

GENERAL CARDIOLOGY

Thyroid disease and the heart

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Cardiologists encounter thyroid disorders frequently. Hyperthyroidism causes and may present with atrial fibrillation, while hypothyroidism is a risk factor for coronary artery disease. Moreover, the use of amiodarone may precipitate a variety of thyroid disorders, and severe heart disease, such as left ventricular failure or acute myocardial infarction, can cause confusing disturbances in thyroid function tests.

Hyperthyroidism

Hyperthyroidism is a common condition with a prevalence of approximately 1%; it affects predominantly women aged 30–50 years and is usually (70%) caused by Graves' disease which is characterised by diffuse goitre, orbitopathy, pretibial myxoedema, and the presence of stimulating thyrotrophin (TSH) receptor antibody in the serum. Most of the remaining cases (20%) are caused by autonomous production of thyroid hormones by a nodular goitre.

Effects of thyroid hormones on the cardiovascular system

The thyroid secretes two active hormones: thyroxine (T₄) which is a prohormone and tri-iodothyronine (T₃) which acts as the final mediator. In hyperthyroidism there is excessive

production of T₃, owing to hypersecretion by the thyroid gland, and an increase in the peripheral monodeiodination of T₄, which leads to profound changes in the cardiovascular system through both nuclear and non-nuclear actions at the cellular level.¹

The interrelation between the direct and indirect actions of T₃ on the peripheral circulation and the heart is shown in fig 1.² Myocardial contractility is increased as a result of a change in the synthesis of myosin heavy chain protein from the β to the α form, increased transcription of the calcium ATPase gene, and enhanced calcium and glucose uptake. These changes make contraction less efficient and increase heat production. Afterload is reduced, with a reduction of as much as 50–70% in systemic vascular resistance, caused by the direct effects of T₃ and the indirect effects of excess lactate production (increased tissue thermogenesis) on vascular smooth muscle. Blood flow, particularly to skin, muscle, and heart, is therefore greatly increased. The preload of the heart rises because blood volume is expanded owing to increases in the serum concentrations of angiotensin converting enzyme and erythropoietin, with resultant increases in renal sodium absorption and red cell mass.

Hyperthyroidism is characterised by a high left ventricular ejection fraction (LVEF) at rest but, paradoxically, by a significant fall during exercise. Restoration of euthyroidism is accompanied by the anticipated rise in LVEF on exercise at the same workload and heart rate.³ This reversible "cardiomyopathy" could explain the reduced exercise tolerance of patients with hyperthyroidism. Rather than being an intermediate state between normal left ventricular function and left ventricular dysfunction at rest, the failure of LVEF to increase on exercise is perhaps better viewed as a consequence of the additional burden of exercise induced increase in afterload on a heart performing near its maximum capacity.

The characteristic tachycardia is caused by a combination of more rapid diastolic depolarisation and shortening of the action potential of the sinoatrial cells. The refractory period of the atrial cells is also shortened which may explain the well known propensity to atrial fibrillation.

There is a complex interaction between thyroid hormones and the adrenergic system, and many of the clinical features of hyperthyroidism such as tachycardia, increased pulse pressure, and tremor resemble the heightened β adrenergic state of pheochromocytoma. However, serum and urinary catecholamine concentrations are normal or even low in hyperthyroidism, and there is no good evidence of greater sensitivity to catecholamines despite an increased density of β_1 adrenoceptors in cardiac muscle. It may well be that thyroid hormones and catecholamines act independently at the cellular level but share a signalling pathway. This would explain why non-selective β adrenoceptor antagonists, such as propranolol or nadolol, improve but do not abolish many of the symptoms of hyperthyroidism.

