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Thyroid Disease and the Heart

Irwin Klein, MD; Sara Danzi, PhD

Abstract—The cardiovascular signs and symptoms of thyroid disease are some of the most profound and clinically relevant findings that accompany both hyperthyroidism and hypothyroidism. On the basis of the understanding of the cellular mechanisms of thyroid hormone action on the heart and cardiovascular system, it is possible to explain the changes in cardiac output, cardiac contractility, blood pressure, vascular resistance, and rhythm disturbances that result from thyroid dysfunction. The importance of the recognition of the effects of thyroid disease on the heart also derives from the observation that restoration of normal thyroid function most often reverses the abnormal cardiovascular hemodynamics. In the present review, we discuss the appropriate thyroid function tests to establish a suspected diagnosis as well as the treatment modalities necessary to restore patients to a euthyroid state. We also review the alterations in thyroid hormone metabolism that accompany chronic congestive heart failure and the approach to the management of patients with amiodarone-induced alterations in thyroid function tests. (*Circulation*. 2007;116:1725-1735.)

Key Words: hyperthyroidism ■ hypothyroidism ■ heart failure ■ tachyarrhythmias ■ thyroid

It has long been recognized that some of the most characteristic and common signs and symptoms of thyroid disease are those that result from the effects of thyroid hormone on the heart and cardiovascular system.¹⁻³ Both hyperthyroidism and hypothyroidism produce changes in cardiac contractility, myocardial oxygen consumption, cardiac output, blood pressure, and systemic vascular resistance (SVR).^{4,5} Although it is well known that hyperthyroidism can produce atrial fibrillation, it is less well recognized that hypothyroidism can predispose to ventricular dysrhythmias.⁶ In almost all cases these cardiovascular changes are reversible when the underlying thyroid disorder is recognized and treated.

Thyroid disease is quite common. Current estimates suggest that it affects as many as 9% to 15% of the adult female population and a smaller percentage of adult males.⁷ This gender-specific prevalence almost certainly results from the underlying autoimmune mechanism for the most common forms of thyroid disease, which include both Graves' and Hashimoto's disease.⁸ However, with advancing age, especially beyond the eighth decade of life, the incidence of disease in males rises to be equal to that of females.⁷

In the present review we will address the clinical manifestations of thyroid disease from a cardiovascular perspective and the thyroid function tests that are most appropriate to confirm the suspected diagnosis. In addition, we will discuss the new data that demonstrate the changes in thyroid hormone metabolism that arise from acute myocardial infarction and chronic congestive heart failure. The latter may have new and novel implications for the management of patients with congestive heart failure.

Thyroid Function Testing

At the present time, a sufficient number of both highly sensitive and specific measures of thyroid function exist to establish a diagnosis of either hyperthyroidism or hypothyroidism with great precision. Based on the classic "feedback" loop mechanism whereby levothyroxine (T_4) and triiodothyronine (T_3) regulate pituitary synthesis and release of thyrotropin, a thyroid-stimulating hormone (TSH), it is possible with a highly sensitive TSH assay to establish a diagnosis of thyroid disease in essentially every case.^{9,10} In patients with overt hypothyroidism, the lack of T_4 feedback leads to TSH levels >20 mIU/L, whereas in milder or subclinical hypothyroidism the TSH levels are between 3 and 20 mIU/L with normal T_4 and T_3 levels.^{9,11} In contrast, all forms of hyperthyroidism are accompanied by TSH levels that are suppressed to <0.1 mIU/L. Thus the TSH test is the appropriate initial test to screen for thyroid dysfunction in a variety of clinical situations known to be affected by thyroid disease (Table 1) as well as to confirm a suspected diagnosis and follow the response to treatment. Various authors have suggested that the reference range for TSH be narrowed especially with regard to the upper limit at which hypothyroidism may be present. For a thorough discussion of this subject, see Demers and Spencer.⁹

Cellular Mechanisms of Thyroid Hormone Action

The precise cellular and molecular mechanisms by which thyroid exerts its action on almost every cell and organ in the body have been well worked out.¹² T_4 and T_3 are synthesized by the thyroid gland in response to TSH. The thyroid gland

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Table 1. Common Diagnoses With ICD-9 Codes That Justify TSH Testing

Diagnosis	ICD-9 Code
Anemia	285.9
Atrial fibrillation	427.31
Hypertension	401.0
Hypercholesterolemia	272.0
Mixed hyperlipidemia	272.4
Diabetes mellitus	250.00
Obesity	278.00
Weight gain	783.1
Weight loss	783.21
Myopathy	359.9

ICD-9 indicates *International Classification of Diseases, Ninth Edition*.

primarily secretes T_4 ($\approx 85\%$), which is converted to T_3 by 5'-monodeiodination in the liver, kidney, and skeletal muscle.^{13,14} The heart relies mainly on serum T_3 because no significant myocyte intracellular deiodinase activity takes place, and it appears that T_3 , and not T_4 , is transported into the myocyte (Figure 1).¹⁵ T_3 exerts its cellular actions through binding to thyroid hormone nuclear receptors (TRs). These receptor proteins mediate the induction of transcription by binding to thyroid hormone response elements (TREs) in the promoter regions of positively regulated genes.^{4,12,16} TRs belong to the superfamily of steroid hormone receptors, but unlike other steroid hormone receptors, TRs bind to TREs in the absence as well as in the presence of ligand. TRs bind to TREs as homodimers or, more commonly, as heterodimers with 1 of 3 isoforms of retinoid X receptor ($RXR\alpha$, $RXR\beta$, or $RXR\gamma$).¹⁶ While bound to T_3 , TRs induce transcription, and in

