REVIEW

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Thyrotoxicosis and the cardiovascular system: Subtle but serious effects

ABSTRACT

Thyrotoxicosis is associated with increased cardiovascular morbidity and mortality, primarily due to heart failure and thromboembolism. However, its signs and symptoms may be subtle and can easily be missed. Therefore, one should suspect thyrotoxicosis in patients with palpitations, exercise intolerance, dyspnea on exertion, and other cardiovascular signs.

KEY POINTS

Sinus tachycardia and atrial fibrillation are frequent cardiovascular signs of thyrotoxicosis, and all patients with atrial fibrillation should be tested for thyrotoxicosis.

Test for amiodarone-induced thyrotoxicosis in all patients receiving amiodarone who have new-onset or recurrent atrial arrhythmias or unexplained weight loss.

Heart failure is rare in thyrotoxicosis but may occur in the presence of underlying heart disease or long-standing atrial fibrillation.

THYROTOXICOSIS INCREASES the risk of cardiovascular disease and death.[1,2] Yet, the cardiovascular effects of thyrotoxicosis may be subtle, like the involvement of other organs such as the central nervous system, gastrointestinal tract, muscle, and skin (**TABLE 1**).[3]

Therefore, to diagnose and treat thyrotoxicosis in a timely manner, one should have a heightened suspicion in patients with palpitations, tachycardia, exercise intolerance, or dyspnea on exertion.

In this article we summarize the cardiovascular manifestations of thyrotoxicosis, be it spontaneous or caused by amiodarone or radiographic contrast agents, and highlight its management. More detailed information on the pathogenesis and treatment of thyrotoxicosis can be found elsewhere.[3,4]

DEFINING TERMS

Even though the terms *hyperthyroidism* and *thyrotoxicosis* are often used interchangeably, there is an important distinction: hyperthyroidism is the increased formation and release of thyroid hormones from the thyroid gland, and thyrotoxicosis is the resulting clinical syndrome.

The term *subclinical hyperthyroidism* is defined by low or undetectable plasma levels of thyroid-stimulating hormone (TSH) and normal free thyroxine (T_4) and triiodothyronine (T_3) concentrations.

CAUSES OF THYROTOXICOSIS

Graves disease accounts for 60% to 90% of cases. Typical features are protrusion of the eyes, an increase in the metabolic rate, muscle weakness, shortness of breath, and tremors.

TABLE 1

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Thyrotoxicosis is most often due to Graves disease

Other causes include excessive thyroid hormone replacement therapy, toxic adenoma (Plummer disease), toxic multinodular goiter, and thyroiditis. Thyrotoxicosis due to amiodarone or iodine-containing radiographic contrast agents is discussed below.

CARDIOVASCULAR EFFECTS OF EXCESS THYROID HORMONE

The cardiovascular manifestations of thyrotoxicosis (TABLE 1) may be due to direct effects of thyroid hormones at the cellular level, to their interactions with the sympathetic nervous system, or to alterations of peripheral circulation and metabolism.[5] For example, exercise intolerance and dyspnea on exertion may be due to inability to raise cardiac output, to weakness of skeletal and respiratory muscles, or to both.

Effects on the sympathetic nervous system

Many of the cardiovascular signs of thyrotoxicosis mimic those of increased beta-adrenergic activity (eg, sinus tachycardia, increased cardiac contractility and cardiac output) and respond to beta-blockers, suggesting an underlying dysfunction of catecholamine metabolism or, alternatively, increased sensitivity to catecholamines. In addition, changes in thyroid status have been reported to alter myocardial beta-adrenergic receptors, guanine-nucleotide regulatory proteins, adenyl cyclase, and ion channel performance.[6]

On the other hand, patients with thyrotoxicosis have normal plasma and urinary catecholamine levels and normal responses to catecholamine infusion. Furthermore, there is no conclusive evidence of increased beta-adrenergic receptor density in the myocardium, increased catecholamine turnover at neural synapses, or increased affinity of adrenergic receptors for catecholamines.[3]

Effects on ventricular function

In the short term, hyperthyroidism is associated with increased cardiac contractility and improved diastolic function.