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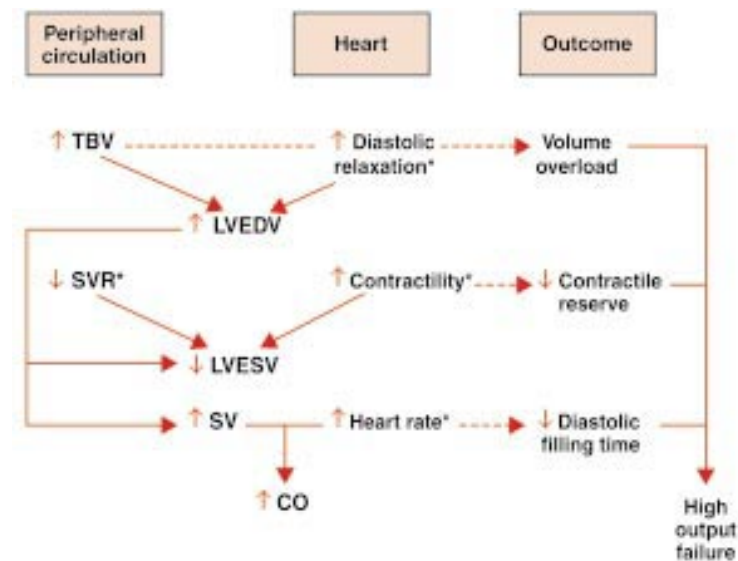


Figure 1. Effects of hyperthyroidism on the cardiovascular system and the possible outcomes. TBV, total blood volume; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; SV stroke volume; SVR systemic vascular resistance; CO, cardiac output; ↑ increased; ↓ decreased. Solid arrows indicate direct effects, and dashed arrows potential outcomes. *Features for which T₃ is directly responsible.

Clinical features

Most patients with hyperthyroidism complain of palpitations and breathlessness on exertion, although symptoms such as weight loss in the presence of a normal or increased appetite, heat intolerance, and irritability tend to predominate. Established angina may become worse and may, exceptionally, be a new development. Myocardial ischaemia is presumably caused by the increased demands of the thyrotoxic myocardium. However, coronary spasm may be an additional factor and myocardial infarction can occur in the absence of significant atheroma.⁴ The ECG is usually normal but in severe hyperthyroidism there may be impressive ST-T wave changes in the absence of ischaemic chest pain (fig 2).

Characteristically there is a sinus tachycardia of approximately 100 per minute with a good volume, often collapsing pulse, and a wide pulse pressure. The apex beat is forceful, flow murmurs are common, and there may be a bruit over the enlarged thyroid gland. Mild ankle oedema is common but is rarely caused by cardiac failure and is, in part, a manifestation of the reduced day:night ratio of urinary sodium excretion by the kidneys.

Overt cardiac failure is uncommon in hyperthyroidism and usually occurs in the context of rapid atrial fibrillation in an elderly patient with pre-existing ischaemic or valvar heart disease. Nevertheless, high output failure is a rare but recognised complication of severe thyrotoxicosis.

Atrial fibrillation

A variety of atrial and ventricular tachycardias have been described in hyperthyroidism, but the most common arrhythmia is atrial fibrillation. In unselected series 10–15% of patients with thyrotoxicosis were in atrial fibrillation at presentation; however, the prevalence is probably falling because the widespread availability of accurate tests of thyroid function means that hyperthyroidism is now diagnosed at an earlier stage in its natural history. Atrial fibrillation is rare in patients under 40 years of age unless there is longstanding severe thyrotoxicosis or coexistent structural heart disease. The prevalence increases with age and is higher in men such that in the authors' experience 50% of hyperthyroid males over the age of 60 are in atrial fibrillation at presentation.