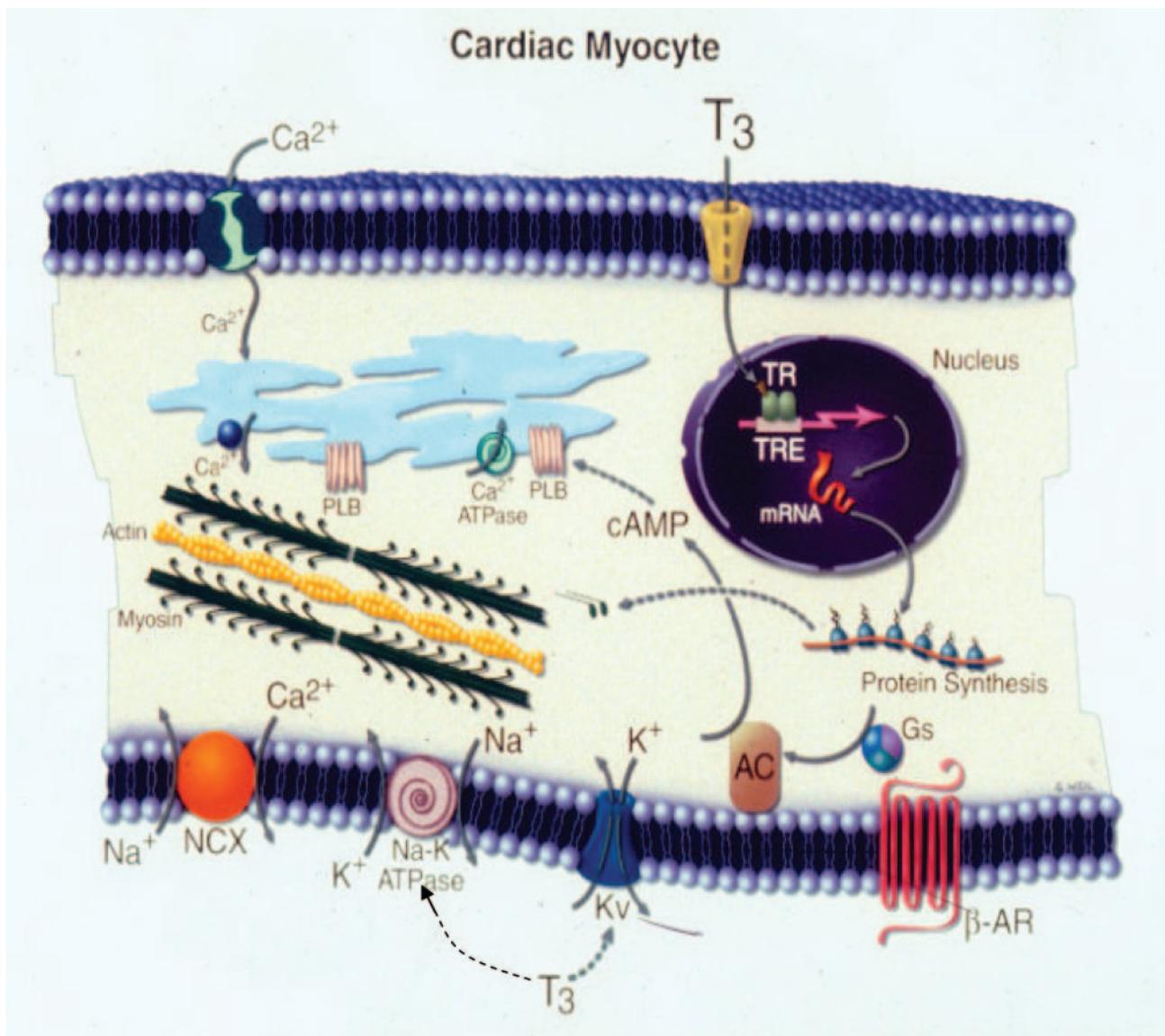


Figure 1. T_3 effects on the cardiac myocyte. T_3 has both genomic and nongenomic effects on the cardiac myocyte. Genomic mechanisms involve T_3 binding to TRs, which regulate transcription of specific cardiac genes. Nongenomic mechanisms include direct modulation of membrane ion channels as indicated by the dashed arrows. AC indicates adenylyl cyclase; β -AR, β adrenergic receptor; Gs, guanine nucleotide binding protein; Kv, voltage-gated potassium channels; NCX, sodium calcium exchanger; and PLB, phospholamban.

Table 2. Effect of Thyroid Hormone on Cardiac Gene Expression

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 α 1
Atrial natriuretic hormone	Na^+/Ca^{2+} exchanger
Voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3)	

the absence of T_3 they repress transcription.¹⁷ Negatively regulated cardiac genes such as β -myosin heavy chain and phospholamban are induced in the absence of T_3 and repressed in the presence of T_3 (Table 2).^{18–20}

Thyroid hormone effects on the cardiac myocyte are intimately associated with cardiac function via regulation of the expression of key structural and regulatory genes. The myosin heavy chain genes encode the 2 contractile protein isoforms of the thick filament in the cardiac myocyte. The sarcoplasmic reticulum Ca^{2+} -ATPase and its inhibitor, phospholamban, regulate intracellular calcium cycling. Together they are largely responsible for enhanced contractile function and diastolic relaxation in the heart.^{21–23} The β -adrenergic receptors and sodium potassium ATPase are also under T_3 regulation (Table 2).

Thyroid hormone also has extranuclear nongenomic effects on the cardiac myocyte and on the systemic vasculature. These effects of T_3 can occur rapidly and do not involve TRE-mediated transcriptional events.^{24–26} These T_3 -mediated effects include changes in various membrane ion channels for sodium, potassium, and calcium, effects on actin polymerization, adenine nucleotide translocator 1 in the mitochondrial membrane, and a variety of intracellular signaling pathways in the heart and vascular smooth muscle cells (VSM).^{25–27} Together, the nongenomic and genomic effects of T_3 act in

concert to regulate cardiac function and cardiovascular hemodynamics.

