

Review

Hyperthyroid Heart Disease

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Summary: The heart is an organ sensitive to the action of thyroid hormone, and measurable changes in cardiac performance are detected with small variations in thyroid hormone serum concentrations. Most patients with hyperthyroidism experience cardiovascular manifestations, and the most serious complications of hyperthyroidism occur as a result of cardiac involvement. Recent studies provide important insights into the molecular pathways that mediate the action of thyroid hormone on the heart and allow a better understanding of the mechanisms that underlie the hemodynamic and clinical manifestations of hyperthyroidism. Several cardiovascular conditions and drugs can interfere with thyroid hormone levels and may pose a difficulty in interpretation of laboratory data in patients with suspected thyroid heart disease. The focus of this report is a review of the current knowledge of thyroid hormone action on the heart and the clinical and hemodynamic laboratory findings as well as therapeutic management of patients with hyperthyroid heart disease.

Key words: hyperthyroidism, thyroid hormone, heart failure, atrial fibrillation

Introduction

The cardiovascular manifestations of hyperthyroidism have been recognized for more than two centuries and are a cornerstone for clinical diagnosis. The action of thyroid hormone involves virtually all organ systems; in particular, the heart responds to minimal changes in serum thyroid hormone levels as seen in individuals with subclinical hyperthyroidism. This condition, characterized by normal T₃ and T₄ levels and suppressed thyroid-stimulating hormone (TSH), causes measurable alterations in several cardiac parameters. These include an increase in resting heart rate, myocardial contractility, left ventricular muscle mass, and a predisposition to atrial arrhythmias. The wide range of hemodynamic changes and cardiovascular complications that accompany hyperthyroidism serve to emphasize the role of thyroid hormone in the physiology of the cardiovascular system.

Molecular and Cellular Mechanisms of Thyroid Hormone Action on the Heart

Changes in cardiac parameters encountered in hyperthyroidism result from the activity of thyroid hormone on certain molecular pathways in the heart and vasculature. The action of thyroid hormone on the heart is mediated through a dual mechanism. The main mode of action is a direct effect on the transcription of specific and nonspecific cardiac genes.¹ The second is a nongenomic action on plasma membranes, mitochondria, and the sarcoplasmic reticulum.²

Because of the lipophilic nature of T₃ and T₄, both circulating hormones diffuse easily across the cytoplasmic membrane of target cells, including cardiomyocytes (Fig. 1). Even though T₄ is converted into T₃ in the cytosol of several cell types, there is no evidence that this conversion takes place in cardiomyocytes. The lipophilic T₃ enters the nucleus where it binds thyroid hormone receptors (THRs), two of which have already been identified.³ Binding of T₃ to a THR converts the receptor into an activated form that either homodimerizes or heterodimerizes with 9-cis-retinoic acid receptor (RXR).⁴ The T₃/THR/THR or T₃/THR/RXR complex recognizes one of

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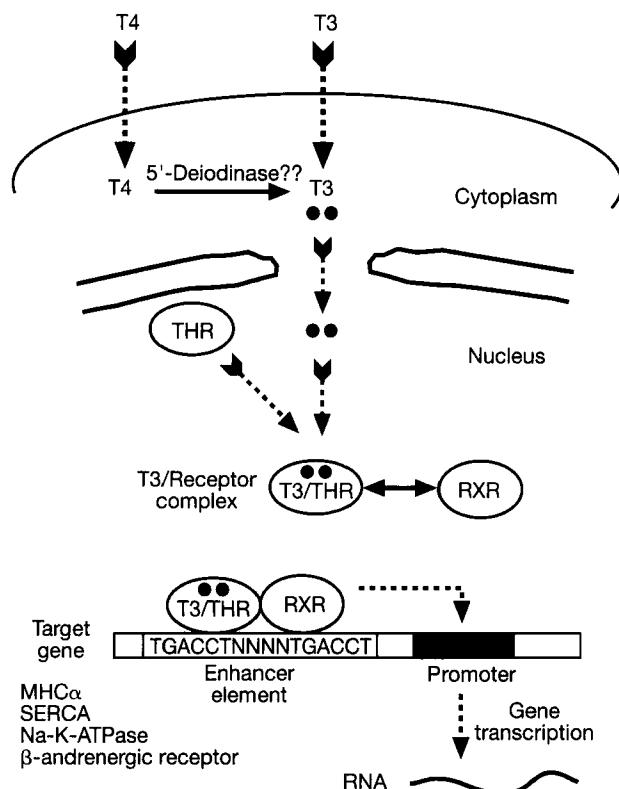


