Thyroid Hormone and the Cardiovascular System

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KEYWORDS

• Thyroid hormone • Cardiovascular system • Heart
• Hemodynamics

Studies of patients with spontaneously occurring hyperthyroidism and hypothyroidism indicate that thyroid hormone has profound effects on the heart and cardiovascular system.[1] This article describes the cellular mechanisms by which thyroid hormone acts at the level of the cardiac myocyte and the vascular smooth muscle cell to alter both phenotype and physiology.[2] Because it is well established that thyroid hormone, specifically T_3, acts on almost every cell and organ in the body, studies on the regulation of thyroid hormone transport into cardiac and vascular tissue take on added clinical significance (**Fig. 1**). The characteristic changes in cardiovascular hemodynamics and metabolism that accompany thyroid disease states can then be best understood at the cellular level.[3]

THYROID HORMONE METABOLISM

Thyroid hormones, tetraiodothyronine (T_4) and triiodothyronine (T_3), are produced in the thyroid gland in a molar ratio of approximately 7:1. All enzymatic steps in the synthesis and secretion of T_4 and T_3 are regulated by thyroid-stimulating hormone (TSH).[4] T_3, the physiologically active form of thyroid hormone, is produced primarily by 5′-monodeiodenation of T_4 in the liver, kidney, skeletal muscle, and pituitary gland.[5] Both T_4 and T_3 circulate in blood almost entirely (>95%) bound to a family of hormone binding proteins. The free hormone, specifically T_3, is transported through a variety of membrane transport proteins and, after transit to the cell nucleus, acts to regulate the expression of selected myocyte genes.[6,7] In addition to the classic regulation of thyroid hormone metabolism, it has been shown recently that 5′-monodeiodinase, which catalyzes the conversion of T_4 to T_3 in both the liver and pituitary, can be altered in a variety of cardiac disease states.[8]

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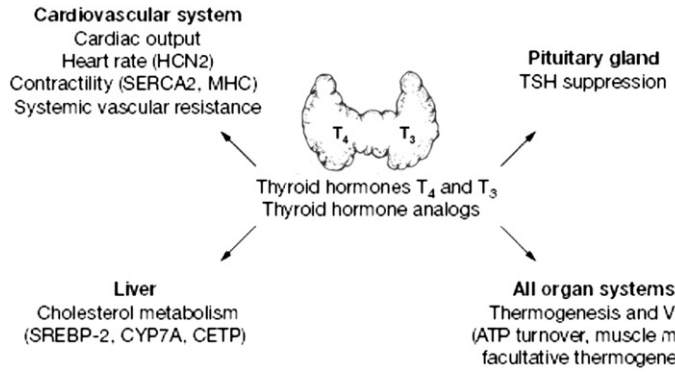

Fig. 1. Sites of action of thyroid hormone on the heart and cardiovascular system. CETP, cholesteryl ester transport protein; CYP7A, cholesterol 7α-hydroxylase; HCN2, hyperpolarization activated cyclic nucleotide-gated potassium channel 2; MHC, myosin heavy chains; SERCA2, sarcoplasmic reticulum (SR) Ca^{2+} ATPase; SREBP-2, sterol regulatory element binding protein 2; VO_2, maximal oxygen uptake.

CELLULAR MECHANISMS OF THYROID HORMONE ACTION ON THE HEART

Thyroid Hormone Transporters

Several families of thyroid hormone transporters have been identified, including the Na^+-taurocholate cotransporting polypeptide (NTCP), the Na^+-independent organic anion transporting polypeptides (OATPs), the heterodimeric L-type amino acid transporters (LAT), and the monocarboxylate transporters (MCTs).[6,9] These proteins transport a variety of ligands but only MCT8 and MCT10 are highly specific for iodothyronines and are expressed in heart (Danzi and Klein, unpublished data, 2011). Conversely, the cardiac plasma membrane transporters that are responsible for thyroid hormone uptake have not been well characterized. Both MCT8 and MCT10 were identified as monocarboxylate transporters and only recently found to be thyroid hormone transporters in an experimental cell system.[6] In humans, MCT8 gene mutations are the cause of Allan-Herndon-Dudley syndrome (AHDS), an X-linked syndrome with specific thyroid and neurologic abnormalities.[10]