Effects of Thyroid Hormone on Cardiovascular Hemodynamics

Thyroid hormone effects on the heart and peripheral vasculature include decreased SVR and increased resting heart rate, left ventricular contractility, and blood volume (Figure 2). Thyroid hormone causes decreased resistance in peripheral arterioles through a direct effect on VSM and decreased mean arterial pressure, which, when sensed in the kidneys, activates the renin-angiotensin-aldosterone system and increases renal sodium absorption. T_3 also increases erythropoietin synthesis, which leads to an increase in red cell mass. These changes combine to promote an increase in blood volume and preload. In hyperthyroidism, these combined effects increase cardiac output 50% to 300% higher than in normal individuals. In hypothyroidism, the cardiovascular effects are diametrically opposite and cardiac output may decrease by 30% to 50%.³ It is important to recognize, however, that the restoration of normal cardiovascular hemodynamics can occur without a significant increase in resting heart rate in the treatment of hypothyroidism.²⁸

Whereas the effects of T_3 on the heart are well recognized, the ability of thyroid hormone to alter VSM and endothelial cell function are also important. In the VSM cell, thyroid hormone-mediated effects are the result of both genomic and nongenomic actions. Nongenomic actions target membrane ion channels and endothelial nitric oxide synthase, which serves to decrease SVR.^{29,30} Relaxation of VSM leads to decreased arterial resistance and pressure, which thereby increases cardiac output. Increased endothelial nitric oxide production may result, in part, from the T_3 -mediated effects of TR on the protein kinase akt pathway either via nongenomic or genomic mechanisms.^{26,31} Nitric oxide synthesized in endothelial cells then acts in a paracrine manner on adjacent VSM cells to facilitate vascular relaxation. In hypothyroidism, arterial compliance is reduced, which leads to

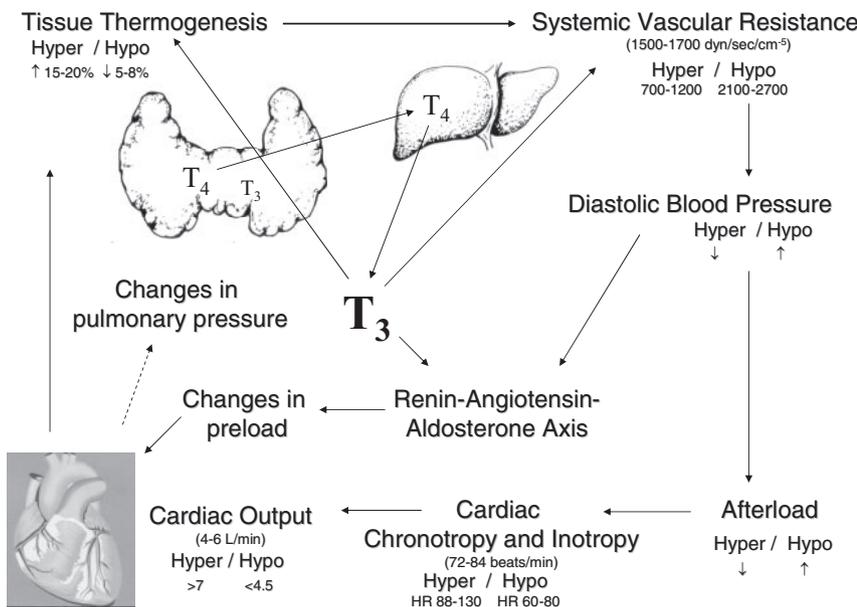


Figure 2. Effects of thyroid hormone on cardiovascular hemodynamics. T_3 affects tissue thermogenesis, systemic vascular resistance, blood volume, cardiac contractility, heart rate, and cardiac output as indicated by the arrows.^{1,3} Hyper indicates hyperthyroidism; hypo, hypothyroidism.

increased SVR. Impaired endothelium-dependent vasodilatation as a result of a reduction in nitric oxide availability has been demonstrated in subclinical hypothyroidism as well.³² In hyperthyroidism, SVR decreases, and blood volume and perfusion in peripheral tissues increase. The observation that hyperthyroidism is associated with increased vascularity suggests that T₃ may increase capillary density via increased angiogenesis.²⁹

Adrenomedullin, a polypeptide of 52 amino acids, is a potent vasodilator transcriptionally regulated by thyroid hormone, and serum levels are increased in thyrotoxicosis.³³ Interestingly, however, Diekman and colleagues³⁴ demonstrated that although SVR is decreased and adrenomedullin is increased in thyrotoxicosis, restoration of euthyroidism normalized SVR but was not correlated with plasma adrenomedullin levels. In the present study, only T₃ was an independent determinant of SVR.

The renin-angiotensin-aldosterone system plays an important role in regulation of blood pressure.³⁵ The juxtaglomerular apparatus of the kidneys is volume and pressure sensitive and in response to a decrease in mean arterial pressure, the renin-angiotensin-aldosterone system is activated and renin secretion is increased. The cascade of events that follow include increased levels of angiotensin I and II, angiotensin-converting enzyme (ACE) (characteristic of hyperthyroidism), and aldosterone. Thyroid hormone acts first to lower SVR through pathways discussed above, which causes mean arterial pressure to decrease. This is sensed by the juxtaglomerular apparatus, which leads to increased renin synthesis and secretion. T₃ also directly stimulates the synthesis of renin substrate in the liver.³⁵ Therefore, whereas thyroid hormone decreases SVR and afterload, it increases renin and aldosterone secretion while increasing blood volume and preload and contributes to the characteristic increase in cardiac output.^{3,5}

In contrast, hypothyroidism is often accompanied by a rise in diastolic blood pressure. Because cardiac output is low, the pulse pressure is narrowed. The increase in diastolic pressure occurs with low serum renin levels³⁵ and is a sodium sensitive form of hypertension.³⁶

The natriuretic peptides (ie, atrial natriuretic peptide and B-type [or brain] natriuretic peptide) are both secreted by cardiac myocytes.³⁷ Natriuretic peptides regulate salt and water balance and play a role in regulation of blood pressure. Atrial natriuretic peptide and B-type (or brain) natriuretic peptide are small peptides of 28 and 32 amino acid residues, respectively. Expression of the prohormone genes for each natriuretic peptide is regulated by thyroid hormone and is altered with changes in blood pressure and disease states that affect cardiac function.³⁷

Serum erythropoietin concentrations are increased in hyperthyroid patients, although the hematocrit and hemoglobin levels remain normal because of the concomitant increase in blood volume.³⁸ In contrast, serum erythropoietin levels are low in hypothyroidism and may explain the normochromic, normocytic anemia found in as many as 35% of those patients.¹⁰

