Thyroid Abnormalities in Heart Failure

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KEYWORDS

• Triiodothyronine • T_3 • Nonthyroidal illness • Cardiac • Thyroid hormone • Low T_3 syndrome • Cardiovascular

KEY POINTS

- Thyroid hormone metabolism is altered in chronic heart failure, after myocardial infarction, after cardiac surgery, and in acute and chronic illness.
- A variety of clinical and physiologic factors suggest that the low levels of T_3 that result from altered thyroid hormone metabolism have adverse consequences similar to that of classical hypothyroidism suggesting a low T_3 syndrome, or nonthyroidal Illness. This low T_3 syndrome is a strong prognostic, independent predictor of death in patients with acute and chronic heart disease.
- T_3 regulates many important genes in the cardiac myocyte. Low T_3 states that accompany cardiac disease states alter gene expression similar to that seen in hypothyroidism.
- 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.
- When serum T_3 levels are low, total and low-density lipoprotein (LDL) cholesterol and apolipoprotein B levels rise. The increase is proportional to the increase in serum TSH.

INTRODUCTION

More than 200 years ago Caleb Hillier Parry, an English physician, described a woman with goiter and palpitations whose "each systole shook the whole thorax." He was the first to suggest the notion that there was a connection between diseases of the heart and enlargement of the thyroid gland.[1] Thyroid dysfunction including hyperthyroidism and hypothyroidism is common and may affect 15% of women and a smaller percentage of men. As such it would be anticipated that many patients seen in the practice of cardiology would be affected by thyroid disease, either diagnosed or not. Often, however, this association is not considered in the evaluation and management of patients with hypercholesterolemia, hypertension, heart failure, and arrhythmias. The challenge to the cardiologist therefore is (1) to recognize the cardiovascular signs and symptoms of hyperthyroidism and hypothyroidism even in their most subtle presentations, (2) to be familiar with appropriate testing to confirm the clinical suspicion, and (3) to initiate therapy either alone or when appropriate in conjunction with an endocrinologist.[2]

The clinical manifestations of thyroid dysfunction include significant effects on the heart and cardiovascular system. In fact, the cardiovascular abnormalities are some of the most characteristic clinical signs and symptoms of hyperthyroidism including, but not limited to, tachycardia, atrial fibrillation, systolic hypertension, and

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hyperdynamic precordium.[2,3] Hypothyroidism has the opposite effects. Hypothyroidism contributes to, or may cause de novo, many of the conditions seen in cardiology practice including hypercholesterolemia, diastolic hypertension, statin myopathy, and left ventricular diastolic dysfunction leading to heart failure with preserved ejection fraction (Table 1). The recognition of the role of thyroid disease in these patients is especially important because in almost every case, restoration of a euthyroid state with thyroid hormone replacement results in improvement or normalization of the cardiovascular abnormality. Heart failure itself can result in reduced serum levels of active thyroid hormone (low T_3 syndrome),[4] and similar to that seen in hypothyroidism, can further impair cardiac function. We discuss the role of changes in thyroid hormone metabolism that may arise in patients with no prior history of primary thyroidal illness but as a result of cardiovascular disease.

THYROID DISEASE

Thyroid disease states, often arise as a result of a genetic predisposition to the autoimmune diathesis giving rise to either Graves or Hashimoto disease. Hypothyroidism is the most common form of thyroid dysfunction and this prevalence increases with advancing age. In contrast hyperthyroidism is significantly less common with the onset characteristically (but not exclusively) occurring in women around the childbearing years. The prevalence of thyroid dysfunction is five to seven times more common in women than men; not surprising given the autoimmune cause of both conditions. There are a sufficient number of sensitive and specific thyroid function tests to establish a diagnosis of either hyperthyroidism (overt or subclinical) or hypothyroidism (overt or subclinical) with a high degree of precision. As such most Societies recommend that physicians use routine laboratory testing (thyroid-stimulating hormone [TSH]) to conform with aggressive case finding.[5] This is especially relevant to the practice of cardiology and many commonly used International Classification of Diseases-10 codes support thyroid function testing.[1–3]

THYROID HORMONE METABOLISM

Thyroid Hormone Regulation

Thyroid hormones produced by the thyroid gland include tetraiodothyronine (T_4) and triiodothyronine (T_3). The gland produces primarily T_4 (~85%) and significantly less T_3 (~15%), although T_3 is the active form of the hormone. The conversion of T_4, a prohormone, to T_3 takes place in the tissues of specific organs and most of the available serum T_3 is provided by enzymatic deiodination of T_4 in the liver and kidney. The enzyme, 5′-monodeiodinase, removes one iodine atom from T_4 to produce T_3. Factors that impair the activity of this enzyme lead to decreased levels of T_3 in the serum and therefore, in dependent tissues.

