Airway response to inhaled salbutamol in hyperthyroid and hypothyroid patients before and after treatment

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ABSTRACT For many years the development of thyrotoxicosis has been known to cause a deterioration in asthma but the mechanism is unknown. We have studied the effect of thyroid function on airway β adrenergic responsiveness in 10 hyperthyroid and six hypothyroid subjects before and after treatment of their thyroid disease. Airway adrenergic responsiveness was assessed by measuring specific airway conductance (sGaw) after increasing doses of inhaled salbutamol (10–410 μ g). After treatment there was no difference in resting FEV₁, sGaw, or thoracic gas volume. FVC increased in the hyperthyroid subjects but did not change in the hypothyroid subjects. In the hyperthyroid subjects there was a significant increase in Δ sGaw after 35, 60, 110, and 410 μ g salbutamol; in sGaw after 60, 110, and 410 μ g salbutamol; and in the area under the salbutamol dose response curve (AUC) after treatment of the thyroid disorder. In the hypothyroid subjects there was a significant reduction in sGaw after 10 and 60 μ g salbutamol and in the AUC after treatment. When all subjects were considered, there was a negative correlation between the AUC and serum thyroxine values. These findings suggest that an inverse relationship exists between the level of thyroid function and airway β adrenergic responsiveness.

An interaction between thyroid disease and asthma has been recognised for over 50 years^{1–3} and confirmed in several recent reports.^{4–11} When thyrotoxicosis occurs in patients with asthma bronchodilator and corticosteroid requirements increase. Asthma improves with antithyroid treatment and has in some instances relapsed on withdrawal of treatment.

The mechanism by which changes in thyroid function affect asthma is not known. It is unlikely that the respiratory muscle weakness¹² or pulmonary vascular congestion¹³ observed in thyrotoxicosis would increase bronchodilator requirements. The need for a larger dose of β agonist is at first sight surprising, since thyrotoxicosis has many features of increased sympathetic activity and many of the symptoms are relieved by β adrenoceptor antagonists. Despite this finding, most recent studies in thyrotoxic patients suggest that endogenous

catecholamine concentrations are normal or low,^{14–17} that cardiovascular responsiveness to catecholamines is not increased,^{18,19} and that β adrenoceptor numbers are normal.²⁰

Tissue responsiveness to adrenergic agents has been studied in the cardiovascular system in patients with thyroid disease but there have been no direct studies on the airways. In this study we examined the effect of thyroid dysfunction on the airway response to an inhaled β adrenoceptor agonist, salbutamol, looking at patients with hyperthyroidism and hypothyroidism before and after appropriate treatment of their thyroid disease.

Methods

SUBJECTS

Subjects were identified through the department of nuclear medicine when abnormal responses to thyroid function tests were detected, and contacted through the referring doctor, usually on the same day. They were studied if they were under 60 years and had clinical features of hyperthyroid or hypothyroid disease accompanied by unequivocal

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abnormalities in thyroid function tests. Total thyroxine (T_4) concentrations were measured on the basis of radioimmunoassay (Amerlex T_4) thyroxine binding capacity (TBC) by Thyopac 3 (Amersham International) and the results were interpreted by a thyroxine/TBC mapping technique.²¹ Subjects were excluded if they had respiratory or cardiovascular disease, were not in sinus rhythm, or were taking β adrenoceptor antagonists or any other drug known to interfere with the response to β agonists.

Eighteen patients with thyrotoxicosis (12 women and six men) aged 27–54 years were studied. Eight patients took part in a time course study, while 10 had measurements of airway responsiveness to salbutamol before and after treatment. In 17 patients thyrotoxicosis was a new diagnosis; in one it was a relapse after withdrawal of antithyroid drugs. Of the 10 patients restudied after treatment, seven had received carbimazole, and three had undergone partial thyroidectomy. The interval between the two visits ranged from three to nine months, by which time all subjects were clinically euthyroid, seven were biochemically euthyroid, and three were biochemically hypothyroid.

Six female hypothyroid patients aged 26–52 years were studied. All were restudied after 4–11 months of treatment with thyroxine, when all were clinically and biochemically euthyroid.

MEASUREMENTS

Spirometry was performed with a Vitalograph dry bellows spirometer. Airway resistance (Raw) and thoracic gas volume (VTG) were measured in a pressure compensated body plethysmograph (Fenyes and Gut), which was on line to an oscilloscope and

ultraviolet recorder. All traces were coded and read blind by one observer. When the patient attended before and after treatment the traces from both visits were pooled before analysis. Measurements were made from at least 10 panting manoeuvres to obtain a mean value for Raw and VTG to calculate specific airway conductance (sGaw), the reciprocal of Raw corrected for VTG. All subjects were shown how to pant correctly in the body plethysmograph and had some practice before baseline measurements were made.