Direct Effects of Thyroid Hormone on the Heart

Thyroid hormone is an important regulator of cardiac gene expression and, many of the cardiac manifestations of thyroid

dysfunction are associated with alterations in T₃-mediated gene expression.^{39–42} Hyperthyroidism in both humans and experimental animals leads to cardiac hypertrophy.^{43–45} This cardiac growth is primarily the result of increased work imposed on the heart through increases in hemodynamic load.⁴³

Thyroid hormone mediates the expression of both structural and regulatory genes in the cardiac myocyte (Table 2).³ The list of thyroid hormone-responsive cardiac genes includes sarcoplasmic reticulum Ca²⁺-ATPase and its inhibitor phospholamban, which regulate the uptake of calcium into the sarcoplasmic reticulum during diastole,^{2,23} α -myosin heavy chain, the fast myosin with higher ATPase activity and β -myosin heavy chain, the slow myosin, and the ion channels sodium potassium ATPase (Na⁺,K⁺-ATPase), the voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3), and the sodium calcium exchanger, which together coordinate the electrochemical responses of the myocardium.^{1,4,39} The β 1 adrenergic and TR α 1 receptors are positively and negatively regulated by thyroid hormone, respectively.⁴⁶

Cardiac pacemaker activity resides in specialized myocytes that generate an action potential without an input signal. Thyroid hormone affects the action potential duration and repolarization currents in cardiac myocytes through both genomic and nongenomic mechanisms.⁴⁷ In the heart the physiological pacemaker is the sinoatrial node.⁴⁸ The pacemaker-related genes, hyperpolarization-activated cyclic nucleotide-gated channels 2 and 4, are transcriptionally regulated by thyroid hormone.⁴⁹ Stimulation of β -adrenergic receptors causes an increase in the intracellular second messenger, cAMP, which in turn accelerates diastolic depolarization and increases heart rate. Despite these well-characterized mechanisms, it is not clear how hyperthyroidism predisposes to atrial fibrillation. It may be that a combination of genomic and nongenomic actions on atrial ion channels plus the enlargement of the atrium as a result of the expanded blood volume are the underlying causes.^{6,50}

It has been suggested that hyperthyroidism resembles a hyperadrenergic state; however, no evidence suggests that thyroid hormone excess enhances the sensitivity of the heart to adrenergic stimulation.⁵¹ In hyperthyroidism, serum levels of catecholamines remain low or normal. Several components of the cardiac myocyte β -adrenergic system are regulated by thyroid hormone, such as the β 1-adrenergic receptor, guanine nucleotide regulatory proteins, and adenylate cyclase.¹ Treatment of hyperthyroidism with β -adrenergic blockade improves many, if not all, of the cardiovascular signs and symptoms associated with hyperthyroidism.⁵² Heart rate is slowed, but the enhanced diastolic performance is not altered after treatment, which indicates that T₃ acts directly on the heart to increase calcium cycling (Figure 3).^{21,22}

Thyroid Hormone Effects on Blood Pressure Regulation

Studies of community-based populations suggest that blood pressure is altered across the entire spectrum of thyroid function.^{53,54} Asvold et al⁵³ report a linear correlation between TSH and both systolic and diastolic blood pressure,

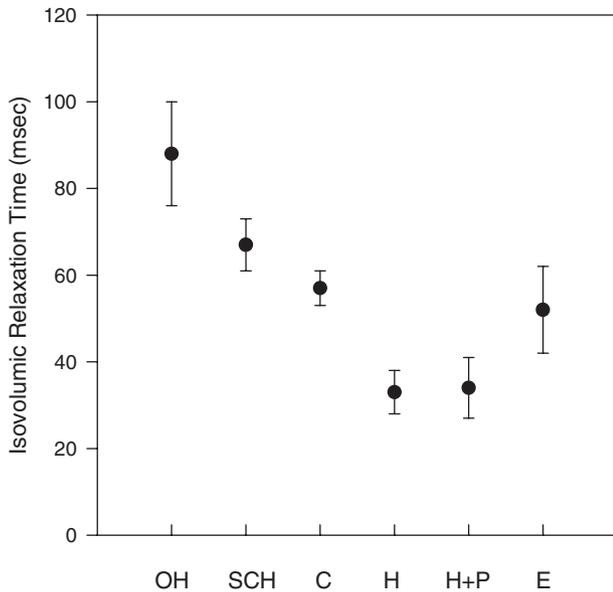


Figure 3. Thyroid status and isovolumic relaxation time. Isovolumic relaxation time, as a measure of diastolic function, is altered across the spectrum of thyroid status. OH indicates overt hypothyroidism; SCH, subclinical hypothyroidism; C, control; H, hyperthyroidism; H+P, hyperthyroidism plus β -adrenergic blockade (propranolol); and E, hyperthyroidism after treatment to restore euthyroidism. Reprinted from Klein⁶ with permission of the publisher. Copyright © 2005, Elsevier.

whereas other studies do not find a correlation.^{55,56} Thyroid hormone increases basal metabolic rate in almost every tissue and organ system in the body, and the increased metabolic demands lead to changes in cardiac output, SVR, and blood pressure (Figure 2).⁵⁴ In many regards these changes are similar to the physiological response to exercise.^{54,57}

A widened pulse pressure is characteristic of hyperthyroidism. Recent reports have shown that arterial stiffness is increased in hyperthyroidism despite the low SVR.⁵⁸ Thus excess thyroid hormone typically causes systolic blood pressure to rise, and the increase can be quite dramatic in older patients with impaired arterial compliance as a result of atherosclerotic disease. Hyperthyroidism has been documented as a secondary cause of isolated systolic hypertension, which is the most common form of hypertension.⁵⁷ Treatment of the hyperthyroidism and the use of β -blockade to slow heart rate reverses these changes.