Thyroid hormone production is regulated by a negative feedback loop. The hypothalamus produces thyrotropin-releasing hormone, which stimulates the anterior pituitary to produce thyrotropin, or TSH. TSH acts on the thyroid gland to release thyroid hormones, T_4 and T_3. It is primarily T_4 that feeds back to the pituitary to decrease production of TSH. Insufficient deiodination of T_4 to T_3 can cause levels of T_3 to be low, when TSH and T_4 are within the normal range (discussed later).

Thyroid Function Testing

There are highly sensitive and specific tests for hyperthyroidism and hypothyroidism. Commonly used tests include serum measures of thyrotropin (TSH), T_4 (total and free), and T_3. A single TSH test

Table 1
Changes in cardiovascular function associated with thyroid disease

	Normal	Hyperthyroid	Hypothyroid
SVR (dyne s cm^{-5})	1500–1700	700–1200	2100–2700
Heart rate (bpm)	72–84	88–130	60–80
% EF	60	>60	<60
IVRT (ms)	60–80	25–40	>80
Cardiac output (L/min)	5.8	>7.0	<4.5
Blood volume (% normal)	100	105.5	84.5

Abbreviation: EF, ejection fraction; IVRT, isovolumic relaxation time; SVR, systemic vascular resistance.
Adapted from Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001;344:502; with permission.

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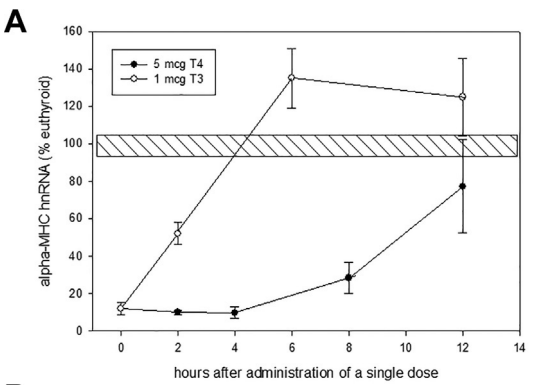
in a nonhospitalized patient is sufficient to establish a diagnosis with low levels of TSH (<0.01 UIU/L) showing pituitary suppression, indicating hyperthyroidism and elevated levels greater than 10 UIU/L indicating primary thyroidal failure. Confirmatory measures of T_4 and T_3 solidify the diagnosis. However, in milder (subclinical) disease states the levels of T_4 may be normal.

The clinical importance of this testing is not only to provide laboratory data to validate a suspected diagnosis but perhaps more importantly safe, effective and inexpensive treatments are available for both conditions.[1–4] Thus the young woman with palpitations, the middle-aged man with the acute onset of atrial fibrillation, or the elderly man with new-onset hypercholesterolemia and myopathy are equally likely to benefit from TSH testing.[2]

EFFECT OF T_3 ON THE CARDIAC MYOCYTE

Cellular Action of T_3

The heart is sensitive to changes in serum T_3. This has been demonstrated by rapid changes in T_3-mediated cardiac gene expression as serum T_3 levels decline in an animal model (**Fig. 1**).[6] Cardiac tissue does not appreciably convert T_4 to T_3; therefore, the heart is dependent on available serum T_3. The monocarboxylate transporters MCT8 and MCT10 are highly specific for thyroid hormones and are the primary thyroid hormone transporters for cardiac myocytes. Although MCT8 and MCT10 facilitate uptake and efflux of T_4 and T_3 in experimental cell systems, our data suggest that T_4 is not transported into the heart.[7] MCT10 has greater affinity for T_3 than T_4 and has a greater capacity to transport T_3 than MCT8.[8]



Serum T_3 (ng/dl)	0h	2h	4h	6h	8h	12h
After 1 μg T_3	26	424	-	230	-	110
After 5 μg T_4	26	23	61	-	57	121

Fig. 1. (*A*) Expression of α-myosin heavy chain hnRNA levels (as % euthyroid) in hypothyroid rats after administration of a single dose of T_3 (1 μg) or T_4 (5 μg). (*B*) Corresponding serum T_3 levels (ng/dL) for same experiment described in A. hnRNA, heterogeneous nuclear RNA, the first product of transcription, or prespliced primary transcript; MHC, myosin heavy chain.