FIG. 1 Diagram summarizing the molecular mechanisms of thyroid hormone action on target genes in cardiomyocytes. There is no evidence that 5'-deiodinase is expressed in cardiomyocytes. THR = thyroid hormone receptor, RXR = retinoic acid receptor, MHC α = myosin heavy chain alpha, SERCA = sarcoplasmic reticulum calcium-ATPase.

several DNA consensus sequences, the thyroid response element (TRE), located in the enhancer region of target genes.³ Following binding of the protein complex to the response element, the promoter of the target gene is activated, resulting in the initiation of transcription. A number of cardiac genes have been recognized as targets for transcriptional activation by thyroid hormone: myosin heavy chain alpha (MHC- α), sarcoplasmic reticulum calcium-ATPase (SERCA), Na-K-ATPase, β_1 -adrenergic receptor, cardiac troponin I, and atrial natriuretic peptide.⁵⁻¹⁰ Conversely, the transcription of other genes such as MHC- β is repressed.¹¹

The improvement in myocardial contractility induced by thyroid hormone is multifactorial and results in part from the differential effect of thyroid hormone on MHC gene expression. Three myosin isoforms have been identified in ventricular muscle; V1 composed of MHC- α/α , V2 of MHC- α/β , and V3 of MHC- β/β . Through its transcriptional activity on MHC- α and MHC- β , thyroid hormone causes a shift in isoform expression by increasing the rate of synthesis of V1 and decreasing the rate of synthesis of V3.^{5, 11, 12} Since V1 has a higher ATPase enzymatic activity, an increase in the velocity of muscle fiber shortening is observed. The contribution of this mechanism to the increased myocardial contractility in human

hyperthyroidism remains to be proven. A possible second mechanism involves calcium release and reuptake by the sarcoplasmic reticulum, which regulates the rate of myocardial fiber contraction and relaxation. Through upregulation of SERCA and downregulation of phospholamban protein expression, thyroid hormone allows an accelerated reuptake of calcium by the sarcoplasmic reticulum, resulting in an increase in cardiomyocyte peak tension development and shortening of the duration of contraction in ventricular muscle.⁶ This mechanism also explains the improvement in diastolic relaxation properties of the hyperthyroid heart. Some studies have suggested that the increased inotropy may as well result from the enhanced number¹³ and sensitivity¹⁴ of cardiac beta-adrenergic receptors to catecholamines despite normal to low circulating levels of these factors.¹⁵ More recent data demonstrate that thyroid hormone does not increase the sensitivity of left ventricular contractility to beta-adrenergic stimulation.^{16, 17}

Contrary to the genomic action of thyroid hormone, the nongenomic pathways mediate processes with rapid onset of action such as the increase in cardiac output following intravenous injection of T₃.¹⁸ Through the nongenomic activity on plasma membranes, thyroid hormone prolongs the inactivation of the Na⁺ channels in cardiomyocytes¹⁹ and enhances the intracellular uptake of Na⁺ and the secondary activation of the myocardial sarcolemmal Na⁺-Ca²⁺ exchange, which may explain the acute inotropic activity of thyroid hormone.² T₃ also exerts a direct effect on L-type calcium channels and enhances calcium entry into cardiomyocytes.²⁰

Hemodynamic Consequences of Hyperthyroidism

The hemodynamic consequences of hyperthyroidism result from a direct effect of thyroid hormone on the heart and vasculature. As a result, there is an increase in heart rate, blood volume, left ventricular stroke volume, ejection fraction, and cardiac output (Fig. 2).