In hypothyroidism, endothelial dysfunction and impaired VSM relaxation lead to increased SVR.³⁰ These effects lead to diastolic hypertension in $\approx 30\%$ of patients, and thyroid hormone replacement therapy restores endothelial-derived vasorelaxation and blood pressure to normal in most.³²

Thyroid Disease and Pulmonary Hypertension

Pulmonary hypertension has been associated with thyroid dysfunction, but primarily with hyperthyroidism. It has been suggested that the effect of thyroid hormone to decrease SVR may not occur in the pulmonary vasculature.⁵⁴ Both pulmonary hypertension and atrioventricular valve regurgitation have been documented to occur with a surprisingly high prevalence.^{59,60} Several case reports have documented that hyperthyroidism may present as right heart failure and tricus-

pid regurgitation.⁶¹ In a recent study of 23 consecutive patients with hyperthyroidism caused by Graves' disease, 65% of patients had pulmonary hypertension. Almost all patients normalized the increased pulmonary artery pressure with definitive treatment of the Graves' disease.⁶⁰ It may be that some component of the "right heart failure" and peripheral edema that can accompany hyperthyroidism is caused by this reversible change in pulmonary artery pressure.^{54,61}

Primary pulmonary hypertension is a progressive disease that leads to right heart failure and premature death and is often of unknown origin. It is most common in young women, and it is defined by a pulmonary artery pressure >25 mm Hg at rest and >30 mm Hg during exercise. Recently, a link to thyroid disease (ie, hypothyroidism and hyperthyroidism) has been identified.⁶² In one study, among 40 patients with primary pulmonary hypertension, $>22\%$ of patients were determined to have hypothyroidism.⁶³

Some evidence exists that autoimmune disease may play a role in both hypothyroid- and hyperthyroid-linked cases of primary pulmonary hypertension.^{60,61,63} Thyroid disease should be considered in the differential diagnosis of primary pulmonary hypertension.

Thyroid Hormone Effects on Lipid Metabolism

It is well known that hypothyroid patients have elevated serum lipid levels. Overt hypothyroidism is characterized by hypercholesterolemia and a marked increase in low-density lipoproteins (LDL) and apolipoprotein B.⁶⁴ Whereas the prevalence of overt hypothyroidism in patients with hypercholesterolemia is estimated to be 1.3% to 2.8%, 90% of patients with hypothyroidism had hypercholesterolemia.^{64–66} Lipid profile changes are also evident in subclinical hypothyroidism. Specifically, some studies have demonstrated that LDL is increased in subclinical hypothyroidism and reversible with thyroid hormone replacement,^{67,68} whereas other studies have shown increased total cholesterol in subclinical hypothyroidism with no changes in LDL. The reported mechanisms for the development of hypercholesterolemia in hypothyroidism include decreased fractional clearance of LDL by a reduced number of LDL receptors in the liver in addition to decreased receptor activity.^{64,69,70} The catabolism of cholesterol into bile is mediated by the enzyme cholesterol 7α -hydroxylase.⁷¹ This liver-specific enzyme is negatively regulated by T_3 and may contribute to the decreased catabolism and increased levels of serum cholesterol associated with hypothyroidism.⁷⁰ The increased serum lipid levels in subclinical hypothyroidism as well as in overt disease are potentially associated with increased cardiovascular risk.⁷² Treatment with thyroid hormone replacement to restore euthyroidism reverses the risk ratio.⁷⁰ If untreated, the dyslipidemia together with the diastolic hypertension associated with hypothyroidism may further predispose the patient to atherosclerosis.^{3,5,6}

Hyperthyroidism

Patients with hyperthyroidism present with characteristic signs and symptoms, many related to the heart and cardiovascular system.^{1,5,44} Hyperthyroidism, excessive endogenous thyroid hormone production, and thyrotoxicosis, the condition that results from excess thyroid hormone, whether endogenous (hy-

Table 3. Cardiovascular Signs and Symptoms of Hyperthyroidism

Palpitations	Anginal chest pain
Exercise intolerance	Atrial fibrillation
Exertional dyspnea	Cardiac hypertrophy
Systolic hypertension	Peripheral edema
Hyperdynamic precordium	Congestive heart failure

perthyroidism) or exogenous (thyroid hormone treatment) are associated with palpitations, tachycardia, exercise intolerance, dyspnea on exertion, widened pulse pressure, and sometimes atrial fibrillation (Table 3). Cardiac contractility is enhanced, and resting heart rate and cardiac output are increased. Cardiac output may be increased by 50% to 300% over that of normal subjects as a result of the combined effect of increases in resting heart rate, contractility, ejection fraction, and blood volume with a decrease in SVR (Figure 2).^{1,5}

In hyperthyroid patients, exercise intolerance may result from an inability to further increase heart rate and ejection fraction or lower SVR as would normally occur with exercise.⁷³ In severe or long-standing disease or in the elderly, respiratory and skeletal muscle weakness may be the predominant cause of exercise intolerance.⁷⁴ In a study of 24 consecutive patients, 67% of patients had objective signs and/or symptoms of neuromuscular dysfunction.⁷⁵

In rare cases, patients with hyperthyroidism can present with or develop chest pain and EKG changes suggestive of cardiac ischemia.⁷⁶ In older patients with known or suspected underlying coronary artery disease, this reflects the increase in myocardial oxygen demand in response to the increase in cardiac contractility and workload associated with thyrotoxicosis.^{1,4} Rarely, however, young patients with no known cardiac disease can manifest similar findings.^{76,77} In such patients, coronary angiography demonstrates normal coronary anatomy, and the cause for these findings has been related to coronary vasospasm.³ Successful treatment of the hyperthyroidism has been associated with a reversal of these symptoms.^{76,78}

Recent reports have documented the occurrence of cerebrovascular ischemic symptoms in young women with Graves' disease.⁷⁷ Most cases have been reported in Asia where a syndrome of Moyamoya disease is characterized by anatomic occlusion of the terminal portions of internal carotid arteries. In these patients, treatment of the hyperthyroidism can prevent further cerebral ischemic symptoms.⁷⁷ This reinforces the importance of routine thyroid function tests (to include TSH) in patients who present with cardiac and cerebral vascular ischemic symptoms.^{1,4,44,78}