The transcriptional actions of T_3 are mediated by nuclear receptor proteins (TRs) that bind to specific thyroid hormone response elements in the upstream region of T_3-responsive genes.[9] These nuclear receptors, which include isoforms of TR-α and TR-β, activate expression of positively regulated genes in the presence of T_3 and in the absence of T_3, repress transcription.

Thyroid hormone also has extranuclear nongenomic effects on the cardiac myocyte and on the systemic vasculature. These T_3-mediated effects include changes in various membrane ion channels for sodium, potassium, and calcium; effects on adenine nucleotide translocator-1 in the mitochondrial membrane; and a variety of intracellular signaling pathways in the heart and vascular smooth muscle cells.[10] Together, the nongenomic and genomic effects of T_3 act to regulate cardiac function and cardiovascular hemodynamics.

T_3-Regulated Cardiac Genes

T_3 is an important regulator of cardiac gene expression and the list of T_3-mediated genes that are altered in heart failure is almost identical to the changes in gene expression in overt hypothyroidism.[11] These include the genes that encode the contractile proteins, α-myosin heavy chain (MHC) and β-MHC, the sodium calcium exchanger (NCX1), the sarcoplasmic reticulum calcium ATPase (SERCA2), phospholamban, and the β-adrenergic receptor. The net effect of these alterations in gene expression is to alter cardiac contractility, calcium cycling, and diastolic relaxation of the myocardium. α-MHC, the fast myosin, is positively regulated by thyroid hormone, whereas the slow myosin ATPase, β-MHC, is negatively regulated. The SERCA2 pump functions to sequester calcium in the sarcoplasmic reticulum during the relaxation phase of myocyte contraction, because calcium is required for the contraction phase. Phospholamban is a membrane protein that negatively regulates SERCA2 function. SERCA2 is positively regulated by thyroid hormone and phospholamban is negatively regulated. These two proteins play a critical role in diastolic function. Changes in the relative amounts of these proteins and the state of phosphorylation of phospholamban may account for altered diastolic function in heart failure and thyroid disease (**Fig. 2**).[12]

Both MCT8 and MCT10, the iodothyronine specific transporters, are also negatively regulated by thyroid hormone (**Table 2**).[7]

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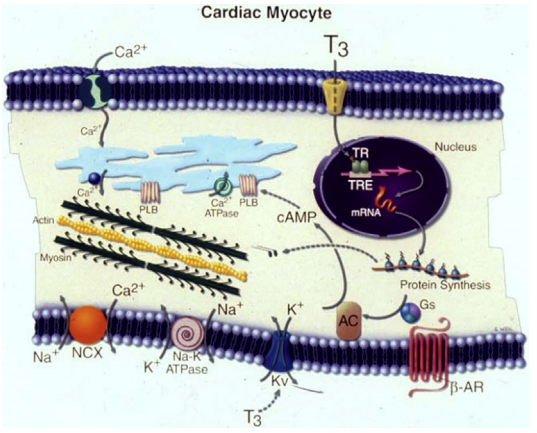

Fig. 2. The cellular pathways and mechanisms of action of thyroid hormone (T_3) on the cardiac myocyte. T_3 has genomic and nongenomic effects on the cardiac myocyte. Genomic mechanisms involve T_3 binding to TRs, which regulate transcription of specific cardiac genes. Nongenomic mechanisms include direct modulation of membrane ion channels (*dashed arrows*). AC, adenylyl cyclase; b-AR, b-adrenergic receptor; Gs, guanine nucleotide binding protein; Kv, voltage-gated potassium channels; NCX, sodium calcium exchanger; PLB, phospholamban; TRE, thyroid hormone response element. (*From* Klein I, Danzi S. Thyroid disease and the heart. Circulation. 2007;116(15):1726; with permission.)