In one series, 13% of patients with "idiopathic" or "lone" atrial fibrillation attending a cardiology clinic were found to have overt or subclinical hyperthyroidism; the discovery of atrial fibrillation, in the absence of an obvious cause, should therefore prompt a request for thyroid function testing.⁵

Atrial fibrillation may be the dominant feature of hyperthyroidism in older patients and is not necessarily accompanied by pronounced elevation of the serum concentrations of T3 and T4. Increases of thyroid hormones within their respective reference ranges associated with a suppressed serum TSH concentration (subclinical hyperthyroidism) may be sufficient to trigger atrial fibrillation in susceptible individuals.⁶ In the Framingham study, for

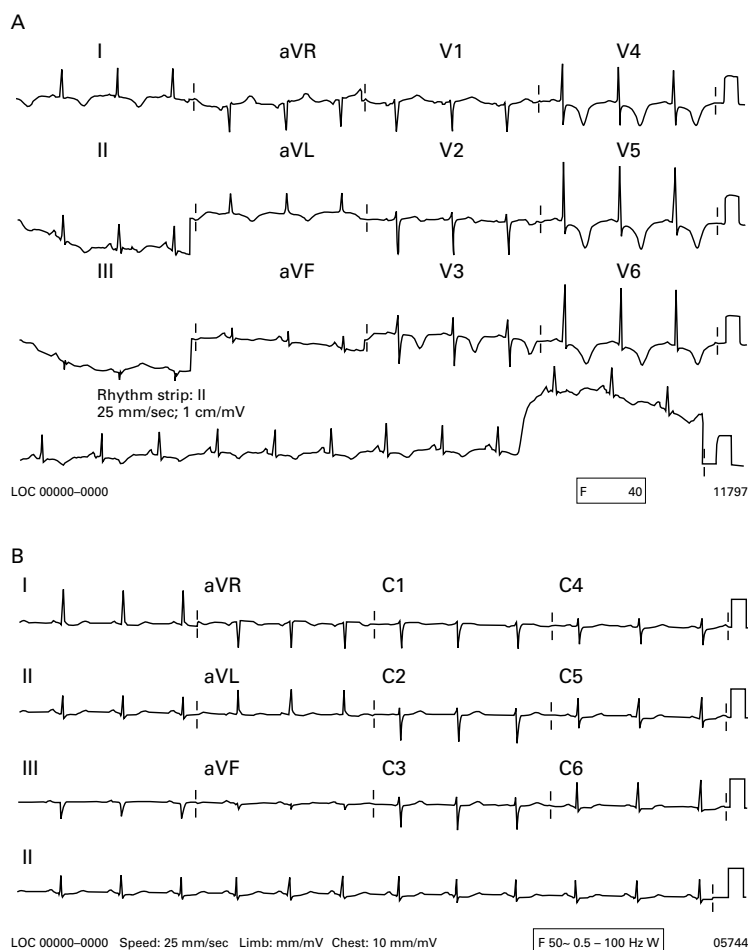


Figure 2. (A) ECG in a 48 year old woman in whom there was an exacerbation of hyperthyroidism 72 hours after treatment with iodine³¹. (B) The pronounced ST changes slowly resolved and the tracing was normal three months after the patient became euthyroid.

example, a low serum TSH was associated with a threefold increase in the incidence of atrial fibrillation among clinically euthyroid elderly subjects, 28% of whom developed atrial fibrillation during 10 years of follow up.⁷

Sixty per cent of patients with hyperthyroid atrial fibrillation will revert spontaneously to sinus rhythm within a few weeks of restoration of normal tests of thyroid function; approximately half of the remainder will respond to DC cardioversion if serum TSH concentrations are normal or raised at the time of the procedure. Failure to achieve stable sinus rhythm is most likely in those in whom the diagnosis of hyperthyroidism has been delayed. These are usually patients with mild hyperthyroidism caused by a small multinodular goitre in whom only serum T3 may be elevated (T3 toxicosis) and in whom other useful diagnostic features, such as ophthalmopathy or major weight loss, are missing.

Hyperthyroid atrial fibrillation is typically resistant to digoxin, caused in part by an increase in the renal clearance and the apparent volume of distribution of the drug. It is often necessary to add a non-selective β adrenoceptor antagonist to achieve adequate rate control.