Peripheral vasodilatation occurs as a result of rapid utilization of oxygen, increased metabolic end products, and induction of arterial smooth muscle cell relaxation by thyroid hormone.^{21, 22} Vasodilatation results in a decrease in systemic vascular resistance (SVR) by an average of 50–60%. The fall in SVR plays a central role in the hemodynamic changes that accompany hyperthyroidism, resulting in an increase in heart rate, a selective increase in blood flow to certain organs such as skin, skeletal muscles, and heart, and a drop in diastolic blood pressure with widening of the pulse pressure.²³ Vasodilatation and the lack of rise in renal blood flow cause a decrease in renal perfusion pressure and an activation of the renin-angiotensin system, thus increasing sodium reabsorption and blood volume.²⁴⁻²⁶ The combination of an expanded blood volume and improvement in diastolic relaxation of the heart contribute to increase left ventricular end-diastolic volume (LVEDV) or preload. Similarly, the drop in SVR and the improved myocardial contractility result in a smaller left ventricular end-systolic volume (LVESV) or afterload. The net effect of an increased preload and a decreased afterload translates into a significant

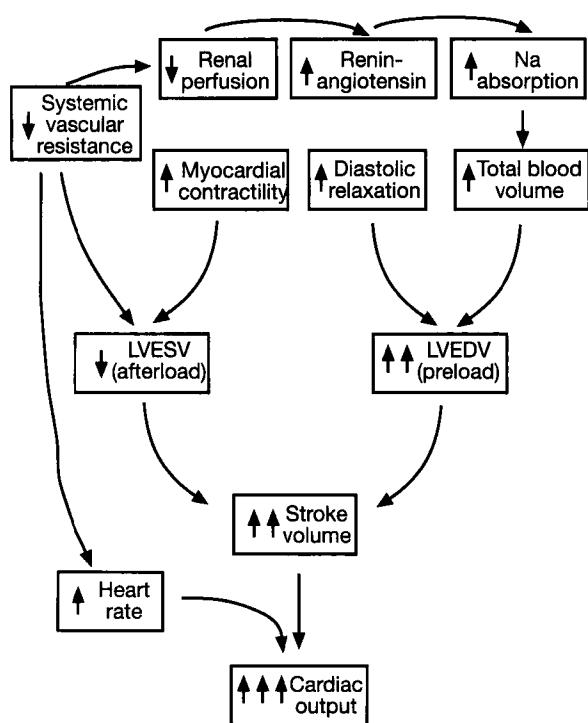


FIG. 2 Schematic representation of the hemodynamic changes that accompany hyperthyroidism. The decrease in systemic vascular resistance is central to many of the other hemodynamic consequences of thyroid hormone excess. LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume.

increase in ventricular stroke volume. In turn, the rise in heart rate and the increased stroke volume combine to cause a two- to threefold increase in cardiac output, greater than accounted for by the changes in the body metabolic rate.²⁴ Of all contributing factors, the increase in preload accounts for most of the increase in cardiac output.²⁷

In addition to the improvement in systolic contractile parameters, echocardiographic data indicate that newly diagnosed hyperthyroidism is accompanied by an improvement in left ventricular diastolic function as manifested by an enhancement in left ventricular relaxation, diastolic flow velocities, and isovolumic relaxation time. All diastolic parameters normalize when hyperthyroid patients are rendered euthyroid.²⁸ This has led to the suggestion that the dyspnea on exertion and exercise intolerance that accompany hyperthyroidism may have a noncardiac origin.²⁸ Findings of improvement in diastolic function have not been confirmed invasively and should be taken with caution since the increase in contractility and in preload that accompany hyperthyroidism may also affect echocardiographic indices of diastolic function.