Although both MCT8 and MCT10 facilitate uptake and efflux of both T_4 and T_3 in experimental cell systems, our recent data suggest that T_4 is not transported into the heart (Danzi and Klein, unpublished data, 2011). MCT10 has greater affinity for T_3 than T_4 and has a greater capacity to transport T_3 than MCT8.[11] As 1 of 2 thyroid hormone transporters shown to be expressed in rat or human heart, the MCT8 knockout mouse heart has not been characterized phenotypically.[12] The mechanism of transport for thyroid hormone via MCT8 and MCT10 in a variety of tissues seems to be via facilitative diffusion. Radiolabeled T_3 transport in rat neonatal ventricular myocytes is adenosine triphosphate (ATP) dependent, inhibited by excess unlabeled T_3, and Na^+-dependent. In that system, the magnitude of transport of T_3 is greater than 2.5-fold higher than T_4 (**Fig. 2**).[7]

Nuclear Receptors

The classic thyroid hormone effects on cardiac myocyte–specific gene transcription are mediated by thyroid hormone receptors (TRs), members of the steroid hormone superfamily of nuclear transcription factors.[13] Two genes encode the TRs and, in the mammalian heart, 2 splice variants of the TRα gene, TRα1 and TRα2, and 1 splice

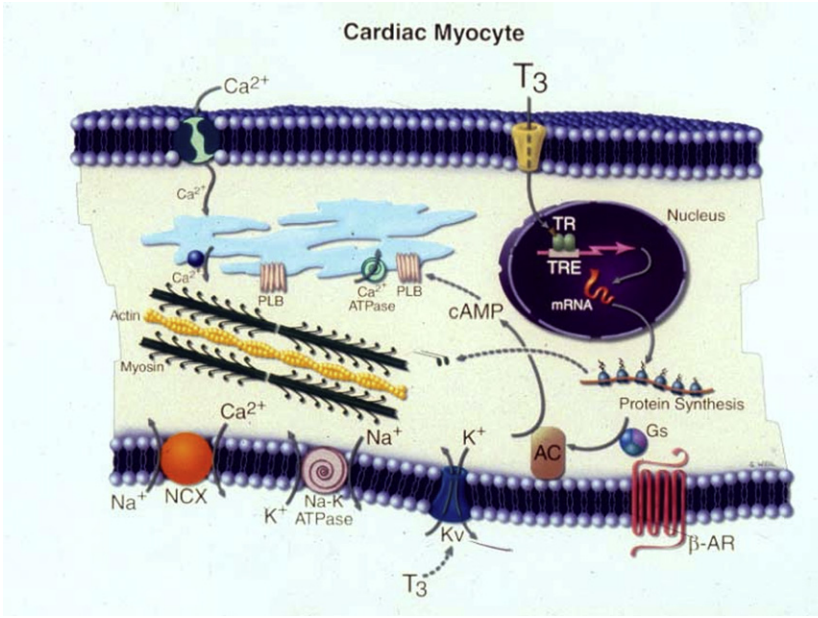

Fig. 2. Effects of T_3 on the cardiac myocyte. T_3 has both genomic and nongenomic effects on the cardiac myocyte. Genomic mechanisms involve T_3 binding to thyroid hormone receptor (TRs), which regulate transcription of specific cardiac genes. Nongenomic mechanisms include direct modulation of membrane ion channels as indicated by the dashed arrows. AC, adenylyl cyclase; β-AR, β-adrenergic receptor; Gs, guanine nucleotide binding protein; Kv, voltage-gated potassium channels; NCX, sodium calcium exchanger; PLB, phospholamban, TRE, thyroid hormone response element.

variant of the TRβ gene, TRβ1, are expressed. These receptor proteins are bound to thyroid hormone response elements (TREs) in the promoter region of certain T_3-responsive genes.[13,14] TRs activate transcription of positively regulated genes in the presence of T_3 by recruiting coactivator complexes, and repress transcription in the absence of ligand by recruiting corepressor complexes.[15]

It seems that the nuclear content of TRs are in turn regulated by T_3 such that, in the myocardium of hypothyroid animals, TRα-1 and α-2 mRNA levels are increased. After 72 hours of treatment with thyroid hormone, TRα-1 and TRα-2 mRNA levels decrease.[16] In a study of human hearts, comparison of TR mRNA in left ventricular tissue of patients with dilated cardiomyopathy showed decreased levels of TRα-1 and decreased TRα-1/TRα-2 ratios compared with normal donor hearts.[17] After heterotopic cardiac transplantation, the expression of TRα-1 and TRα-2 is altered in the rat heart.[18]