Atrial Fibrillation

Sinus tachycardia is the most common rhythm disturbance and is recorded in almost all patients with hyperthyroidism.^{44,79} An increase in resting heart rate is characteristic of this disease.⁸⁰ However, it is atrial fibrillation that is most commonly identified with thyrotoxicosis.⁸¹ The prevalence of atrial fibrillation in this disease ranges between 2% and 20%. When compared with a control population with normal thyroid function, a prevalence of atrial fibrillation of 2.3% stands in contrast to 13.8% in patients with overt hyperthy-

roidism.⁶ A recent report found that in >13 000 hyperthyroid patients the prevalence rate for atrial fibrillation was <2%, perhaps as the result of earlier disease recognition and treatment.⁸¹ When analyzed by age, a stepwise increase in prevalence was present, which peaked at \approx 15% in patients >70 years old. This confirms data from the cohort of 40 628 hyperthyroid patients in the Danish National Registry, in which it was found that although 8.3% of patients developed atrial fibrillation, male gender, ischemic or valvular heart disease, or congestive heart failure were associated with the highest risk rates. It appears that subclinical (mild) hyperthyroidism carries the same relative risk for atrial fibrillation as does overt disease.^{82,83} This apparent paradox is best explained by the older age and other disease states that occur in the former population. In unselected patients who present with atrial fibrillation, <1% were the result of overt hyperthyroidism.⁸⁴ Thus, although the yield of abnormal thyroid function tests appears to be low in patients with new-onset atrial fibrillation, the ability to restore thyrotoxic patients to a euthyroid state and sinus rhythm justifies TSH testing.¹

Treatment of atrial fibrillation in the setting of hyperthyroidism includes β -adrenergic blockade.^{5,10,52} This can be accomplished with one of a variety of β 1-selective or nonselective agents, and can be accomplished rapidly with oral drug administration, whereas treatments such as antithyroid therapy or radioiodine, which lead to a restoration of a chemical euthyroid state, require more time.⁸⁵ Although digitalis has been used in hyperthyroidism-associated atrial fibrillation, the increased rate of digitalis clearance as well as the decreased sensitivity of the hyperthyroid heart to this drug results in the need for higher doses of this medication with less predictable responses.⁸⁶ Treatment with calcium channel blockers, especially when administered parenterally, should be avoided because of the potential unwanted effects of blood pressure reduction through effects on the smooth muscle cells of the resistance arterioles. Such therapy has been linked to acute hypotension and cardiovascular collapse.⁸⁷

Anticoagulation of patients with hyperthyroidism and atrial fibrillation is controversial.^{1,50} The risk of systemic or cerebral embolization must be weighed against the potential for bleeding and other complications of this therapy. The risk for systemic embolization in the setting of thyrotoxicosis is not precisely known.^{81,88} In patients with hyperthyroidism it was advancing age rather than the presence of atrial fibrillation that was the main risk factor.⁵⁰ Review of large series of patients failed to demonstrate a prevalence of thromboembolic events greater than the risk reported for major bleeding events from warfarin therapy.⁶ We conclude that in younger patients with hyperthyroidism and atrial fibrillation, in the absence of organic heart disease, hypertension, or other independent risk factors for embolization, the benefits of anticoagulation may be outweighed by the risk. However, aspirin provides for a reduction of risk for embolic events and appears to offer a safe alternative.

Rapid diagnosis of hyperthyroidism and successful treatment with either radioiodine or thioureas is associated with a reversion to sinus rhythm in a majority of patients within 2 to 3 months.⁸¹ Older patients (>60 years old) with atrial fibrillation of longer duration are less likely to spontaneously

revert to sinus rhythm. Therefore, after the patient has been rendered chemically euthyroid, if atrial fibrillation persists, electrical or pharmacological cardioversion should be attempted. When so treated, the majority of patients can be restored to sinus rhythm and will remain so for prolonged periods of time. When disopyramide (300 mg/d) was added after successful cardioversion, patients were more likely to remain in sinus rhythm than those not treated.⁸⁹

Heart Failure

Patients with hyperthyroidism may have signs and symptoms indicative of heart failure.^{1,4,78} In view of most studies that demonstrate enhanced cardiac output and cardiac contractility, this finding is paradoxical.²² Prior literature has referred to this as an example of high-output failure.^{1,73} This term does not accurately apply. However, in a subset of patients with both severe and chronic hyperthyroidism, exaggerated sinus tachycardia or atrial fibrillation can produce rate-related left ventricular dysfunction and heart failure.⁶ This explains the observation that many patients with the combination of hyperthyroidism, low cardiac output, and impaired left ventricular function are in atrial fibrillation at the time of diagnosis.¹ Preexistent ischemic or hypertensive heart disease may also predispose the hyperthyroid patient to the development of heart failure.^{4,6} Both Graves' and Hashimoto's diseases are reported to be associated with an increased prevalence of mitral valve prolapse. The latter in turn may predispose to enlargement of the left atrium and atrial fibrillation.⁹⁰ Among people >60 years of age, a low TSH level is associated with increased risk for atrial fibrillation, which in turn could lead to congestive heart failure.^{83,91}

It is interesting to speculate on the basis of the high prevalence of pulmonary artery hypertension that many of the signs of heart failure, such as neck vein distension and peripheral edema, may be caused by right heart strain.^{59,61} Similarly, much of the exercise intolerance and exertional dyspnea in these patients may be the result of decreased pulmonary compliance or decreased respiratory and skeletal muscle function.^{4,74}

Although initially thought to be contraindicated, treatment of the thyrotoxic cardiac patient with β -adrenergic blockade to reduce heart rate should be first-line therapy.^{52,85} In patients with overt heart failure involving pulmonary congestion, the use of digitalis and diuretics is appropriate.⁵⁴ The definitive treatment of choice for the hyperthyroidism is with ¹³¹I-radioiodine.^{85,92} This is both safe and effective especially when used in conjunction with β -adrenergic blockade. Cure of the hyperthyroidism and a restoration of the euthyroid state frequently results in a reversion of the atrial fibrillation to sinus rhythm and a resolution of the cardiac manifestations (Table 3).^{78,89} The importance of appropriate and adequate therapy has been demonstrated by studies in which the cardiovascular complications of thyrotoxicosis were shown to be the primary cause of death.^{93,94}

Hypothyroidism

The most common cardiovascular signs and symptoms of hypothyroidism are diametrically opposed to those described for hyperthyroidism and may include bradycardia, mild