Cardiac Manifestations of Hyperthyroidism

The clinical manifestations of hyperthyroidism are dramatic examples of the myriad actions of thyroid hormone on tar-

get organs. Classically, patients with hyperthyroidism develop heat intolerance, irritability, nervousness, emotional lability, muscle weakness, menstrual abnormalities, and weight loss despite an increased appetite. Cardiovascular symptoms include palpitations in up to 85% of patients and dyspnea on exertion and fatigue in approximately 50% of patients. Angina pectoris is uncommon and may result from either a mismatch between myocardial oxygen demand and supply or from vasospasm; however, it usually indicates the presence of obstructive coronary artery disease. On physical examination, the most common cardiovascular finding is tachycardia, with 90% of patients having a resting heart rate that exceeds 90 beats/min. Most patients also demonstrate bounding peripheral pulses, a wide pulse pressure, an active precordium, an increase in the intensity of heart sounds, and a systolic ejection murmur in up to 50% of cases. A systolic scratchy sound, the Means-Lerman scratch, is less common and is thought to result from rubbing of the hyperdynamic pericardium against the pleura, mimicking pericarditis.²⁹

An increased incidence of mitral valve prolapse has been reported in patients with Grave's disease.^{30, 31} While early studies have implicated the hemodynamic changes that accompany hyperthyroidism as the cause of this abnormality, a genetic role has also been proposed. The presence of a systolic murmur in a hyperthyroid patient should raise the possibility of mitral regurgitation secondary to mitral valve prolapse.

Cardiac Complications of Hyperthyroidism

Hyperthyroidism may complicate preexisting cardiac disease or may cause cardiac complications in individuals with structurally normal hearts.³² Because of the accompanying increase in heart rate, myocardial contractility, and oxygen demand, hyperthyroidism can unmask conditions such as silent coronary artery disease and compensated heart failure.

Rhythm Disturbances

Atrial fibrillation is the most common cardiac complication of hyperthyroidism. It occurs in approximately 15% of patients and is usually associated with a rapid ventricular response. It is more common among men, and its incidence increases significantly with advancing age.^{33, 34} While it is rare in patients <40 years of age, 25–40% of hyperthyroid individuals over the age of 60 experience atrial fibrillation. The majority of patients with hyperthyroidism and atrial fibrillation have an enlarged left atrium on echocardiography, compared with less than 7% of hyperthyroid patients in sinus rhythm.³⁵ Similar to angina pectoris and heart failure, the development of atrial fibrillation should not be considered as solely due to hyperthyroidism and should prompt the search for underlying organic heart disease. Contrary to atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardia are both uncommon. Ventricular tachycardia is also uncommon, and its presence should indicate the existence of underlying heart disease.

Subclinical hyperthyroidism is a risk factor for the development of atrial fibrillation. A report from the Framingham study described the 10-year outcome of 2,007 individuals >60 years of age who are clinically euthyroid and in sinus rhythm.³⁶ Of 61 subjects with low TSH levels (<0.1 mU/l), 28% developed atrial fibrillation compared with 11% of 1,576 subjects with normal levels (>0.1 mU/l). Data analysis indicates that low-serum TSH concentration is associated with more than a three-fold increase in the risk of developing atrial fibrillation. Of interest is that overt hyperthyroidism developed in only two subjects with low TSH levels and in one with a normal value. These data agree with other studies, indicating that most patients with low TSH levels do not progress to overt hyperthyroidism.³⁷

Common electrocardiographic findings in hyperthyroid patients include sinus tachycardia and a short PR interval. Despite the improvement in atrioventricular conduction, intra-atrial and intraventricular conduction disturbances occur occasionally. Most common is the prolongation in intra-atrial conduction manifested by an increase in the duration or notching of the P wave.³⁸ A delay in intraventricular conduction with a right bundle-branch block morphology is encountered in as many as 15% of patients. For unknown reasons, advanced atrioventricular blocks may also occur.