Transcriptional Regulation of Cardiac Myocyte Genes

T_3 regulates multiple myocyte genes intimately related to cardiac contractile function, including sarcoplasmic reticulum (SR) Ca^{2+} ATPase (SERCA2), phospholamban (PLB), and the myosin heavy chains (MHC), α and β (see **Fig. 2**; **Table 1**).[1,16] Some of these genes are positively regulated (SERCA2, α-MHC), whereas others are negatively regulated (PLB, β-MHC).[19] Cardiac muscle contraction and relaxation are regulated in turn by the intracellular free calcium concentration $[Ca^{2+}]_i$, which is largely

Table 1
T_3-regulated cardiac genes

Positively Regulated	Negatively Regulated
α-MHC	β-MHC
Voltage-gated K^+ channels (Kv1.5, Kv4.2)	Na^+/Ca^{2+} exchanger (NCX1)
SERCA2	Phospholamban
Na^+/K^+ ATPase	Adenylyl cyclase types V,VI
β1-Adrenergic receptor	Thyroid hormone receptor α1
Adenine nucleotide translocase 1	

determined by SR Ca^{2+} release via the ryanodine receptors,[20] and reuptake into the SR by the Ca^{2+} ATPase. PLB, an integral SR protein that regulates SERCA2 activity, is the mechanism by which β-adrenergic agonists exert positive inotropic action on the heart.[21] Varying degrees of impaired SR calcium uptake have been associated with human and experimental models of heart failure.[22] PLB-deficient transgenic mice showed increased contractility and knockout of PLB in the hypothyroid animal in the study by Kranias and colleagues,[23] which resulted in measures of contractility similar to that in wild-type animals treated with thyroid hormone, thus confirming the importance of the family of thyroid hormone–responsive genes in determining cardiac contractility.[1–3] Similarly, in a series of studies using transgenic overexpression of SERCA2 in hypothyroid mice, myocyte contractile function was restored to levels seen in euthyroid animals, confirming the role of SERCA2 in mediating the effects of thyroid disease on the heart.[24]

The cardiac phenotype is extremely sensitive to changes in serum T_3. In a rat model of thyroid hormone deficiency, administration of 5 μg/kg of T_3 induced transcription of the positively regulated, cardiac-specific, α-MHC within 30 minutes.[25] Maximal transcription, at more than euthyroid levels, occurred 6 hours after hormone administration, showing that the receptor saturating dose of T_3 is lower than previously suggested and the half-life of T_3 in vivo was 7 hours.[25] In experimental animal models of the low T_3 syndrome, when T_4 levels remain normal, the genotype, phenotype, and contractile function are those seen with more classic hypothyroidism.[26]

CARDIOVASCULAR HEMODYNAMICS

Hyperthyroidism

Cardiac contractility is enhanced including both systolic and diastolic function, and cardiac output and resting heart rate are increased in hyperthyroidism.[27] A decrease in systemic vascular resistance decreases afterload and improves myocardial efficiency.[28] An increase in blood volume and an increase in venous return cause the preload of the heart to increase, further augmenting cardiac output.[29] The increase in cardiovascular hemodynamics allows for increased blood flow leading to enhanced perfusion to provide for the substrate and oxygen demands of peripheral tissues (**Fig. 3**, **Table 2**).[1]

An increase in cardiac mass occurs in hyperthyroidism, both in animals and humans. Hypertrophy, usually increased left ventricular mass, results from sustained volume overload and the resulting increase in cardiac work and is a compensatory adaptation that, in turn, increases protein synthesis in the terminally differentiated cardiac myocyte.[30] Recent studies have shown that, in contrast with mean systemic pressures, pulmonary artery pressure is increased in hyperthyroidism, which in turn

