Left ventricular function in hypothyroidism
Responses to exercise and beta adrenoceptor blockade

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SUMMARY The effects of exercise and beta adrenoceptor blockade on left ventricular function were assessed in eight patients with hypothyroidism before and during thyroxine replacement treatment. Left ventricular ejection fraction, measured by radionuclide ventriculography, was reduced in hypothyroid patients at rest and on exercise. The rise in ejection fraction with exercise was, however, similar in both groups. Pretreatment with intravenous propranolol reduced the ejection fraction at rest 9% in both hypothyroid and euthyroid patients and reduced the rise on exercise. Directional changes in a second index of myocardial contractility based on the shape of the ventricular volume curve paralleled the changes in the ejection fraction. Left ventricular function is therefore reversibly depressed by thyroid hormone deficiency but responses to exercise and beta adrenoceptor blockade are normal. There is no evidence of altered adrenergic sensitivity in the control of myocardial contractility in hypothyroidism.

The clinical effects of varying thyroid function on the cardiovascular system have been recognised for many years. The mechanism of altered myocardial contractile function in hypothyroidism has, however, been less intensively studied. The bradycardia and cardiomegaly of myxoedema are familiar, and experimentally impaired myocardial contractility is well documented.1-3 A few studies in man, mainly using measurement of systolic time intervals, have confirmed impaired myocardial contractile function by showing prolongation of the pre-ejection period4-6 though changes in left ventricular ejection time have been inconsistent.4 6 7 More recently, echocardiographic techniques have been used to show the relation between thyroid hormone levels and velocity of circumferential fibre shortening at all levels of thyroid function.8

The influence of the sympathetic nervous system in maintaining myocardial contractile function in states of thyroid hormone deficiency is unknown. Early studies suggested that alterations in cardiac sensitivity to catecholamines could not explain the hypodynamic circulatory state characteristic of the condition.9 10 Radioligand binding studies, however, have shown that both beta and alpha adrenoceptor density is decreased in ventricles from propylthiouracil-treated rats,11 thus providing a mechanism for reduced adrenergic sensitivity. Myocardial cyclic AMP and contractile responses to beta adrenoceptor agonists were not assessed and therefore the functional significance of these observations remains uncertain.

The purpose of this study was to examine left ventricular contractile function and its response to exercise and beta adrenoceptor blockade in patients with hypothyroidism before and after thyroxine replacement treatment. In the absence of major changes in preload and afterload, left ventricular ejection fraction reflects the intrinsically contractile state of the heart. Radionuclide ventriculography is a sensitive and non-invasive technique for assessment of ventricular function at rest and on exercise.

Patients and methods
Eight hypothyroid patients, all women, with a mean age of 53 years (range 37 to 69 years) were investigated. The diagnosis of hypothyroidism was made clinically and on the basis of reduced levels of plasma total thyroxine (T4) associated with a rise in plasma thyrotrophin (TSH) (Table 1). No patients were receiving drugs at the time of the first investigation. Seven had spontaneous primary hypothyroidism and one (case 8) developed hypothyroidism after 15 mCi radiiodine 131I for hyperthyroidism four months...
previous.

One patient (case 2) gave a history of mild chest pain on exertion compatible with angina pectoris but specific cardiac symptoms were absent in the remainder. All gave informed consent to the investigations that were approved by our local ethical committee. All patients were clinically free from heart failure at the time of study. Cardiomegaly (cardiothoracic ratio 55%) was noted on routine chest radiograph in case 7. Seven of the eight patients showed non-specific ST/T wave changes on the resting electrocardiogram.

Each patient was restudied between four and eight months after thyroxine replacement treatment when clinically and biochemically euthyroid. Details of thyroxine treatment and thyroid function tests when euthyroid are shown in Table 1. Patients had been biochemically euthyroid for at least four weeks before restudy. Case 2 showed an increase in the frequency of exertional chest pain in the first six weeks after starting thyroxine and for this reason thyroxine replacement was increased gradually over six months and combined with propranolol and long acting nitrates. Both of these drugs were discontinued in this patient four weeks before repeat study without change in symptomatology.