In the long term, however, chronic thyrotoxicosis induces left ventricular hypertrophy in both humans and animals. Thyroid hormone excess has been linked to increased cardiac protein synthesis, leading to the hypothesis that this is the trigger of hypertrophy.[7] However, beta-blockers have been shown to block or reverse hypertrophy, suggesting that increased cardiac workload may be the mediator of hypertrophy.[3]

A recent report suggests that even subclinical hyperthyroidism may affect cardiac morphology and function.[8]

Arrhythmias

Sinus tachycardia is the most common arrhythmia associated with thyroid hormone excess. Other rhythm disturbances frequently associated with thyrotoxicosis include atrial premature contractions and atrial fibrillation. Less often, patients may present with paroxysmal atrial tachycardia or atrial flutter. Ventricular premature contractions and ventricular tachyarrhythmias are rare.

Sinus tachycardia in thyrotoxicosis can occur at rest, during sleep, and during exercise. It is speculated that thyroid hormones have direct effects on the conduction system, possibly via cellular changes in cation transport, including a decrease of atrial excitation threshold, an increase of sinoatrial node firing, and a shortening of conduction tissue refractory time.[9]

Atrial fibrillation (TABLE 2) occurs in 5% to 15% of hyperthyroid patients.[6] Higher rates may be found in patients with known or suspected heart disease, or at risk for heart disease such as the elderly or men.

As this arrhythmia may be the only manifestation of thyrotoxicosis, TSH levels should be routinely checked in patients with atrial fibrillation. Low levels call for additional measurements of free T_4 and free T_3.

One report[10] showed subtle hyperthyroidism in 12% of elderly patients with atrial fibrillation previously considered idiopathic.[10] However, in a large cohort of patients with new-onset atrial fibrillation and no signs or symptoms of thyroid dysfunction, the prevalence of hyperthyroidism was low (< 1%).[11]

Of note, even subclinical hyperthyroidism has been associated with an increased risk of atrial fibrillation.[12]

Hemodynamic effects

The hemodynamic effects of thyrotoxicosis include tachycardia, systolic hypertension, increased cardiac output and stroke volume, and decreased systemic vascular resistance.[9]

Isolated systolic hypertension may be due to the inability of the vasculature to accommodate increased cardiac output and stroke volume. Decreased systemic vascular resistance may be due to a direct vasodilator effect of thyroid hormones on vascular smooth muscle cells.[13]

Heart failure: Hormonally mediated cardiomyopathy or underlying heart disease?

Elderly hyperthyroid patients may occasionally present with heart failure or angina.

Several factors may contribute to heart failure in thyrotoxicosis (FIGURE 1). Heart failure may occur when the hemodynamic changes of hyperthyroidism are insufficient to meet the increased metabolic demands of peripheral tissue or when the high-output state or tachyarrhythmias exacerbate underlying coronary artery disease.

Diastolic function deteriorates in the course of the disease due to left ventricular hypertrophy and progressive ventricular stiffness, impairing ventricular filling, particularly in the setting of tachycardia or atrial fibrillation. Additionally, thyrotoxicosis is associated with increased total blood volume and plasma volume, further increasing filling pressures. Occasionally, the decreased systemic resistance may overwhelm the cardiac capacity and cause high-output failure. More often, however, the high-output state, tachyarrhythmias, or both may unmask coronary artery disease, and heart failure is precipitated by ischemia.

It remains open to debate whether the hemodynamic changes induced by thyrotoxicosis itself lead to heart failure. Myocardial dysfunction in thyrotoxic patients has also been described in the absence of underlying cardiac disease,[14] even in children,[15] and improvement in myocardial contractility after restoration of euthyroidism has been reported.[16,17]

Excess thyroid hormone raises cardiovascular risk

TABLE 2

Thyroid hormone excess and atrial fibrillation: Clinical pearls

- Up to 15% of hyperthyroid patients have atrial fibrillation
- Always rule out hyperthyroidism in patients with atrial fibrillation
- Antithyroid treatment is likely to convert atrial fibrillation to sinus rhythm
- Defer cardioversion until euthyroidism is restored
- Anticoagulation is indicated

TREATING THYROTOXICOSIS

Beta-blockers

Beta-adrenergic blockers relieve symptoms such as tachycardia, tremor, anxiety, and heat intolerance.