Anticoagulation

Systemic embolisation is increased in hyperthyroid atrial fibrillation, but the risk is difficult to quantify with estimates in cross sectional studies ranging from 2–20%. Patients over 50 years of age with valvar or hypertensive heart disease would appear to be at greatest risk. Whether younger patients with structurally normal hearts benefit from anticoagulation is not known, but a decision to withhold warfarin would be more secure if there was no evidence of atrial thrombus at transoesophageal echocardiography. As the development of a dense hemiplegia complicating a readily reversible metabolic disorder is a clinical disaster, it is our policy to consider anticoagulation with warfarin (target international normalised ratio (INR) 2–3:1) in all patients with hyperthyroid atrial fibrillation. Anticoagulant control may be difficult because hyperthyroidism is associated with an increased sensitivity to warfarin.⁸

Treatment of hyperthyroidism

Radioiodine (iodine¹³¹) is the treatment of choice in patients over 40 years of age, but in younger patients most centres adopt the empirical approach of prescribing a 12–18 month course of carbimazole and recommending surgery if relapse occurs. There should be a noticeable clinical improvement within 10–14 days, and most patients will be biochemically euthyroid within 4–6 weeks of starting carbimazole 40 mg daily. Patients with Graves' disease are likely to become hypothyroid within a year of treatment with radioiodine, but this is an unusual occurrence in patients with nodular goitre. There may be an exacerbation of hyperthyroidism a few days after treatment with radioiodine, owing to a transient increase in serum thyroid hormone concentrations; in patients with atrial fibrillation and cardiac failure it is therefore good practice to render the patient euthyroid with an antithyroid drug before giving radioiodine.

Hyperthyroidism is associated with an increase in cardiovascular and cerebrovascular mortality, which is most evident in the first year following treatment with radioiodine. For example, a large series from a single centre, based on more than 100 000 patient years of follow up, showed that the standardised mortality ratio, in the year after ablative radioiodine, was 1.8:1 (95% confidence interval (CI) 1.6 to 2:1).⁹ At least some of this excess mortality could probably be avoided by earlier diagnosis and more aggressive treatment of the hyperthyroidism and its cardiovascular complications.

Hypothyroidism

Symptomatic thyroid failure is present in 1–2% of the population and tends to affect women. In the absence of previous radioiodine or surgical treatment of Graves' disease, the condition is usually caused by autoimmune mediated atrophy of the gland, or Hashimoto's thyroiditis which is characterised by diffuse firm thyroid enlargement. In contrast to hyperthyroidism,

the low serum concentrations of thyroid hormones are associated with a decrease in cardiac output, heart rate, stroke volume, and myocardial contractility, and an increase in systemic vascular resistance. The clinical features are not as dramatic as those of thyrotoxicosis and are usually only evident in patients with profound longstanding thyroid failure in whom there may be a characteristic facies. The cardiac manifestations of hypothyroidism include sinus bradycardia, pericardial effusion, heart failure (fig 3), and coronary atheroma.

Ischaemic heart disease

Overt hypothyroidism is associated with hyperlipidaemia and coronary artery disease. Approximately 3% of patients with longstanding hypothyroidism report angina, and a similar proportion report it during treatment with thyroxine. In most patients the angina does not change, diminishes or disappears when thyroxine is introduced; however, it may worsen and up to 40% of those patients who present with hypothyroidism and angina cannot tolerate full replacement treatment. Moreover, myocardial infarction and sudden death are well recognised complications of starting treatment, even in patients receiving as little as 25 µg of thyroxine daily. For these reasons it is customary to begin treatment with thyroxine in patients with symptomatic ischaemic heart disease in a dose of 25 µg daily, increasing by 25 µg increments every three weeks until a dose of 100 µg daily is reached. After a further six weeks, serum free T4 and TSH should be measured and the dose of thyroxine adjusted to ensure that free T4 and TSH concentrations are in the upper and lower parts respectively of the reference range. It should be exceptional not to achieve full replacement treatment.