Isotope ventriculograms were performed in the supine position with cardiac imaging in the 30° left anterior oblique projection using a Nuclear Enterprises Mk 5 HR gamma camera. After an intravenous bolus injection of 15 mCi 99mTc technetium electrotyically labelled human serum albumin, precardial counts were transferred and stored in 20 ms frame format in a PDP 11/34 computer (Digital Equipment Corporation). The accumulation was triggered by the R wave of the patient's electrocardiogram, recorded from chest lead V5, each frame being updated by successive cardiac cycles until 300 to 500 beats had been accumulated. At the end of the accumulation period, the frames were displayed in rapid sequence or movie format on a screen. The ventricular outline was selected from the display using a joy-stick and data

from within this outline displayed to produce the uncorrected ventricular volume curve. The ventricular region displayed could be checked and where necessary altered by displaying the volume curves from individual pixels. Background subtraction was made from a crescentic shell of the lateral and inferior ventricular border corrected to provide an area equal to the left ventricle and the left ventricular ejection fraction was calculated from this corrected time activity curve. A further index of ventricular function was calculated as the mean ejection time, (Ts) expressed as a proportion of ventricular ejection time. Ts was defined by

\[
\frac{\sum (V_i - V_{i+1}) (t_i + t_{i+1})}{\sum (V_i - V_{i+1})}
\]

where V_i is the relative volume at time t_i during systole. Ts was therefore derived from the sum of the products of successive volume changes and the average time between these frames. Left ventricular ejection time (LVET) was taken to be the time during which 98% of the total volume change in systole took place. The Ts: LVET ratio thus measures the shape of the volume curve in systole; if a greater proportion of the volume emptied in early systole then the ratio will be reduced. Regional myocardial fibre shortening is maximal during early systole and the ratio will thus correlate inversely with the intrinsic contractile state of the heart.

Patients rested for 15 minutes before the start of each study. Ventricular volume curves were constructed over 500 beats at rest and over 300 to 500 beats during supine exercise on a bicycle ergometer. The work rate was adjusted for each patient between 300 and 600 kpm/min and exercise continued for a further two to three minutes before initiating data accumulation. After a further 30 minute rest period,
propranolol 0·15 mg/kg (ICI Pharmaceuticals, UK) was given over five minutes by intravenous injection and the procedure repeated after 15 minutes. Systolic blood pressure was measured by the same observer using a mercury sphygmomanometer at rest and on exercise before and after propranolol. The same procedure at the same work loads was used for each patient at restudy when euthyroid.

Thyroid function tests were undertaken before each study. Plasma total T₄ was measured by specific radioimmunoassay. The interassay precision level using anonymous control sera averaged 11·7% for T₄, as shown by the coefficient of variation. The normal range for plasma total T₄ in our laboratory is 60 to 150 nmol/l. Plasma thyroid stimulating hormone was also measured by radioimmunoassay in which the between assay coefficient of variation was 11·2%. The normal range for plasma thyroid stimulating hormone is less than 0·7 to 5·7 mU/l.

Statistical analysis used the Wilcoxon ranked sum and signed rank two-tailed test for pair differences. Correlations between left ventricular ejection fraction, heart rate, and plasma thyroxine used a linear regression coefficient with least squares method of analysis. A 5% level of confidence was considered statistically significant. All data are quoted as mean±standard error of the mean (SEM).

Results

The resting left ventricular ejection fraction was significantly less when hypothyroid (0·46±0·02) compared with the same patients when euthyroid (0·53±0·02; p<0·01) (Fig. 1). On exercise, left ventricular ejection fraction increased in the hypothyroid patients to 0·51±0·02 (p<0·05 compared with resting level). One patient (case 8) showed no change in ejection fraction on exercise and case 2 showed a modest fall from 0·53 to 0·49. All patients showed an increase in left ventricular ejection fraction on exercise when euthyroid (exercise ejection fraction 0·58±0·01; p<0·01 compared with resting levels). The rise in left ventricular ejection fraction with exercise was not significantly different between the two groups.

Resting left ventricular ejection fraction in the hypothyroid patients fell to 0·42±0·02 after intravenous propranolol and in the euthyroid patients fell to 0·48±0·02 with beta adrenoceptor blockade (Fig. 1). This represents a 9% fall in ejection fraction with propranolol when hypothyroid and when euthyroid (p<0·05). With exercise, propranolol caused a 10% fall in left ventricular ejection fraction in the hypothyroid patients and a 15% fall in the euthyroid patients (p<0·01 compared with resting levels before propranolol). Thus, propranolol attenuated the rise in left ventricular ejection fraction with exercise rather more in the euthyroid than in the hypothyroid groups.

The increase in left ventricular ejection fraction with exercise and the decrease with propranolol are summarised in Fig. 2a and 2b. There was a trend for propranolol to cause a greater attenuation of the exercise-induced rise in left ventricular ejection fraction and a greater absolute fall in left ventricular ejection fraction on exercise in the euthyroid compared with hypothyroid groups, but no statistically significant differences were identified.