Heart Failure

The hemodynamic burden imposed by the hyperthyroid state diminishes myocardial contractile reserve and prevents any further increase in cardiac output and ejection fraction during exercise.³⁹ This is likely to result from failure of an already low SVR to decrease further during exercise. Thus, the hyperthyroid heart performs at the limit of its capacity even under resting conditions. The imposed increase in preload and total blood volume increases cardiac work and induces the development of myocardial hypertrophy, thus allowing the heart to cope better with the hemodynamic burden.⁴⁰ Accordingly, the majority of hyperthyroid patients are in a high cardiac output state in the absence of symptomatic heart failure. However, despite doubling or tripling of the cardiac output and a supernormal contractile function, the increase in both preload and blood volume causes an elevation in ventricular filling pressures and may lead to mild pulmonary and peripheral congestion. This "high-output heart failure" usually occurs in young individuals with severe and long-standing hyperthyroidism in the absence of any underlying heart disease and responds well to treatment with diuretics.⁴¹

In a small subset of patients, especially in the elderly with either atrial fibrillation or underlying organic heart disease, true heart failure develops manifested by a decline in myocardial contractility and left ventricular ejection fraction and an increase in ventricular dimensions.⁴² This is accompanied by a widening of the AVO₂ difference, a decline in cardiac output, a further rise in ventricular filling pressures and SVR, and a new third heart sound. This form of systolic dysfunction is often but not always reversible once a euthyroid state is reestablished.^{42, 43} The reason why some patients develop

"hyperthyroid cardiomyopathy" and advanced heart failure remains unknown. One possibility is the detrimental effect of sustained tachycardia on the heart.^{41, 44} This is emphasized by the fact that no cardiomyocyte damage was observed on light and electron microscopy in one hyperthyroid patient with dilated cardiomyopathy.⁴⁵

Hypertension

Hyperthyroidism is accompanied by systolic hypertension in up to one-third of patients, especially in the elderly. This results in part from the inability of the vascular system to accommodate the increase in stroke volume. The fall in SVR causes a decrease in diastolic blood pressure and explains the low mean arterial pressure and the rare occurrence of diastolic hypertension in hyperthyroidism.⁴⁶ The establishment of a euthyroid state leads to a complete reversal of these changes.

Diagnosis of Suspected Hyperthyroidism

Measurement of serum TSH concentration by a reliable laboratory using a third-generation immunoradiometric methodology is currently the most reliable test for diagnosing hyperthyroidism.⁴⁷ Current methods should allow to distinguish normal TSH levels (>0.1 mU/l) from low (<0.1 mU/l) and undetectable levels (<0.01 mU/l). The latter two indicate the presence of hyperthyroidism. This measurement permits the detection of subclinical and occult hyperthyroidism when T₃ and T₄ levels fall within normal limits. Measurement of T₄ is helpful, however T₃ should be also measured to detect patients with T₃-toxicosis. Because of the frequency with which disease and/or drugs alter binding of thyroid hormones to plasma proteins, one should obtain an estimate of unbound hormone such as free T₄, using immunoassay or equilibrium dialysis. Free T₃ measurement is more complex and is usually not required. Measurement of serum concentration of total T₄ and T₃ alone may give misleading results since elderly patients

TABLE I Summary of the cardiovascular manifestations of hyperthyroidism

Symptoms and signs	Prevalence (%)
Palpitations	85
Exercise intolerance	65
Dyspnea on exertion	50
Fatigue	50
Angina pectoris	5
Tachycardia	90
Bounding pulses	75
Wide pulse pressure	75
Hyperactive precordium	75
Systolic murmurs	50
Systolic hypertension	30
Atrial fibrillation	15

TABLE II Causes of hyperthyroidism

Grave's disease
Hyperfunctioning adenoma
Toxic multinodular goiter
Subacute thyroiditis
Chronic thyroiditis with transient thyrotoxicosis
Thyrotoxicosis factitia
Ectopic thyroid hormone production
Struma ovarii
Metastatic follicular carcinoma
Excess production of thyroid-stimulating hormone
Trophoblastic tumor

and those with heart disease or other serious illnesses may have decreased peripheral conversion of T4 to T3 and decreased plasma protein binding of both hormones. A normal serum T3 concentration in an elderly patient with heart failure or atrial fibrillation may suggest the presence of hyperthyroidism.⁴⁸ Once the diagnosis of hyperthyroidism is established, the specific cause should be identified for appropriate long-term management. The causes of hyperthyroidism are listed in Table II.