The nonselective agent propranolol has been traditionally used for this purpose, but selective beta-1 agents such as atenolol or metoprolol appear to be equally effective. However, as the tremor associated with thyrotoxicosis is primarily mediated by beta-2-adrenergic receptors, it may be appropriate to switch to a nonselective agent if a beta-1 blocker does not relieve tremor adequately.

Calcium channel blockers

In patients who do not tolerate beta-blockers, a calcium channel blocker such as verapamil or

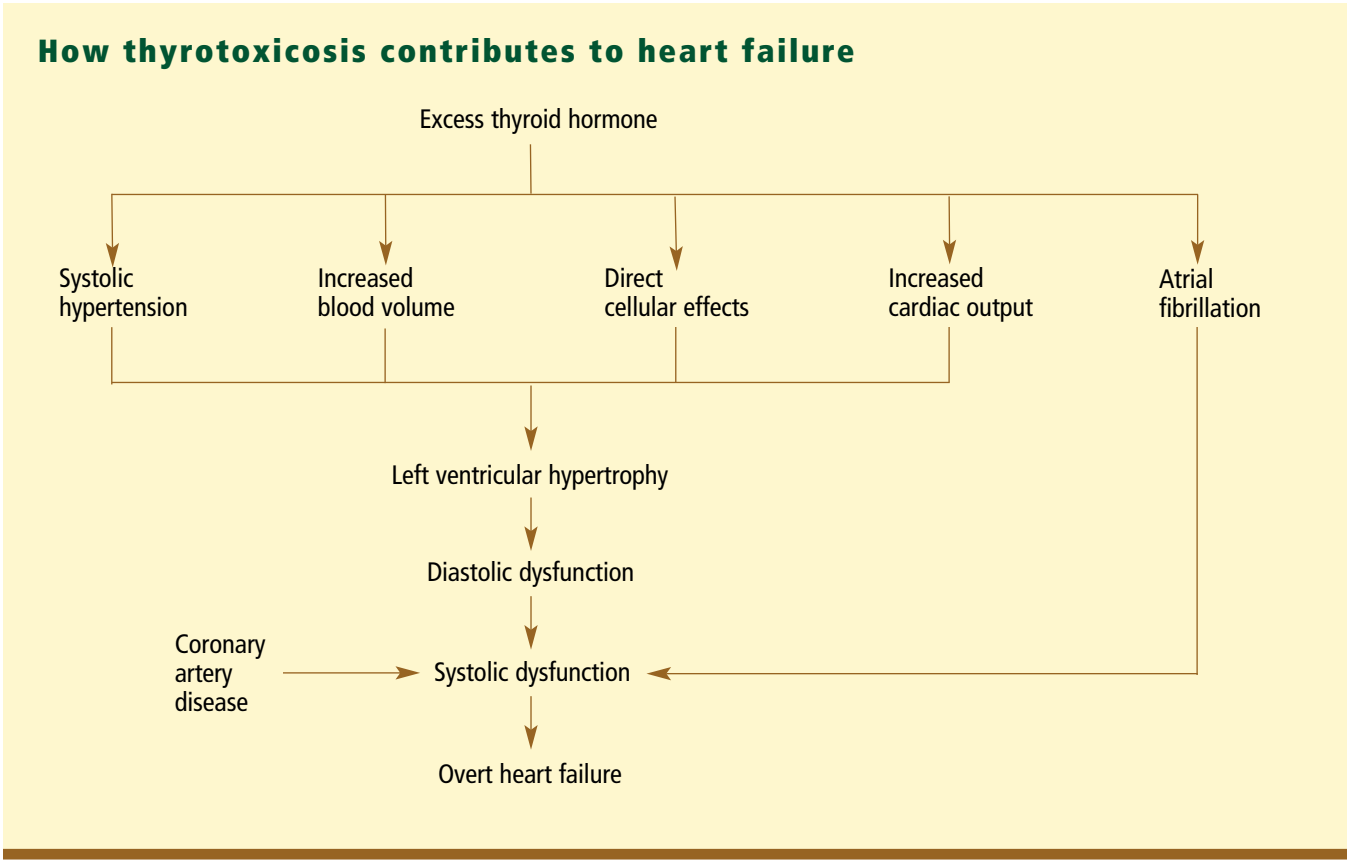

FIGURE 1

diltiazem can be used as a negative chronotropic agent. Caution is warranted, however, as these agents may lead to hemodynamic instability by further reducing systemic vascular resistance and myocardial contractility.

Antithyroid therapy

Treatment options to decrease thyroid hormone synthesis include antithyroid drugs, radioactive iodine, and surgery.

Treating atrial fibrillation in thyrotoxicosis

In the absence of chronic atrial fibrillation or underlying heart disease, thyrotoxic atrial fibrillation usually converts spontaneously to sinus rhythm within the first few months of antithyroid treatment. Conversely, reversion to atrial fibrillation is likely in persistently thyrotoxic patients. Therefore, cardioversion should be deferred until euthyroidism is restored.

Thyrotoxic thromboembolism associated with atrial fibrillation may occur even in patients with no associated heart disease.[18–20] Therefore, in the absence of contraindications, all patients with thyrotoxic atrial fibrillation should receive anticoagulation therapy.

Tachycardia-related cardiomyopathy. Atrial fibrillation per se is known to induce changes of ventricular function and structure known as *tachycardia-related cardiomyopathy*. The mechanisms have not been fully elucidated and may include myocardial ischemia, impaired myocardial energy utilization, and extracellular matrix remodeling.[21] Of importance: the effects of tachycardia may be reversible with adequate rate control.