Changes in T₄: LVET ratio were in close agreement with changes in left ventricular ejection fraction (Fig. 3). When hypothyroid, the ratio reduced from 0·560±0·016 at rest to 0·519±0·022 on exercise (p<0·01) in keeping with an increase in left ventricular ejection fraction. After propranolol, the resting T₄:LVET ratio increased to 0·587±0·016 (p=0·10) in hypothyroid patients, and fell to 0·492±0·016 (p<0·01) in euthyroid patients.

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Table 2  Heart rate and blood pressure responses to exercise and beta adrenoceptor blockade in patients when euthyroid and when hypothyroid on thyroxine replacement treatment

<table>
<thead>
<tr>
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<th>Hypothyroid</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Euthyroid</th>
<th>Systolic blood pressure (mmHg)</th>
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<tbody>
<tr>
<td></td>
<td>Mean heart rate (beats/min)</td>
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<td>Mean heart rate (beats/min)</td>
<td></td>
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<tr>
<td>Rest</td>
<td>67±4</td>
<td>135±6</td>
<td>79±2</td>
<td>128±6</td>
</tr>
<tr>
<td>Exercise</td>
<td>97±5</td>
<td>167±6</td>
<td>106±4</td>
<td>167±8</td>
</tr>
<tr>
<td>Rest (propranolol)</td>
<td>59±4</td>
<td>131±6</td>
<td>71±4</td>
<td>123±5</td>
</tr>
<tr>
<td>Exercise (propranolol)</td>
<td>82±6</td>
<td>151±8</td>
<td>90±3</td>
<td>151±5</td>
</tr>
</tbody>
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Fig. 3 Ts:LVET ratio (see methods) in hypothyroid and euthyroid groups. A fall in the ratio indicates an increase in myocardial contractile performance.

the hypothyroid group and the fall on exercise was somewhat reduced (0.548±0.021). In the euthyroid state the ratios were significantly less than when hypothyroid both at rest and on exercise (p<0.05), but a similar reduction was seen on exercise before propranolol (from 0.527±0.018 to 0.471±0.020; p<0.025) with an attenuated fall after propranolol (from 0.542±0.016 to 0.517±0.021; p<0.05).

Changes in systolic blood pressure and mean heart rate are detailed in Table 2. No significant differences in resting or exercise systolic blood pressure were detectable in the two groups either before or after propranolol. Mean heart rate was reduced when hypothyroid at rest (67±4 beats/min against 79±2 beats/min euthyroid; p<0.01), and on exercise (97±5 beats/min against 106±4 beats/min euthyroid; p<0.05). Propranolol caused a 12% reduction in resting heart rate when hypothyroid and a 10% reduction when euthyroid. The percentage reduction in exercise heart rate with propranolol was also similar, being 10% when hypothyroid and 15% when euthyroid.

There was no correlation between left ventricular ejection fraction or Ts:LVET ratio and thyroid hormone levels in either the hypothyroid or euthyroid state. When hypothyroid, resting heart rate was related to plasma total thyroxine, the correlation coefficient (r=0.59; p<0.05) being improved by beta adrenoceptor blockade (r=0.69; p<0.05). Heart rate at rest or on exercise was unrelated to plasma total thyroxine when euthyroid.

No abnormalities in regional wall motion were detected in any patient at rest or on exercise before or after propranolol.

Discussion

Although the mode of action of thyroid hormones has not been fully elucidated, much evidence favours binding to nuclear chromatin as the principal site of action, with secondary modulation of protein synthetic pathways.17 It is therefore not surprising that alterations in many aspects of cellular function have been reported in thyroid hormone deficiency as well as thyroid hormone excess.18 A nuclear binding site does not, however, exclude effects on the plasma membrane or mitochondrial membrane in initiating thyroid hormone action. A reduction in beta adrenoceptor density in ventricular membranes from hypothyroid rats11 suggests that a change in the number of catecholamine receptor sites, leading to adrenergic hyposensitivity, might be an important effect of hypothyroidism. It is far from clear, however, whether altered beta adrenoceptor density in vitro would cause a change in sympathetic sensitivity in vivo in view of the close relation between the presynaptic nerve terminal and postsynaptic myocardial cells in the regulation of inotropic and chronotropic responses to neurotransmitter release.