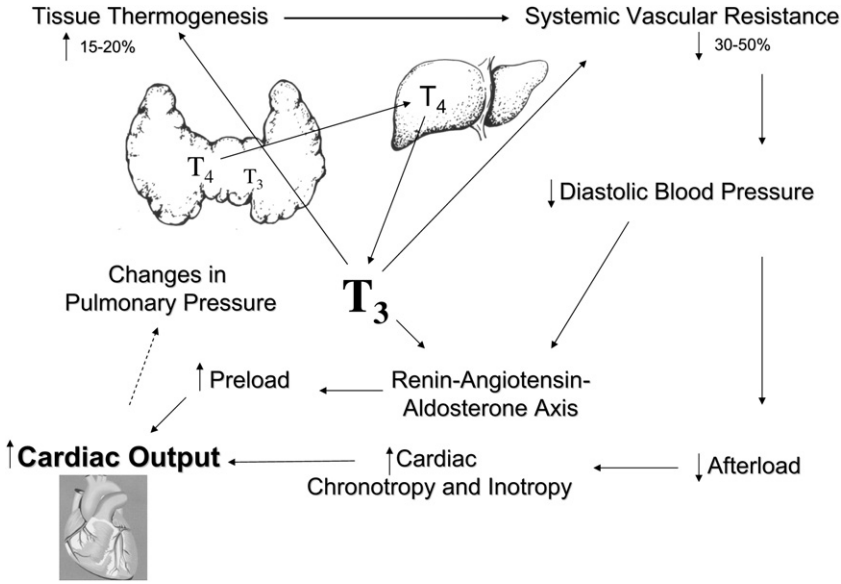

Fig. 3. Effects of thyroid hormone on cardiovascular hemodynamics. T_3 affects tissue thermogenesis, systemic vascular resistance, blood volume, cardiac contractility, heart rate, and cardiac output, as indicated by the arrows.

imparts an increase in right ventricular strain, increasing chamber size, mass, and filling pressure. The consequences of this may include the appearance of right heart or backward failure with neck vein distension and peripheral edema.[31,32]

Heterotopic cardiac transplantation into the abdominal cavity of a host animal provides a vascularly perfused, spontaneously beating, nonworking heart exposed to the same plasma thyroid hormone levels as the in situ working heart.[30] When these animals are exposed to excess amounts of thyroid hormone, only the in situ working heart became hypertrophic. This finding confirms the hypothesis that it is the excess workload resulting from the cardiovascular hemodynamics of hyperthyroidism that is responsible for the increase in cardiac mass.

The clinical manifestations of hyperthyroidism include characteristic cardiac-related signs and symptoms that are independent of the cause of the increased levels of

Table 2
Changes in cardiovascular hemodynamics accompanying thyroid dysfunction

Parameter	Normal	Hyperthyroid	Hypothyroid
Systemic vascular resistance (dyn-cm s^{-5})	1500–1700	700–1200	2100–2700
Heart rate (beats/min)	72–84	88–130	60–80
Pulmonary artery pressure	25	35–40	Unknown
% Ejection fraction	60	>60	<60
Isovolumic relaxation time (ms)	60–80	25–40	>80
Cardiac output (L/min)	5.8	>7.0	<4.5
Blood volume (% of normal)	100	105.5	84.5

thyroid hormone.[1,3,33] On physical examination, tachycardia is the most common finding. Heart rate is increased both at rest and with exercise and, commonly, rapid and forceful palpitations occur.[34] Occasionally atrial arrhythmias, including atrial fibrillation, can occur, but this is more common in older patients.[35] Other findings include widened pulse pressure, increased systolic and lowered diastolic pressure, dyspnea on exertion, and exercise intolerance with sustained activity.[36] Advanced disease may cause further exercise intolerance with limitations such as climbing 1 flight of stairs resulting from both skeletal muscle and respiratory weakness as well as a decrement in cardiac reserve capacity.[37,38]

Rarely, signs and symptoms of heart failure may occur in patients with thyrotoxicosis.[1,36] This condition usually occurs in the setting of prolonged and severe hyperthyroidism or after the onset of atrial fibrillation.[33] Because cardiac output at rest is increased in hyperthyroidism, the increased output that normally accompanies exercise is blunted.[38] Pulmonary and peripheral edema can occur as atrial filling pressure increases, causing a congested circulation. True heart failure in hyperthyroidism, characterized by decreased cardiac contractility, abnormal diastolic compliance, and pulmonary congestion, has been referred to as rate-related heart failure because sustained tachycardia impairs left ventricular contractility.[1,3,36] This finding should be confirmed by noninvasive cardiac measures such as echocardiography followed by the usual course of diuretics. β-Adrenergic blocking drugs are indicated to control the heart rate, and should be used within an intensive care unit setting if the degree of heart failure is significant enough to impair cardiovascular hemodynamics. Although propranolol is the most commonly used agent, intravenous use should be avoided and the short-acting agent esmolol can be used if concern about negative inotropy outweighs the goal of rate reduction. Attention to other potential medical comorbidities, such as infection, should also be addressed. Definitive treatment of the hyperthyroidism in almost all cases returns cardiac function to normal.[39–41]

Hypothyroidism

Overt hypothyroidism affects approximately 3% of the adult female population, with an increased prevalence in individuals more than 40 years of age. The cardiac manifestations of hypothyroidism are the result of decreased thyroid hormone action on both the heart and the peripheral vasculature.[1] The most common clinical signs are a narrowed pulse pressure, diastolic hypertension, low cardiac output with a decreased ejection fraction, impaired diastolic filling, and various degrees of bradycardia.[27] The increase in diastolic pressure is accompanied by a decrease in systolic pressure, so the pulse pressure is low. Hypothyroidism results in increased systemic vascular resistance, further contributing to the decrease in cardiac output.