AMIODARONE-INDUCED THYROTOXICOSIS

Amiodarone-induced thyrotoxicosis is a potentially serious condition that requires prompt diagnosis and careful treatment.

Clinical suspicion is essential, since amiodarone's antiadrenergic effect may conceal symptoms. The diagnosis should be considered in any patient taking amiodarone who has new-onset or recurrent atrial arrhythmias or unexplained weight loss.

Amiodarone is iodine-rich

Amiodarone, used in the treatment of supraventricular and ventricular arrhythmias, is rich in iodine. A daily dose of 200 mg corresponds to an intake of 75 mg of organic iodide and generates about 7 mg of free iodine. In comparison, the normal dietary iodine requirement is only 100 to 200 µg/day.

Therefore, amiodarone therapy is associated with an enormous iodide load, reflected in a 40-fold increase in plasma and urinary iodide levels.[22]

Risk is higher where iodine intake is lower

Amiodarone-induced thyrotoxicosis is more prevalent in areas with low iodine intake (eg, many European countries), whereas hypothyroidism is more frequent in areas with high iodine intake (eg, the United States and the United Kingdom). In countries with high iodine intake, the incidence of amiodarone-induced thyrotoxicosis is about 2% among patients taking the drug, whereas in countries with low iodine intake it may be as high as 10%.[23]

Pathogenesis of amiodarone-induced thyrotoxicosis

The pathogenesis of amiodarone-induced thyrotoxicosis is complex and not completely understood. Three mechanisms have been postulated[22]:

- Iodine may affect thyroid autoregulatory mechanisms and lead to excessive hormone synthesis, particularly in patients with underlying thyroid autonomy.
- Amiodarone may have a direct cytotoxic effect, suggested by the destructive, inflammatory histologic changes and increased levels of cytokines and thyroglobulin that have been demonstrated in this setting.
- Amiodarone may trigger an autoimmune response to the thyroid gland, although this mechanism remains controversial.