T_3 EFFECTS ON CARDIOVASCULAR HEMODYNAMICS

Thyroid hormone acts directly on the heart and vasculature and indirectly to influence cardiovascular hemodynamics. The net result is that contractility is enhanced and vascular resistance is decreased in response to thyroid hormone action, whereas in the absence of sufficient thyroid hormone, contractility is decreased and resistance is increased. This is caused by direct effects of T_3 on tissue thermogenesis, system vascular resistance, and cardiac chronotropy and inotropy, resulting in changes in blood volume and cardiac output (**Fig. 3**).[2]

Table 2
Effect of T_3 on cardiac-specific genes

Positively Regulated	Negatively Regulated
α-Myosin heavy chain	β-Myosin heavy chain
Sarcoplasmic reticulum Ca^{2+}-ATPase	Phospholamban
Na^+/K^+ ATPase	Adenylyl cyclase catalytic subunits
β_1-Adrenergic receptor	Thyroid hormone receptor alpha-1
Atrial natriuretic hormone	Na^+/Ca^{2+} exchanger
Voltage-gated potassium channels	Thyroid hormone transporters (MCT8, MCT10)
	Adenine nucleotide translocase-1 (ANT1)

From Danzi S, Klein I. Thyroid disease and the cardiovascular system. Endocrinol Metab Clin North Am. 2014;43:518; with permission.

In hyperthyroidism, cardiac contractility is enhanced and cardiac output and resting heart rate are increased. Systolic and diastolic functions are enhanced and the decrease in system vascular resistance decreases afterload. The enhanced cardiovascular hemodynamics leads to increased blood flow and tissue perfusion. The clinical manifestations of hyperthyroidism include atrial arrhythmias in older patients along with tachycardia, widened pulse pressure, and dyspnea on exertion.[13]

In hypothyroidism, signs are opposite to those of hyperthyroidism and are more subtle, but may include bradycardia, diastolic hypertension, and a narrowed pulse pressure. Cardiac contractility is decreased and systemic vascular resistance is increased. As in the clinically hypothyroid patient, the characteristic hemodynamic profile of heart failure includes a low cardiac output caused by impaired cardiac contractility, and an elevated systemic vascular resistance.[4]

T_3 seems to reduce systemic vascular resistance by direct effects on vascular smooth muscle cells and through changes in the vascular endothelium. Nongenomic actions target membrane ion channels and endothelial nitric oxide synthase. Increased endothelial nitric oxide production may result, in part, from the T_3-mediated effects on the protein kinase akt pathway either via nongenomic or genomic mechanisms. Nitric oxide synthesized in endothelial cells then acts in a paracrine manner on adjacent vascular smooth muscle cells to facilitate vascular relaxation. Relaxation of vascular smooth muscle leads to decreased arterial resistance and pressure, which thereby increases cardiac output.[14–16]

Nonthyroidal Disease

In contrast to primary thyroid disease, over the last three decades there has been the recognition that there are a variety of nonthyroidal disease states that can alter measures of thyroid function. Because these were first characterized by normal levels of TSH (the prime measure of thyroid hormone metabolism) in the face of low levels of liothyronine (T_3) these were referred to as euthyroid

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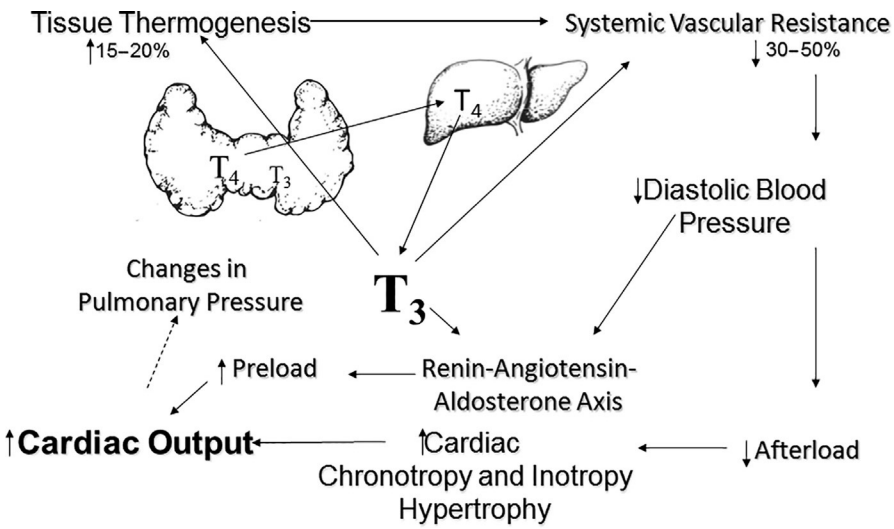

Fig. 3. Effects of thyroid hormone on cardiovascular hemodynamics. The individual changes for hyperthyroidism are noted for each parameter. The effects of hypothyroidism are diametrically opposite. (*Adapted from* Klein I, Danzi S. Thyroid disease and the heart. Circulation. 2007;116(15):1727; with permission.)

sick states. However, a variety of clinical and physiologic factors suggested that the low levels of T_3 had adverse consequences similar to that of classical hypothyroidism, leading to an alternative designation of "nonthyroidal illnesses" (NTI).