This study has therefore investigated myocardial contractile function in hypothyroid and euthyroid patients at rest and on exercise before and after beta adrenoceptor blockade. By using the same patients as controls, the problems of inter-individual variability are avoided. The findings suggest that there are no significant differences in left ventricular contractile responses to increased sympathetic tone (exercise) or to sympathetic blockade (propranolol) in the hypothyroid and euthyroid state. There is, however, an absolute reduction in myocardial contractile performance at rest and on exercise in hypothyroidism that is independent of beta adrenoceptor activation and is presumably a direct effect of thyroid hormone deficiency. The changes in contractile function at rest and on exercise when euthyroid are within the normal range of response in our laboratory.

Heart rate itself may be a determinant of contractile
The fall in left ventricular ejection fraction in hypothyroidism might be partly caused by the reduction in heart rate at rest and on exercise (Table 2). We have, however, shown that increase in heart rate after vagal blockade with atropine has no effect on left ventricular ejection fraction or Ts:LVET ratio. Furthermore, Wainwright et al.20 showed that with incremental right ventricular pacing up to 125 beats/min, left ventricular ejection fraction progressively decreases. In the present study, exercise left ventricular ejection fraction when hypothyroid was still slightly less than resting left ventricular ejection fraction when euthyroid despite a substantially higher heart rate in the former group. It is likely therefore that there is a true reduction in myocardial contractile performance at rest and on exercise in hypothyroidism.

Both clinical21 and necropsy22 studies have shown that coronary artery disease occurs more frequently in hypothyroid patients than in controls matched for age, sex, blood pressure, and associated extrathyroid disorders. This agrees with experimental data to show that thyroid hormone deficiency potentiates the development of atherosclerosis in cholesterol-fed animals and that thyroid hormone administration can inhibit atherogenesis.23 The incidence of coronary disease in our series is unknown but it is of interest that the patient in whom a clinical diagnosis of angina pectoris was made was the only patient to show a small fall in left ventricular ejection fraction on exercise in the hypothyroid state. A fall in left ventricular contractile performance on exercise is readily demonstrable in patients with coronary disease24 and this is the probable explanation in this patient. Intriguingly, left ventricular ejection fraction increased normally in this patient when euthyroid. Histological study of the myocardium in cases of severe hypothyroidism shows non-specific changes of myofibrillar swelling, oedema, and interstitial fibrosis.25 It is possible that irreversible impairment of cardiac function may develop in such extreme cases, though all of our patients showed a return to normal function a maximum of eight months after starting oral thyroxine.

Previous studies into the effect of propranolol on resting left ventricular ejection fraction in normal subjects have given conflicting results, with either no effect or a depressant effect on resting ventricular performance.24 26–29 Differences are probably related to variability in drug dosage and route of administration, subject selection, and methods of assessment of contractile performance. On exercise ventricular performance is consistently depressed29 independent of its effect on heart rate.30 31 Our studies have shown that propranolol does not modify the pattern of change in contractile performance at rest or on exercise in the hypothyroid state. Attenuation of the exercise-induced rise in contractility was similar to that when euthyroid.

Although absorption of propranolol32 and other drugs33 34 is impaired in hypothyroidism, propranolol metabolism32 and plasma protein binding35 are not influenced by thyroid status. It is thus unlikely that there would be major differences in plasma propranolol concentrations after intravenous administration when hypothyroid or euthyroid. A reduction in peak exercise tachycardia of 16% when hypothyroid and 15% when euthyroid suggests similar functional beta adrenoceptor antagonism in both groups. The dose of propranolol used (0–15 mg/kg) has been shown to cause a 20 to 30 fold increase in the isoprenaline dose required to increase heart rate by 25 beats/min and to give plasma propranolol concentrations in the range 50 to 100 ng/ml,36 suggesting satisfactory beta adrenoceptor blockade over the study periods.

Propranolol administration causes a fall in levels of circulating triiodothyronine, physiologically the most important thyroid hormone, and a rise in levels of the metabolically inactive isomer “reverse” triiodothyronine.37 The drug probably acts similarly to non-thyroidal illness, either by alternative peripheral monodeiodination of thyroxine38 or by reduction in activity of the deiodinase enzyme activity responsible for tri-iodothyronine production.39 Although this may have important consequences in hyperthyroidism,40 it is unlikely to contribute to the acute effects of propranolol in hypothyroidism.

Left ventricular function is reversibly depressed by thyroid hormone deficiency but responses to exercise before and during beta adrenoceptor blockade are normal. We have not shown any evidence of altered adrenergic sensitivity in the control of myocardial contractile function in hypothyroidism. This suggests that myocardial depression in thyroid failure is independent of the cardiac neurosympathetic axis. Changes in adrenoceptor density in this condition, if they occur in man, appear not to be associated with a change in functional response of the heart to altered sympathetic tone.

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