Effect of Cardiovascular Conditions and Drugs on Thyroid Hormone Levels

Nonthyroidal systemic illnesses can cause dramatic alterations in thyroid hormone levels in patients with no apparent thyroid disease. They usually manifest themselves as a low T3 state or, in severely ill patients, as a low T3/T4 state with normal TSH levels. A low T3 level may be found in up to 50% of hospitalized patients, and in many patients with heart failure and following coronary artery bypass surgery.⁴⁹

A number of drugs commonly used by cardiologists can alter the levels of thyroid hormones in otherwise euthyroid patients (Table III). More than 50% of patients receiving chronic amiodarone therapy exhibit significant changes in thyroid hormone levels manifested by elevated T4 levels at an average of 44% of baseline with normal T3 and TSH levels.⁵⁰ Thus, an elevated serum T4 in a patient receiving amiodarone should not be interpreted as a sign of hyperthyroidism. Since amiodarone can induce hyperthyroidism in 2–24% of treated patients, the interpretation of thyroid hormone levels may prove difficult. The onset of hyperthyroidism usually results in a further rise in T4 levels with a parallel and significant decrease in TSH, and most patients develop clinical manifestations suggestive of thyroid hormone excess.⁵⁰ In patients receiving chronic amiodarone therapy, serum TSH remains the most valuable measure for assessing thyroid function.⁵⁰

Treatment of Cardiovascular Disease Associated with Hyperthyroidism

For patients with tachyarrhythmias without associated cardiac complications such as unstable angina or heart failure, conservative management with antithyroid agents is appropriate. In patients with tachyarrhythmias accompanied by unstable angina as a result of underlying coronary artery disease or vasospasm and in those with thyrotoxic storm, a rapid decrease in heart rate should be achieved with the use of intravenous beta blockers.^{51,52} Because of the potential risk of adverse effects, such patients should be hemodynamically monitored in an intensive care setting. Beta blockers will also help alleviate beta receptor-mediated symptoms such as anxiety and tremulousness. Higher than usual doses of beta blockers are often required because of increased plasma clearance in hyperthyroidism.⁵³ Of the beta blockers, propranolol has the advantage of reducing T4 to T3 conversion in peripheral tis-

TABLE III Effect of cardiovascular drugs on thyroid hormone levels

Drugs	Mechanism of action	Alterations in thyroid hormone serum concentrations
Amiodarone (IV)	Inhibition of T4-T3 conversion	↑TSH, ↑T4, ↓T3
Amiodarone chronic therapy	Inhibition of T4-T3 conversion	↑T4, →T3 and TSH
Furosemide ^a (IV)	Inhibition of T3/T4 binding to TBG	↓T4, slight ↑free T4
Heparin ^a (IV)	Inhibition of tissue distribution of T4	slight ↑T4 and free T4
Propranolol	Inhibition of T4 peripheral conversion	slight ↓T3
Propranolol (high doses)	Inhibition of T4 cellular uptake	↑T4 and free T4
Metoprolol/atenolol	No effect	→T3/T4, →TSH
Calcium-channel blockers	Inhibition of tissue T3 uptake	?
Clofibrate	Increase in TBG serum concentrations	↑T4
Nicotinic acid	Decrease in TBG serum concentrations	↓T4
Dopamine	Suppression of TSH production	↓TSH, →T3/T4

^aOnly at high doses.