To investigate this at the preclinical level our laboratory adopted the energy-restricted rodent model to simulate the low T_3 level in otherwise euthyroid animals. Various physiologic and biochemical measures of thyroid and cardiovascular functional activity were compared with animals rendered classically hypothyroid by thyroidectomy. Both groups of animals were treated with replacement doses of T_4 or T_3 and at sacrifice, thyroid function tests were measured and left ventricular contractility was assessed in the Langendorf isolated perfused heart model (**Fig. 4**).[17] The NTI animals displayed impaired inotropic and lusitropic changes identical to the hypothyroid hearts. In vivo treatment with replacement doses of T_3 but not T_4 treatment restored the NTI animals to control euthyroid functional levels. Based on analysis of gene expression from the myocytes of these five groups of animals it was shown that these changes arose at the classical nuclear transcriptional level well known as the site of action for T_3.[18]

Cardiovascular Diseases as Causes of Nonthyroidal Illness

Thyroid hormone metabolism, specifically the deiodination of T_4, is decreased in chronic heart failure, after myocardial infarction, after cardiac surgery, and in acute and chronic illness. Recent studies have characterized the changes in thyroid hormone metabolism that accompany a variety of cardiovascular disease states.[2,19,20] 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 functional classification.[4,19,21,22] This seems to result from a cytokine-mediated inhibition in the normal hepatic conversion of T_4 to the active T_3 and is well characterized as part of the spectrum of NTI or the low T_3 syndrome.[23,24] Interleukin-6 and tumor necrosis factor-α levels are increased in the low T_3 syndrome.[25] The effect on serum T_3 seems to result from a cytokine-induced blockade of 5-monodeiodinase synthesis and activity.[26] There is ample evidence that multiple mechanisms contribute to the low T_3 syndrome. In more severe cases, serum T_4 may also be decreased and the term NTI may be used to

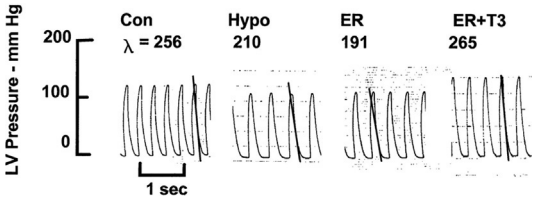

Fig. 4. Effect of the low T_3 syndrome on cardiac contractile function. Con, control; ER + T3, energy restricted with T3 treatment; ER, energy restricted; Hypo, hypothyroid; LV, left ventricular. (*From* Katzeff HL, Powell SR, Ojamaa K. Alterations in cardiac contractility and gene expression during low-T3 syndrome: prevention with T3. Am J Physiol. 1997;273:E951–E953; with permission.)

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describe the same syndrome.[27] This low T_3 syndrome is a strong prognostic, independent predictor of death in patients with acute and chronic heart disease.[19,20,28] In human and animal studies, T_3 replacement in heart failure improved left ventricular function and restored myocyte gene expression to euthyroid levels, similar to that seen in the treatment of hypothyroidism. These low T_3 levels may contribute further to impaired diastolic function in patients with preserved and reduced ejection fraction.[29–33]

Although TSH levels may remain normal, serum levels of total T_3 fall in proportion to the severity of heart failure and also serve as a predictor of poor outcome. Similarly, low T_3 levels, despite normal TSH, are associated with worse outcomes after cardiac surgery.[33] It is interesting to speculate that these low levels of T_3 may contribute further to impaired diastolic function in patients with preserved and reduced ejection fraction.[4,11,29] Whether thyroid hormone–based therapies, including T_3 or novel thyroid hormone analogues, prove useful, especially in patients with heart failure with preserved ejection fraction, remains to be established (**Fig. 5**).