Subclinical hypothyroidism

Subclinical hypothyroidism (normal serum T4, raised TSH) is usually caused by autoimmune (lymphocytic) thyroiditis, characterised by the presence of antiperoxidase antibodies in the serum, and may be associated with coronary artery disease. For example, in one postmortem study there was histological evidence of lymphocytic thyroiditis in 20% of men and 50% of women with fatal myocardial infarction and only 10% of men and women who died from other causes.¹⁰ Although hyperlipidaemia is common in overt hypothyroidism this may not explain the putative link between subclinical autoimmune thyroid disease and ischaemic heart disease. A meta-analysis of the many studies published between 1976 and 1996 on the effect of thyroxine replacement on lipids in subclinical hypothyroidism showed that restoration of serum TSH to normal reduced total cholesterol by only 0.4 mmol/l, and had little effect on high density lipoprotein (HDL) cholesterol.¹¹

Over replacement with thyroxine?

There is some concern that administering thyroxine in a dose which suppresses serum TSH may provoke significant cardiovascular problems, including abnormal ventricular diastolic relaxation, a reduced exercise capacity, an



Figure 3. Sequential chest x rays from a patient with longstanding hypothyroidism that was complicated by congestive cardiac failure. (A) Before treatment. Cardiomegaly was caused by a combination of dilatation of all the cardiac chambers and pericardial effusion. (B) After treatment with thyroxine for nine months. (C) Seven years later, two years after the patient has stopped taking thyroxine, against medical advice, and had re-presented to the same physician with the symptoms and signs of heart failure. Reproduced from *Davidson's principles and practice of medicine*, 18th ed, p 570, with permission of the publisher Churchill Livingstone.

increase in mean basal heart rate, and atrial premature contractions.¹² Apart from an increase in left ventricular mass index within the normal range, these observations have not been verified.¹³ Moreover, there is no evidence, despite the findings of the Framingham study,

that a suppressed serum TSH concentration in a patient taking thyroxine in whom serum T₃ is unequivocally normal is a risk factor for atrial fibrillation.

Influence of heart disease on thyroid function tests

The interpretation of thyroid function test results may be difficult in the presence of acute or chronic non-thyroidal illness such as myocardial infarction or congestive cardiac failure for a variety of metabolic and technical reasons. In these situations there is a reduction in the peripheral monodeiodination of T₄ to T₃, resulting in the so called "low T₃ syndrome" and, depending upon the assay employed, a low, normal or raised serum concentration of free T₄. Secretion of TSH is inhibited centrally and may also be influenced by drugs such as dopamine, so that concentrations of less than 0.05 mU/l are not uncommon. Conversely, serum TSH may rise into the hypothyroid range during recovery from illness. Moreover, certain inhibitors in the serum, and possibly also the tissues, of some patients with non-thyroidal illness may interfere with binding of thyroid hormones to their carrier proteins, prevent transport of T₃ and T₄ into cells, and block the attachment of T₃ to intracellular nuclear and cytoplasmic receptors. Many of these problems are amplified by the refusal of some commercial kit manufacturers to disclose the exact nature of their products, and by the manipulation of some assay systems in order to provide a result thought to be consistent with thyroid status. As a result low, normal or raised concentrations of free T₃ and T₄ may be recorded in the same patient using different assays.

The difficulty of relying upon serum TSH measurements to assess thyroid function in ill patients is highlighted by the finding that in a large series of hospitalised patients a low serum TSH concentration was three times as likely to be caused by non-thyroidal illness as hyperthyroidism, and a raised TSH of greater than 20 mU/l was as commonly due to illness as to primary hypothyroidism.¹⁴ The combination of low serum TSH and high free T₄ is, therefore, not uncommon in euthyroid patients with significant cardiovascular disease, and some would take the view that thyroid function testing should not be requested unless there is good evidence of thyroid disease, such as goitre, ophthalmopathy or unexplained atrial fibrillation. Even adopting such a counsel of perfection, there will be occasional patients in whom it is not possible to make an unequivocal diagnosis of euthyroidism or hyperthyroidism using the whole panoply of thyroid function testing. In this situation there is little choice but to recommend a trial of antithyroid drugs for three months.