Table 4. Cardiovascular Risks Associated With Hypothyroidism

Impaired cardiac contractility and diastolic function
Increased systemic vascular resistance
Decreased endothelial-derived relaxation factor
Increased serum cholesterol
Increased C-reactive protein
Increased homocysteine

hypertension (diastolic), narrowed pulse pressure, cold intolerance, and fatigue.^{10,28} Overt hypothyroidism affects $\approx 3\%$ of the adult female population and is associated with increased SVR, decreased cardiac contractility, decreased cardiac output, and accelerated atherosclerosis and coronary artery disease.^{6,28,95} These findings may be the result of increased hypercholesterolemia and diastolic hypertension in these patients.⁹⁶ Hypothyroid patients have other atherosclerotic cardiovascular disease risk factors and an apparent increase in risk of stroke as well (Table 4).^{54,97} The blood pressure changes, alterations in lipid metabolism, decreased cardiac contractility, and increased SVR that accompany hypothyroidism are caused by decreased thyroid hormone action on multiple organs such as the heart, liver, and peripheral vasculature and are potentially reversible with thyroid hormone replacement.⁹⁸

In contrast to hyperthyroidism, which can lead to atrial arrhythmias, a variety of case reports have demonstrated that hypothyroidism may cause a prolongation of the QT interval that predisposes the patient to ventricular irritability.⁹⁹ Rarely, torsade de pointes may result and this is reversible by treatment.

The decreased cardiac contractility associated with hypothyroidism results, in part, from changes in cardiac gene expression, specifically reduced expression of the sarcoplasmic reticulum Ca^{2+} -ATPase, and increased expression of its inhibitor, phospholamban.^{1,2,23,100} Together these proteins function in intracellular calcium cycling and thereby regulate diastolic function. These genomic changes explain the physiological changes such as the slowing of the isovolumic relaxation phase of diastolic function characteristic of hypothyroidism (Figure 3). It is well recognized that patients with hypothyroidism can develop a protein-rich pericardial and/or pleural effusion.^{10,101} Most, if not all, of the changes in cardiac structure and function associated with hypothyroidism are responsive to T_4 replacement.^{28,101}

The treatment of hypothyroidism in the setting of known or suspected cardiac disease poses some challenges. In young, otherwise healthy patients with overt hypothyroidism, treatment with a full replacement dose of L-thyroxine (Levoxyl, Synthroid) of $\approx 1.6 \mu\text{g}/\text{kg}$ per d can be initiated at the outset. In older patients, the adage of start low (25 to 50 $\mu\text{g}/\text{d}$) and go slow (increase the dose no more rapidly than every 6 to 8 weeks) applies. When so treated, a predictable improvement occurs in thyroid and cardiovascular functional measures.²⁸ Concerns that restoration of the heart to a euthyroid state might adversely affect underlying ischemic heart disease are largely unfounded. As reported by Keating,¹⁰² patients with

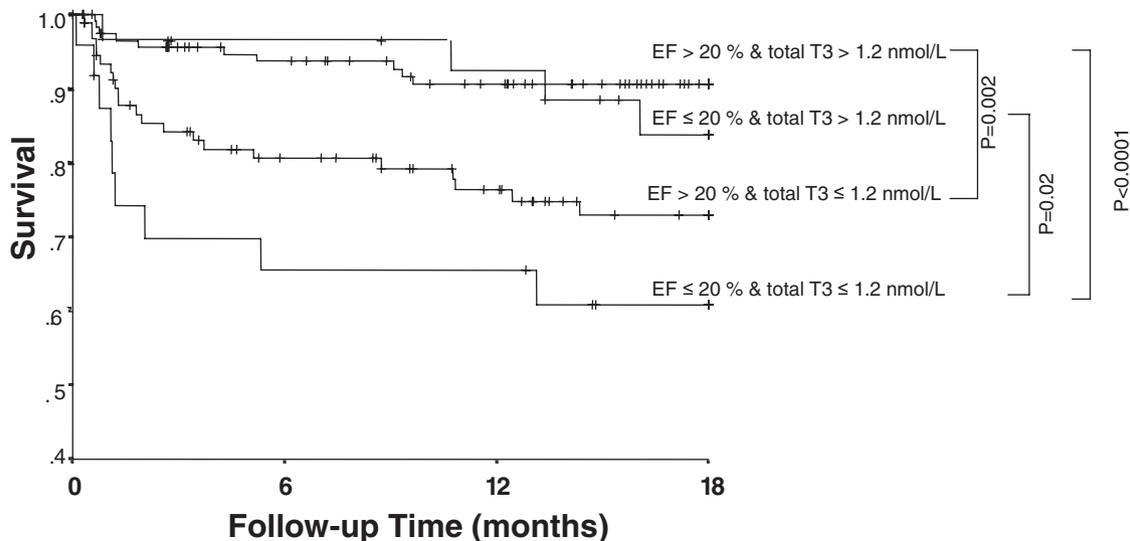


Figure 4. Low T_3 syndrome and ejection fraction as predictors of mortality. A low T_3 level is a better predictor of all-cause and cardiovascular mortality than is an abnormal left ventricular ejection fraction. EF indicates ejection fraction. Reprinted from Pingitore et al¹⁰⁸ with permission of the publisher. Copyright © 2005, Elsevier.

atherosclerotic cardiovascular disease more often improve, rather than worsen, with treatment.