Diagnosis of amiodarone-induced thyrotoxicosis

Since the antiadrenergic effects of amiodarone may partially conceal the symptoms of thyrotoxicosis, the clinical diagnosis of amiodarone-induced thyrotoxicosis is difficult. As stated above, it should be considered in any patient taking amiodarone who has new or recurrent atrial arrhythmias or unexplained weight loss; it can occur throughout the treatment period and up to several months after amiodarone is stopped, due to the extremely long terminal half-life of the drug.[24]

The diagnosis is based on low concentrations of TSH with normal or elevated free T_4 and free T_3 levels, negative thyroid-stimulating immunoglobulins, and low or absent tracer uptake on thyroid scintigraphy.

TSH levels should be assessed in all patients before starting amiodarone therapy, at 6 months, and once or twice yearly thereafter.

Medical treatment

Amiodarone treatment should be stopped whenever possible. The cardiovascular risk associated with continuing amiodarone is unknown, but the remission rate of thyrotoxicosis following antithyroid drug therapy may be decreased if amiodarone treatment is maintained.

Caution is warranted when using beta-blockers to treat symptoms, in view of the long terminal half-life of amiodarone and the risk of severe bradycardia or conduction abnormalities.

The choice of antithyroid treatment can be guided by distinguishing two forms of amiodarone-induced thyrotoxicosis.[25]

In type 1, patients have a goiter, positive thyroid antibodies, abnormal (ie, measurable or even high) 24-hour radioiodine uptake, and only slightly increased interleukin-6 levels. Treatment consists of a combination of a thionamide (propylthiouracil, methimazole) to inhibit hormone biosynthesis, and potassium perchlorate to block thyroid iodide transport.[26,27]

Type 2 patients have no goiter, no thyroid antibodies, no radioiodine uptake, and markedly increased serum interleukin-6 levels. Corticosteroids, alone or in combination with thionamides, have been convincingly demonstrated to be effective in this setting.[25,28,29]

However, since a mixed form of amiodarone-induced thyrotoxicosis is common, patients should be approached pragmatically

Sinus tachycardia is the most common arrhythmia in thyrotoxicosis

FIGURE 2

with an initial combination of propylthiouracil or methimazole and potassium perchlorate, with steroids added after 2 weeks if no improvement occurs (FIGURE 2).[4] If the thyrotoxicosis does not respond to this therapy, lithium may be a valid alternative.[30]

Radioactive iodine is not effective in this form of thyrotoxicosis, since the high iodide plasma concentrations typically suppress iodine uptake in the thyroid.

Surgery

Subtotal thyroidectomy is indicated in patients with:

- Large goiters causing airway obstruction
- Malignant or equivocal nodules on fine-needle aspiration
- Severe hyperthyroidism that does not respond to conservative treatment.

Surgery has been associated with low rates of perioperative morbidity and mortality, even in the presence of thyroid storm, heart failure, and refractory arrhythmias.[31,32]

Thyrotoxicosis due to radiologic contrast agents

Patients at special risk of thyrotoxicosis when given radiologic contrast agents are those with preexisting thyroid autonomy (ie, with areas of hyperfunction within the thyroid gland as assessed by nuclear scans in the absence of laboratory hyperthyroidism), iodine deficiency, goiter, and baseline low TSH levels.

This form of iodine-induced thyrotoxicosis is more common in geographic areas of low iodine intake, but its overall incidence appears to be low, and its course is more benign than that of amiodarone-induced thyrotoxicosis. Among almost 800 unselected patients from an iodine-deficient area undergoing coronary angiography, the incidence of thyrotoxicosis was less than 0.3%, despite a significant prevalence of low levels of TSH (4%) and goiter (23%).[33] However, another study showed that among 51 patients with known thyroid autonomy who underwent cardiac catheterization, mild hyperthyroidism developed in 4 (8%),

despite prophylactic use of thyrostatic drugs in some of them.[34]

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Thyrotoxicosis can occur months after amiodarone is stopped