Atrial fibrillation and the pituitary-thyroid axis: a re-evaluation

Atrial fibrillation is by far the most common important cardiac rhythm disturbance in general practice and a frequent reason for hospital referral. Cardiologists are comfortable with most aspects of patient evaluation in atrial fibrillation and with management strategies. But is measurement of serum total thyroxine (T4) and/or triiodothyronine (T3) sufficient to exclude hyperthyroidism in the clinically euthyroid patient?

It has long been known that reduced activity of the 5'-deiodinase enzyme1 caused by non-thyroidal illness, such as heart failure, reduces peripheral formation of T3 and increases the formation of metabolically inactive reverse T3, which is not detected by the radioenzymatic assay for total T3.2 Drugs such as β blockers and corticosteroids reduce T3 in a similar way; corticosteroids also reduce both T4 and T3 through a pituitary effect and aspirin and non-steroidal agents reduce T4 and T3 by displacing thyroid hormones from their plasma protein-binding sites. Furthermore, T3 concentrations fall with increasing age over 65 yet most reference ranges are derived from healthy young volunteers. The incidence of atrial fibrillation in overt hyperthyroidism ranges from 14% to 30% and increases with age.3 4 In hyperthyroid patients with atrial fibrillation, T3 concentrations may be within the reference range.5

Measurement of T4 alone is also unsatisfactory because a few patients present with T3 thyrotoxicosis, particularly if they have been treated for hyperthyroidism or have a nodular goitre or an autonomous thyroid nodule. For these reasons measurement of T4 and T3 is insufficient as a screening test for the diagnosis of hyperthyroidism when cardiovascular symptoms predominate. The sensitive assays for thyrotrophin (TSH) that are now widely available6 7 allow low but normal TSH concentrations (>0.1 mU/l) to be distinguished from subnormal (<0.01 mU/l) or absent concentrations (<0.01 mU/l) caused by suppression of TSH secretion. These assays have largely replaced the earlier thyrotrophin-releasing hormone (TRH) stimulation test.8 The TSH-producing cells of the anterior pituitary are sensitive to minor changes in circulating thyroid hormones and absent or subnormal TSH concentrations may be found in hyperthyroid patients in whom the T3 and T4 concentrations are higher than normal for the individual but may be found within or at the upper end of the accepted reference range.9 Thus screening thyroid function tests to exclude occult hyperthyroidism as the cause of atrial fibrillation should include total or free T3 and T4 and high sensitivity TSH measurements.

Serum sex hormone binding globulin (SHBG) is increased in hyperthyroidism and may help in the diagnosis in patients with low concentrations of TSH. SHBG does not seem to fall with intercurrent illness but is affected by liver disease, some drugs, and gonadal dysfunction and may be less useful in elderly men than in women.8 About 50% of patients with suppressed TSH have increases in SHBG, and in the presence of atrial fibrillation this may reflect the effects of thyroid hormone excess on the liver.10

Treatment of hyperthyroidism causing atrial fibrillation with specific antithyroid agents allows about 60% of patients to revert spontaneously to sustained sinus rhythm. As with other causes of atrial fibrillation, the main determinant of reversion seems to be the duration of atrial fibrillation.11 DC cardioversion to sustained sinus rhythm is successful in just under half of the remaining group. Similar conversion rates to sinus rhythm appear possible after antithyroid treatment for isolated suppression of the pituitary-thyroid axis.12 The frequency of reversion to sinus rhythm is greater in those patients who become hyperthyroid with six months of radiiodine treatment, presumably reflecting more rapid control of the hyperthyroid state by use of larger doses of radiiodine rather than a feature of the hypothyroid state per se which of course usually requires longer thyroid hormone replacement.13

The sensitivity of TSH to small changes in T4 and T3 raises the question whether the pituitary is a uniquely sensitive target organ or whether changes indicative of excessive thyroid hormone production are measurable elsewhere. Doses of thyroxine that suppress TSH secretion increase nocturnal heart rate, change indices of ventricular contractile performance, increase urinary sodium excretion and serum enzyme activity from liver and muscle, decrease serum cholesterol, and increase bone resorption.14-16 All of these actions are similar to but less marked than those in overt hyperthyroidism. Although a retrospective study found no increase in morbidity or mortality in thyroxine-treated patients with a low TSH,17 it is reasonable to postulate that long term adverse effects can follow isolated suppression of the pituitary-thyroid axis.

An interesting recent study suggests that low TSH is also a risk factor for later development of atrial fibrillation.18 2007 clinically euthyroid subjects from the Framingham Heart Study who were over 60 years and in sinus rhythm were followed to determine the frequency of atrial fibrillation over the next 10 years. The cumulative incidence of atrial fibrillation was 28% among 61 subjects with low TSH (<0.1 mU per litre) and 11% among 1576 subjects with normal values. Overt hyperthyroidism (but not atrial fibrillation) subsequently developed in two people with low TSH and one with normal TSH. After adjustment for other known risk factors, the relative risk of atrial fibrillation in the subjects with low TSH was 3.1 (95% confidence interval 1.7 to 5.5). Two thirds (59%) of the low TSH subjects were being treated with thyroxine replacement therapy, however, excluding these subjects had little effect on the relative risk of atrial fibrillation associated with low TSH. The mean (SD) T4 concentration was slightly higher in the low TSH group (115 (31) nmol/l versus 94 (22) nmol/l) but was within the normal range in 84% of those not on thyroxine replacement and was not correlated with the subsequent occurrence of atrial fibrillation.

Thus it appears that subclinical hyperthyroidism (low TSH and normal T4 and T3), present over may years, is associated with long term adverse consequences for several organs, particularly the heart. The condition, however, may be transient19 and progression to overt
hyperthyroidism is unusual. Appropriate antithyroid therapy is indicated in the presence of atrial fibrillation. If the patient is receiving thyroxine replacement therapy, the dose should be adjusted downwards to normalise the TSH concentration. It is not known whether antithyroid therapy can prevent atrial fibrillation in this situation and for most such patients a wait and see approach with follow up of thyroid function seems most appropriate.

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