Subclinical Thyroid Disease

Subclinical hyperthyroidism is characterized by a low or undetectable serum TSH concentration in the presence of normal levels of serum T_4 and T_3 .⁹ Patients may have no clinical signs or symptoms; however, studies show that they are at risk for many of the cardiovascular manifestations associated with overt hyperthyroidism.^{6,44} The prevalence of subclinical hyperthyroidism appears to increase with advancing age. In a 10-year cohort study of older patients, a low TSH was associated with increased risk for cardiovascular mortality¹⁰³ and atrial fibrillation.⁹¹ As long as the treatment is somewhat controversial, it seems prudent to recommend therapy to older patients with multinodular goiter or Graves' disease especially if they are deemed to be at risk for cardiovascular disease.¹⁰⁴

It is estimated that as many as 7% to 10% of older women have subclinical hypothyroidism.⁷ Although subclinical disease is frequently "asymptomatic," many patients have symptoms of thyroid hormone deficiency.^{65,66} Lipid metabolism is altered in subclinical hypothyroidism.^{64,67} Patients have increased serum lipid levels, and cholesterol levels appear to rise in parallel with serum TSH.^{7,66} C-Reactive protein, a risk factor for heart disease, is increased in subclinical hypothyroidism.¹⁰⁵ In addition, atherosclerosis, coronary heart disease, and myocardial infarction risk are increased in women with subclinical hypothyroidism (Table 4).^{72,106}

Although treatment of subclinical hypothyroidism with appropriate doses of L-thyroxine has been controversial, and a position paper found insufficient evidence to recommend treatment,¹¹ a recent study confirms the cardiovascular benefits of therapy.⁶⁷ As previously suggested, the benefits of the restoration of TSH levels to normal can be considered to outweigh the risks.¹

Heart Disease and Thyroid Function

Review of multiple cross-sectional studies demonstrates that $\approx 30\%$ of patients with congestive heart failure have low T_3

levels.^{107–109} The decrease in serum T_3 is proportional to the severity of the heart disease as assessed by the New York Heart Association functional classification.¹⁰⁷ The low T_3 syndrome is defined as a fall in serum T_3 accompanied by normal serum T_4 and TSH levels, and the syndrome results from impaired hepatic conversion of T_4 to the biologically active hormone, T_3 , by 5'-monodeiodination.⁶ The cardiac myocyte has no appreciable deiodinase activity and therefore relies on the plasma as the source of T_3 . In experimental animals the low T_3 syndrome leads to the same changes in cardiac function and gene expression as does primary hypothyroidism.¹¹⁰

Significant similarities exist between the hypothyroid phenotype and the heart failure phenotype.⁴¹ The cardiovascular changes that occur in both include decreased cardiac contractility and cardiac output, and an altered gene expression profile. These changes are the net result of decreased serum T_3 levels on both genomic and nongenomic mechanisms on the heart and vasculature in the setting of congestive heart failure.^{12,24,25} Reduced serum T_3 is a strong predictor of all-cause and cardiovascular mortality and, in fact, is a stronger predictor than age, left ventricular ejection fraction, or dyslipidemia (Figure 4).¹⁰⁸ It has been suggested that physiological T_3 therapy might improve cardiac function in this clinical situation.¹

Amiodarone and Thyroid Function

Amiodarone is a highly effective antiarrhythmic drug used for the treatment of both atrial and ventricular cardiac rhythm disturbances. Because of its high iodine content, amiodarone can cause changes in thyroid function tests that result in either hypothyroidism (5% to 25% of treated patients) or hyperthyroidism (2% to 10% of treated patients).^{111–113} The latter is more common in iodine-deficient areas, but seems to be more frequently observed in the US population.^{113,114}

Amiodarone inhibits the conversion of T_4 to T_3 as a result of the inhibition of 5'-deiodinase activity.¹¹² The iodine released from amiodarone metabolism can directly inhibit thyroid gland function and, if the effect persists, can lead to amiodarone-induced hypothyroidism.¹¹¹ Both preexistent

thyroid disease and Hashimoto's thyroiditis are risk factors for amiodarone-induced hypothyroidism.¹¹³ In general, patients treated with amiodarone should have thyroid function (specifically TSH) testing periodically throughout therapy.^{6,111} Should hypothyroidism develop with a persistent rise in TSH, the patient should be treated with L-thyroxine therapy.¹¹⁴ Such treatment does not impair the antiarrhythmic effect, and indeed those effects appear to be independent of the effect of the drug on thyroid hormone metabolism.¹

Estimates for drug-induced hyperthyroidism range from 2% to 10% and vary directly with duration of treatment. As initially described in a large Italian patient population, 2 forms of amiodarone-induced hyperthyroidism exist.¹¹⁵ Type 1 hyperthyroidism occurs in patients with preexistent thyroid disease and goiter and occurs more often in regions where iodine intake is low. Type 2 hyperthyroidism is caused by an inflammatory process that causes increased release of thyroid hormones from a previously normal thyroid gland.¹¹⁴ It is frequently not possible to distinguish between these 2 types.¹¹⁵ Signs of inflammation with elevated erythrocyte sedimentation rate and interleukin-6 levels are common, as are modest increases in thyroid gland size. Radioiodine uptake studies are almost always low.^{113,115}

The management of patients with amiodarone-induced hyperthyroidism can be difficult, and no uniform consensus exists among thyroidologists on the proper form of treatment.¹¹⁶ It is important to measure serum TSH, total and free T₄, and total T₃ as well as antithyroid antibodies. β -Adrenergic blockade, if not already in place, is appropriate.⁵² A trial of glucocorticoids that used 20 to 30 mg of prednisone per day for 14 to 21 days in all but patients with diabetes mellitus quickly lowered T₄ levels.¹¹⁵ Although most treatment protocols suggest cessation of the amiodarone and use of thioureas in relatively high doses, neither of these interventions have been shown to lead to predictable benefits.^{115,117} The course of the disease may last for anywhere between 1 to 3 months. In rare cases, surgical thyroidectomy under local anesthesia has proven to be effective.¹¹⁸ Not infrequently, patients treated with amiodarone also receive treatment with the warfarin anticoagulant coumadin. In these patients it is important to recognize that amiodarone-induced hyperthyroidism increases vitamin D metabolism and clearance. This in turn lowers the therapeutic coumadin dosage requirement. Thus prothrombin times should be closely monitored in these patients both during the period of hyperthyroidism and in the subsequent months. As with other types of destructive thyroiditis, the phase of hyperthyroidism may often be followed by a period of clinical and chemical hypothyroidism.^{10,113,114}

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Correction

In the article, “Thyroid Disease and the Heart,” by Klein and Danzi, which appeared in the October 9, 2007, issue of the journal (*Circulation*. 2007;116;1725–1735), the following correction should be made:

In the last paragraph, “vitamin D” should be changed to “vitamin K.”

This error has been corrected in the current online version of the article. The authors regret this error.

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