The biochemical changes (that is, low TSH and low T₃) associated with illness or starvation are often considered teleologically as an adaptive response to spare calories and protein; however, it is not clear whether chronic disease can, in some circumstances, cause the poten-

Key points

- Serious non-thyroidal illness, such as heart failure, can cause high T4 and low TSH concentrations, suggesting hyperthyroidism.
- Measurements of T3 may help to exclude thyrotoxicosis in this situation but can be inconclusive, and in some situations a trial of antithyroid drugs may be warranted.
- In view of these difficulties thyroid function tests should only be requested in patients with credible evidence of thyroid disease such as goitre or unexplained atrial fibrillation.

tially detrimental entity of “tissue hypothyroidism”.¹⁵ Although the present consensus is that thyroid hormone treatment is not indicated in patients with significant non-thyroidal illness, this has become a controversial issue. There are some studies which have shown improvements in cardiac output and systemic vascular resistance in patients with chronic cardiac failure following treatment with intravenous T3 or oral T4.¹⁶

Amiodarone induced thyroid disease

Amiodarone is a lipid soluble benzofuranic antiarrhythmic drug that has complex effects on the thyroid and may interfere significantly with thyroid hormone metabolism.^{17, 18} Owing to its high iodine content amiodarone may cause thyroid dysfunction in patients with pre-existing thyroid disease; it can also cause a destructive thyroiditis in patients with an inherently normal thyroid gland. The combined incidence of hyper- and hypothyroidism in patients taking amiodarone is 14–18% and, because of its extraordinarily long half life, either problem may occur several months after stopping the drug.

Effects on thyroid hormone metabolism

Amiodarone administered chronically to euthyroid patients with no evidence of underlying thyroid disease results in raised serum T4 concentrations (free T4 up to 80 pmol/l) with low normal T3. These changes are caused by the potent inhibition of 5'-deiodinase which converts T4 to T3. Serum TSH concentrations may increase initially then return to normal, but in some patients are suppressed at less than

0.05 mU/l. This may make it difficult to decide whether a patient is euthyroid or hyperthyroid, particularly as the antiadrenergic effects of amiodarone can mask the clinical features of hyperthyroidism.

Type I amiodarone induced hyperthyroidism
Each 200 mg tablet of amiodarone contains 25 mg of iodine of which approximately 9 mg is released during metabolism. A patient taking a maintenance dose of 400 mg of amiodarone daily will therefore receive approximately 18 mg of inorganic iodine which is 100 times the recommended daily allowance. Chronic exposure of patients with underlying thyroid autonomy, such as Graves' disease in remission or nodular goitre, to these excessive quantities of iodine may induce hyperthyroidism (type I amiodarone induced hyperthyroidism). This is not necessarily an indication to stop amiodarone because many patients can be managed satisfactorily by introducing concomitant antithyroid medication. However, this form of hyperthyroidism can be difficult to treat, especially in areas with relative iodine deficiency as is the case in much of mainland Europe. Standard doses of carbimazole, methimazole or propylthiouracil are often ineffective and it may be necessary to add potassium perchlorate in an attempt to reduce further the iodine uptake, and therefore hormone synthesis, by the thyroid. Treatment with iodine¹³¹ is not usually advisable because of the relatively poor ability of the already iodine rich gland to concentrate the radioisotope. Total thyroidectomy may be the only method of rapid reversal of the thyrotoxicosis and has been successfully performed in patients with significant heart disease.

Type II amiodarone induced hyperthyroidism
Amiodarone per se may cause a drug induced destructive thyroiditis in patients with no pre-existing thyroid disease (type II amiodarone induced hyperthyroidism). In most cases this will resolve within 3–4 months whether or not amiodarone is discontinued. The disturbance of thyroid function is similar to that found in other forms of destructive thyroiditis, such as de Quervain's (subacute) or postpartum thyroiditis, with a few weeks of hyperthyroidism caused by the release of preformed thyroid hormones, followed by a brief spell of hypothyroidism, and then recovery.