Abbreviations: IV = intravenous administration, TBG = thyroid-binding globulin, TSH = thyroid-stimulating hormones, ↑ = increase, ↓ = decrease, → = no change, ? = unknown.

sues; however, this effect is of minor therapeutic value and other cardioselective agents with a longer half-life are equally effective. Release of hormone from the thyroid gland is inhibited by inorganic iodide, and such agents can prove useful because of their rapid onset of action.⁵⁴ Correction of the hyperthyroid state should also be initiated with agents such as propylthiouracil to inhibit synthesis of thyroid hormone.⁵⁵

In patients in whom thyrotoxicosis is associated with congestive heart failure, conventional therapy with diuretics such as intravenous furosemide helps reverse the volume overload. Digoxin is less useful in hyperthyroid than euthyroid patients because of the relative resistance to its action.⁵⁶ This is partly due to a larger volume of distribution and the need to inhibit more active Na-K-ATPase transport units in cardiac muscle.⁵⁷ Thus, systemic toxicity may develop at doses that have little cardiac therapeutic effect. Despite these limitations, digoxin should still be considered in patients with heart failure and concomitant atrial fibrillation. The use of beta blockers should be carefully considered in patients with heart failure because of the risk of exacerbation, and the decision should be based on the extent to which an increased heart rate is thought to be contributing to heart failure. A short-acting agent such as intravenous esmolol can be tried under hemodynamic monitoring to determine whether a potential benefit may exist.⁵⁸

In patients with rapid atrial fibrillation, attempts at cardioversion should not be made before restoration of a euthyroid state since maintenance of a sinus rhythm is unlikely as long as the patient remains hyperthyroid.⁵⁹ The initial aim of therapy should be directed at controlling the ventricular rate, usually with a beta blocker. Oral calcium-channel blockers such as diltiazem or verapamil can also be useful for long-term control of ventricular rate. However, intravenous calcium-channel blockers should be avoided since they may cause a further fall in SVR and severe hypotension.⁵⁵ Once a euthyroid state is achieved, spontaneous restoration of sinus rhythm will depend on several factors including the patient's age, duration of atrial fibrillation, left atrial size, and the presence of underlying heart disease. In those with a relatively short duration of atrial fibrillation, up to two-thirds of patients will experience spontaneous reversal to sinus rhythm after achievement of an euthyroid state.⁵⁹

The issue of anticoagulation therapy for patients with hyperthyroidism and concomitant atrial fibrillation has not been fully resolved. Contrary to earlier uncontrolled and relatively small studies, a more careful study demonstrates that patients with hyperthyroidism and atrial fibrillation are not at increased risk of thromboembolism and stroke compared with age-matched control patients with other forms of atrial fibrillation (34, and personal communications, P.W. Ladenson). Similar to other causes of atrial fibrillation, age and the presence of underlying heart disease increase the risk of thromboembolism.³⁴ Some investigators recommend that anticoagulation is not warranted in young patients with a short duration of atrial fibrillation (less than 2–3 months) and no underlying heart disease, in whom a rapid conversion to sinus rhythm is expected following institution of antithyroid therapy. In older patients with longstanding atrial fibrillation, and especially

in those with underlying organic heart disease who are at a higher risk of an embolic event, anticoagulation is indicated.^{34, 41} Whereas the recommended loading dose of warfarin is similar, hyperthyroid patients may require a lower maintenance dose than euthyroid patients because of accelerated clearance of vitamin K-dependent clotting factors.⁵³

Conclusion

The past few years have witnessed a significant progress in our understanding of the molecular mechanisms that underlie the numerous cardiovascular consequences of hyperthyroidism. Since the heart is a target to many of the genomic and nongenomic actions of thyroid hormone, most patients with hyperthyroidism demonstrate hemodynamic and cardiovascular manifestations of this disease. Measurement of serum levels of thyroid hormones and TSH remains the mainstay of diagnosis. Several conditions and cardiovascular drugs can affect serum level and may pose a challenge to the diagnosis of thyroid dysfunction. Serious cardiac complications such as congestive heart failure, atrial fibrillation, and angina pectoris may arise in hyperthyroid patients, and their treatment requires the control of the underlying hyperthyroid state.

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