Overt hypothyroidism is also associated with accelerated atherosclerosis and coronary artery disease, possibly caused by the higher incidence of hypercholesterolemia and hypertension (see **Fig. 1**).[42,43] Hypothyroidism, like hypertension and the effects of aging, leads to reduced SERCA2 activity and therefore, impaired calcium cycling, resulting in increased myocardial stiffness and left ventricular diastolic dysfunction.[3,24] Even mild (subclinical) hypothyroidism can increase the prevalence of heart failure and diastolic dysfunction.[44]

SPECIAL CONSIDERATIONS

Atrial Fibrillation

Sinus tachycardia is the most common rhythm disturbance in patients with hyperthyroidism.[45] However, atrial fibrillation caused by hyperthyroidism (especially subclinical

hyperthyroidism) is more common with advancing age.[46] Although the yield of abnormal thyroid function testing, including a low serum TSH level, seems to be low in patients with new-onset atrial fibrillation, the benefit associated with the ability to restore thyrotoxic patients to a euthyroid state and sinus rhythm justifies TSH testing in most patients with recent onset of otherwise unexplained atrial fibrillation or other supraventricular arrhythmias.[47]

Symptomatic treatment of thyrotoxic atrial fibrillation includes β-adrenergic blockade.[48] This can be accomplished rapidly, whereas treatments leading to restoration of the euthyroid state require a longer time.[40] Digitalis has been used to control the ventricular response in hyperthyroidism-associated atrial fibrillation, but usually requires higher doses of this medication. Anticoagulation in patients with hyperthyroidism and atrial fibrillation is controversial because the potential for systemic or cerebral embolization must be weighed against the risk of bleeding and complications.[40] The major risk factor for systemic embolization in thyrotoxicosis seems to be age and not the presence of atrial fibrillation.[49] Therefore, unless there is a separate cardiac indication for warfarin or other forms of anticoagulation, aspirin can be safely used in this setting as an alternative in younger individuals.

Successful treatment of hyperthyroidism with radioiodine or antithyroid drugs to restore normal serum levels of T_4 and T_3 leads to reversion to sinus rhythm in most patients within a few months.[47] In the setting of atrial fibrillation of longer duration and in older patients, the rate of reversion to sinus rhythm is lower and electrical or pharmacologic cardioversion should therefore be attempted, but only after the patient has been rendered euthyroid.[47]

Pulmonary Artery Hypertension

There are reports of pulmonary artery hypertension in patients with thyrotoxicosis.[31,32,34] An apparent failure of pulmonary arterial resistance to decline, similar to that seen in the systemic circulation, results in significant increases of both mean and peak pulmonary artery pressures. These pressures usually normalized with a return to a chemically euthyroid state.[32] Although primary pulmonary hypertension is a rare, often fatal, disease of unknown cause that primarily affects young women, the frequency of both Graves disease (and chronic autoimmune thyroiditis, Hashimoto disease) is increased in this patient population as well, suggesting the value of routine thyroid function tests in all patients with pulmonary hypertension.[4,34]

Cholesterol Metabolism

Increased low-density lipoprotein (LDL) cholesterol occurs in the setting of hypothyroidism and in proportion to the increase in serum TSH levels.[42,50] Thyroid hormone alters cholesterol metabolism through a variety of mechanisms, including a decrease in LDL receptor expression but, perhaps more importantly, a decrease in biliary excretion. Further support for the role of thyroid hormone in the regulation of cholesterol metabolism comes from a recent study that describes a liver-selective thyroid hormone agonist, eprotirome, that can synergistically lower cholesterol levels in statin-treated patients.[50] Not only was high-density lipoprotein significantly decreased but a unique ability to lower Lp(a), an especially atherogenic lipid particle, was seen.