Which type of hyperthyroidism?

Although there are features which help to distinguish between the two types of hyperthyroidism (table 1), the differentiation may be difficult and in some patients both mechanisms may be operating. In such circumstances it is sensible to institute a trial of carbimazole and to withdraw the drug after 3–4 months. If the patient remains euthyroid or becomes hypothyroid the diagnosis is likely to be type II hyperthyroidism; evidence of persistent hyperthyroidism suggests a diagnosis of type I hyperthyroidism and the need to maintain carbimazole treatment for as long as the amiodarone is necessary and beyond.

Table 1 Features which may help to distinguish between type I and type II amiodarone induced hyperthyroidism

| | Type I | Type II |
|---|-----------------------------|-------------------------|
| Pre-existing thyroid disease | Yes | No |
| Goitre | Diffuse or nodular | Uncommon, may be tender |
| Radioiodine uptake by thyroid | Low normal | Negligible |
| TSH receptor antibodies in serum | May be present | Absent |
| Antiperoxidase (microsomal antibodies in serum) | May be present | May be present |
| Serum IL-6 | Normal or slightly elevated | Very elevated |
| Subsequent hypothyroidism | No | Possible |

IL-6, interleukin 6.

Table 2 Patterns of thyroid function tests which may occur during treatment with amiodarone

| | Euthyroid (effect of amiodarone on thyroid hormone metabolism) | Type I or II hyperthyroidism | Hypothyroid |
|-----|--|------------------------------|-------------------|
| T3 | Normal or low normal | Raised > 3.0 nmol/l | Low or low normal |
| T4 | Raised, may be in excess of 60 pmol/l | Raised | Low, normal |
| TSH | Raised, normal or low | Low | Raised |

Reference ranges: total T3 1.1 to 2.8 nmol/l; free T4 10 to 25 pmol/l; TSH 0.15 to 3.50 mU/l.

AMIODARONE INDUCED HYPOTHYROIDISM

Amiodarone may cause hypothyroidism in patients with pre-existing Hashimoto's thyroiditis. However, the presence of a raised serum TSH concentration before or during treatment is not a contraindication to the use of amiodarone as the thyroid failure is readily treated with thyroxine.

ASSESSMENT OF THYROID FUNCTION BEFORE AND DURING TREATMENT

In an attempt to minimise the risk of type I hyperthyroidism we recommend that before initiating treatment with amiodarone patients should be examined for the presence of goitre or Graves' ophthalmopathy and measurements made of serum T3, T4, TSH, antiperoxidase (microsomal) and, if possible, TSH receptor antibodies. Clinical evidence of thyroid disease and/or a suppressed serum TSH concentration, particularly if associated with antithyroid antibodies, should prompt a reconsideration of the use of amiodarone, and discussion with an endocrinologist.

Measurement of serum concentrations of T3, T4, and TSH should be made three and six months after starting amiodarone treatment and every six months thereafter, including during the first year after the drug is stopped. Table 2 shows the different patterns of abnormal thyroid function test results which may occur. Serum T3 concentration is the best indicator of hyperthyroidism, but in some circumstances a trial of carbimazole for 6–8 weeks may be necessary to establish whether the patient is hyperthyroid or not.

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Key points

- Amiodarone will induce hyper- or hypothyroidism in up to 20% of subjects, and thyroid dysfunction may persist for several months or develop for the first time after the drug has been stopped.
- Thyroid status should be evaluated thoroughly before introducing the drug because patients with pre-existing (often occult) thyroid disease are at particularly high risk.
- T3 is the most valuable and sensitive measure of thyroid function in patients who have received amiodarone because, even among euthyroid patients, the inhibition of the peripheral conversion of T4 to T3 may produce a high T4 and low TSH.

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