B-type natriuretic peptide (BNP) is a hormone produced by the heart and released in response to changes in pressure inside the heart, which can be related to heart failure and other cardiac problems. In a recent, large study of patients in a primary care setting, BNP was found to be a predictor of all-cause mortality.[34] The N-terminal pro-BNP (NT-proBNP) levels are easily measured, objective markers of cardiac function and are used to diagnose heart failure, including diastolic dysfunction. Selvaraj and colleagues[29] demonstrated an association of serum T_3 with BNP and severe left ventricular diastolic dysfunction in heart failure with preserved ejection fraction. As T_3 levels decrease, NT-proBNP levels increase. There is an inverse correlation between BNP levels and heart failure. Levels goes up when heart failure develops or gets worse, and levels goes down when heart failure is stable. Although low T_3 levels have been shown to be independent predictors of all-cause and cardiac mortalities among critically ill patients with heart failure, the combination of high NT-proBNP with low T_3 levels predict a worse long-term outcome.[35]

THYROID HORMONE EFFECTS ON LIPID METABOLISM

Thyroid hormone alters the lipid profile, specifically to decrease serum cholesterol levels. Therefore, in hypothyroidism, similar to heart failure, total and low density lipoprotein (LDL) cholesterol and apolipoprotein B levels rise. The increase is proportional to the increase in serum TSH.[36] A recent study demonstrated that after thyroidectomy for thyroid cancer, treatment of hypothyroid patients with levothyroxine resulted in a reduction of cardiac lipid content and improved cardiac index.[37]

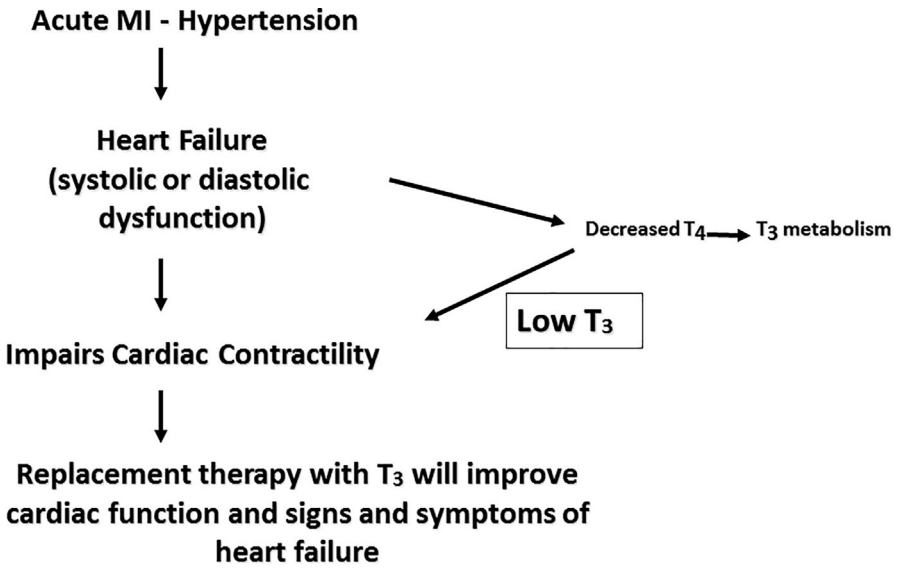

Fig. 5. A working hypothesis for the changes in thyroid hormone metabolism in patients with varying degrees of heart failure that can contribute to progression of impaired cardiac contractility. MI, myocardial infarction. (*Adapted from* Klein I, Danzi S. Thyroid hormone treatment to mend a broken heart. J Clin Endocrinol Metab. 2008;93:1173; with permission.)

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Cholesterol Metabolism

Increased LDL cholesterol occurs in the setting of hypothyroidism and in proportion to the rise in serum TSH levels.[36,37] 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. The cholesterol-lowering effect of thyroid hormone in patients with hypothyroidism was originally described in 1930. LDL is the principal lipoprotein that is reduced; the reduction is induced by increased hepatic clearance caused by increased expression of the hepatic LDL-receptor gene. In rodents, thyromimetic compounds also accelerate clearance of cholesterol by the liver by increasing the high-density lipoprotein receptor called scavenger receptor B1 (SR-B1), increasing the activity of cholesterol 7α-hydroxylase and increasing fecal excretion of cholesterol and bile acids. Previous attempts to mimic these actions with thyroid hormone metabolites and analogues have confirmed their cholesterol-lowering properties. 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.[38] Not only was LDL significantly decreased, but a rather unique ability to lower Lp(a), an especially atherogenic lipid particle, was seen.

