expression and activity in the cardiovascular system (Croteau et al 1996; Mizuma et al 2001) suggests new potential lines of investigation. The existence in the microcirculatory system of a deiodinating pathway that is able to produce local T3 and the documented vasodilating activity of neo-generated T3 (Colantuoni et al 2004) are fundamental findings in defining the vascular system as a direct target of TH. Taken together, these data could open the way to new therapeutic perspectives involving novel molecular and pharmacological strategies. For example, a recent experimental approach was used to overexpress 5′-type 2 deiodinase gene in the cardiac myocytes to increase the cellular action of TH (Pachucki et al 2001). Even though all the target genes of TH action in vascular smooth muscle cells are still unknown, similar approaches perhaps could be employed as a new strategy to regulate systemic vascular resistance during progression of HF.

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