Amiodarone-Induced Thyroid Disease

Amiodarone is an iodine-rich antiarrhythmic agent effective for the treatment of ventricular and atrial tachyarrhythmias. Its iodine content and structural similarity to levothyroxine causes abnormalities in thyroid function tests in as many as 60% of patients treated with the drug.[51,52] Dronedarone, a recently approved noniodinated

benzofuran antiarrhythmic, does not alter thyroid function and confirms this concept.[52,53] Amiodarone inhibits the 5′-monodeiodination of T_4 in the liver and pituitary, thereby decreasing serum T_3 and increasing serum T_4 levels. Serum TSH levels initially remain normal. In patients with underlying goiter, autoimmune thyroid disease, defects in thyroid hormone biosynthesis, and in some patients without any risk factors, there may be a progression to overt chemical and clinical hypothyroidism with a marked increase in serum TSH levels.[51,54]

Thyroid function should be measured every 3 months in all patients receiving amiodarone and for at least 6 months after stopping treatment because the effect on thyroid function can occur at any time after initiating treatment (and, because of the long half-life of the drug, alterations in thyroid function may still occur up to 1 year after discontinuing therapy).[52]

Less common than amiodarone-induced hypothyroidism, but perhaps more challenging, is the development of amiodarone-induced thyrotoxicosis. The development of this condition may be signaled by the new onset or recurrence of ventricular irritability, decreased warfarin sodium dose requirements, or the return or worsening of heart failure symptoms.[52] Early studies distinguished 2 forms of amiodarone-induced thyrotoxicosis. Type I occurs primarily in patients with preexisting thyroid disease and most commonly in iodine-deficient areas. These patients frequently have some measures of thyroid autoimmunity, including antithyroid antibodies.[51] In contrast, type II disease was identified as a form of thyroiditis, presumably mediated by a variety of proinflammatory cytokines. This process is destructive, causing release of preformed thyroid hormone, which may continue for weeks or months and most often is associated with low to absent radioiodine uptake.[54] Clinically important is the report that amiodarone-induced thyrotoxicosis is associated with a 3-fold increased risk for major adverse cardiovascular events.[55]

Therapy for these patients is especially challenging because the use of iodine 131 is almost always ineffective and treatment with antithyroid drugs has marginal effectiveness.[40,51,52,54] Treatment with corticosteroids may provide benefit and, in most cases, lowers serum levels of both T_4 and T_3 within 2 to 3 weeks.[54] In patients unresponsive to glucocorticoids with evidence of hyperthyroidism, including weight loss, tachycardia, palpitations, worsening angina, ventricular tachycardia, or other untoward cardiac effects, treatment with antithyroid therapy such as methimazole is variably effective.[54] Total thyroidectomy with preoperative treatment with β-blockers can be performed safely and is an effective means of reversing the hyperthyroidism rapidly.[55] Discontinuation of amiodarone is a cardiology decision.

ALTERATIONS IN THYROID HORMONE METABOLISM THAT ACCOMPANY HEART DISEASE

The prohormone T_4 is metabolized to T_3 primarily in the liver, kidney, and skeletal muscle by 5′-monodeiodination.[56] Altered thyroid hormone metabolism occurs in heart disease, after cardiac surgery, or after acute myocardial infarction, resulting in low serum T_3 levels despite normal TSH and T_4.[57] In patients with heart failure, the decrease in serum T_3 concentration is proportional to the severity of the heart disease as assessed by the New York Heart Association (NYHA) functional classification, and a low serum T_3 level is a powerful predictor of mortality in patients with NYHA Class III to IV heart failure.[58]

The heart failure phenotype is similar to the hypothyroid cardiac phenotype.[59] Hypothyroidism may also be associated with accelerated atherosclerosis and coronary artery disease.[43] The T_3-regulated genes that are altered in overt hypothyroidism

are almost identical to the changes in gene expression in heart failure and include the genes that encode the contractile proteins, α-MHC and β-MHC, the sodium calcium exchanger (NCX1), SERCA2, PLB, and the β-adrenergic receptor (β-AR).[3] The net effect of these alterations in gene expression is to alter cardiac contractility, calcium cycling, and diastolic relaxation of the myocardium.[22,44]

Interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) levels are increased in the low T_3 syndrome and can impair the expression and the activity of hepatic monodeiodinase, leading to decreased metabolism of T_4. The cardiac myocyte seems to transport T_3 in marked preference to T_4 and is exquisitely sensitive to changes in serum T_3.[60] Evidence is accumulating that suggests that low T_3 levels contribute to the heart failure phenotype and that normalization of T_3 might improve cardiac function in this setting. A recent study of T_3 treatment of humans with NYHA Class III or IV heart failure has shown beneficial effects.[8] Further studies are required to determine whether thyroid hormone–based treatments may be useful in selected patients with heart failure.[3,8]

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