Statin-Induced Myopathy

Hypothyroidism is well known to produce a skeletal muscle myopathy associated with cramps; stiffness; decreased muscle endurance; and in severe cases, pseudohypertrophy and pseudomyotonia. The deep tendon reflexes are delayed and serum creatine kinase (CK) levels can be markedly increased to 20 times normal with a predominately MM isoform pattern. All abnormalities resolve with thyroid hormone replacement.[39] HMG-CoA reductase inhibitors (statins) can also produce a myopathic syndrome as many as 10% of patients with a clinical spectrum extending from mild cramping to full blown rhabdomyolysis. The overlap between hypothyroid myopathy and statin-induced myopathy is characterized in **Table 3**. It has been the experience of our group and others that patients with hypothyroidism are at increased risk of developing a statin-induced myopathy.[40] This point is especially clinically relevant because patients with hypothyroidism are likely to have some degree of endogenous hypercholesterolemia and be candidates for lipid-lowering therapy. It may be that T_4 treatment alone can accomplish the desired effect.[40]

Thyroid Hormone–Based Treatment of Heart Failure

Current treatment of heart failure requires multiple medications including β-adrenergic blocking drugs, angiotensin-converting enzyme inhibitors, aldosterone antagonists, digitalis, and diuretics. Within the last 2 years two new Food and Drug Administration–approved medications have entered the market. Angiotensin receptor-neprilysin inhibitor (Entresto), a combination of sacubitril and valsartan, and a novel channel inhibitor of the sinoatrial node (Corlanor) are now available for treatment of patients with symptomatic heart failure. Despite maximum medical therapy, mortality remains high and novel treatment strategies are actively sought. One field of investigation is that of gene therapy in which a variety of viral vectors encoding specific cardiac regulatory and structural proteins are directed to the impaired myocyte. Because calcium uptake and release by the sarcoplasmic reticulum is frequently impaired in heart failure, the ability to increase

Table 3
Muscle disease syndromes

Statin-Induced	Hypothyroid-Related
Myopathy: any associated disease	Myalgia: nonspecific muscle symptoms, cramping, especially nocturnal, variable CK level
Myalgia: muscle aches/weakness without CK elevation	Myopathy: impaired endurance usually with CK elevation; pseudomyotonia
Myositis: symptoms plus elevated CK	Hoffmann syndrome: impaired function; pseudohypertrophy, often marked CK elevations
Rhabdomyolysis: symptoms plus markedly elevated CK levels	

CK, creatine kinase.

From Rush J, Danzi S, Klein I. Role of thyroid disease in the development of statin-induced myopathy. The Endocrinologist. 2006;16(5):279–85; with permission.

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SERCA or to lower its inhibitory regulator phospholamban are attractive targets for genetic manipulation. Studies of the cellular mechanisms of thyroid hormone action described previously on the cardiac myocyte have demonstrated that similar to the hypothyroid myocardium, treatment of the failing heart with T_3 produces a similar and desirable change in the cardiac phenotype. Other thyroid hormone responsive genes, which may play a role in the improved cardiac contractile function, include β_1-adrenergic receptor, stimulatory guanine nucleotide binding proteins (G_s), α-MHC, sodium-calcium exchanger, and perhaps the voltage-gated potassium channels (K_v). Because most patients who die of heart failure do so as the result of a ventricular arrhythmia, a positive effect on K_v expression leading to a shortening of the QT interval on the electrocardiogram is therapeutically desirable.

Perhaps most importantly is the observation from many studies, that T_3 treatment does not produce untoward effects when administered in either physiologic or short-term pharmacologic doses to patients with concomitant cardiac disease.[41] There have been no reported episodes of supraventricular arrhythmias, increases in heart rate, or worsening of cardiac ischemia in any of the reported series to date. To restore serum T_3 levels to normal, investigations have used short-term intravenous administration of drug. Although potentially useful in acute studies, this does not address the more relevant question of long-term therapy. Thus, any long-term studies undertaken to establish safety and efficacy of T_3 treatment of heart failure need to use a formulation of T_3 not currently available. The clinical reality that such patients will already be treated with β-adrenergic blockade provides a combination of treatments with therapeutic synergy.

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