PROTOCOL

Time course study

Eight patients with untreated thyrotoxicosis were studied on a single occasion. After baseline measurements of sGaw, subjects inhaled a single dose of 400 μ g salbutamol from a metered dose inhaler. Further measurements of sGaw were made at intervals for four hours.

Airway salbutamol dose response study

Subjects attended the laboratory at the same time of day on two occasions, before and after treatment of their thyroid disease. On the second visit patients took their usual medication on the study day. After familiarisation with the panting technique subjects rested for 15 minutes, after which sGaw, FEV₁, and FVC were measured. Salbutamol dose response studies were then performed as previously described²² with cumulative doses ranging from 10 to 410 μ g.

ANALYSIS OF RESULTS

Resting heart rates and FEV₁ and FVC values

Fig 1 Changes in sGaw (means and SEM) with increasing doses of inhaled salbutamol in 10 hyperthyroid subjects before ($\square$) and after ($\blacksquare$) treatment and in six hypothyroid subjects before ($\triangle$) and after ($\blacktriangle$) treatment.

Table 1 Baseline pulmonary function (means with SEM in parentheses) in 10 hyperthyroid and six hypothyroid subjects before and after treatment

	FEV ₁ (l)	FVC (l)	VTG (l)	sGaw (s ⁻¹ kPa ⁻¹)
Hyperthyroid patients				
Before treatment	3.45 (0.26)	3.99 (0.25)	4.61 (0.38)	2.19 (0.19)
After treatment	3.58 (0.30)	4.28 (0.31)*	4.60 (0.41)	2.24 (0.21)
Hypothyroid patients				
Before treatment	2.92 (0.28)	3.33 (0.35)	2.81 (0.24)	2.57 (0.50)
After treatment	2.88 (0.22)	3.24 (0.27)	2.98 (0.19)	2.16 (0.20)

*p < 0.025 compared with pretreatment FVC.

VTG—thoracic gas volume; sGaw—specific airway conductance.

before and after treatment were compared by Student's paired *t* test and sGaw values by Wilcoxon's signed rank test. Airway dose response curves were constructed by plotting sGaw and change in sGaw from baseline (Δ sGaw) against log cumulative dose of salbutamol. Data from the study days before and after treatment were compared at each point on the dose response curve by the Wilcoxon signed rank test. The area under each dose response curve of sGaw versus log dose salbutamol (from 10 to 410 μ g) (AUC) was calculated by trapezoid integration and the values before and after treatment were compared by Student's *t* test. Linear regression of AUC against plasma thyroxine was determined by the method of least squares.

Results

Time course study

Mean (SD) baseline sGaw for the eight thyrotoxic subjects was 1.66 (0.12) s⁻¹kPa⁻¹. sGaw increased

two minutes after they had inhaled 400 μ g salbutamol ($p < 0.002$), showed a maximum increase of 0.75 (0.14) s⁻¹kPa⁻¹ at 1 hour, and had returned to baseline values at 4 hours.

Airway salbutamol dose response studies

Baseline measurements (table 1) There was no significant change in FEV₁, VTG, or sGaw after treatment of hyperthyroid or hypothyroid subjects. Mean FVC increased in the thyrotoxic patients from 3.99 to 4.28 l ($p < 0.025$) after treatment.

Salbutamol dose response curves After treatment of thyrotoxicosis the absolute sGaw was greater after 60, 110, and 410 μ g salbutamol and Δ sGaw was greater after 35, 60, 110, and 410 μ g (table 2). The AUC (fig 2) was also greater after treatment ($p < 0.05$). In the hypothyroid subjects absolute sGaw was significantly lower after treatment with 10 and 60 μ g salbutamol. The AUC (fig 2) was also lower after treatment ($p < 0.05$). There was an

Table 2 Response to inhaled salbutamol in terms of specific airway conductance (sGaw) and Δ sGaw (s⁻¹kPa⁻¹, means with SEM in parentheses) in hyperthyroid and hypothyroid subjects before and after treatment

	Baseline	After inhaled salbutamol in doses (μ g) of				
		10	35	60	110	410
Hyperthyroid patients						
sGaw						
Before treatment	2.19 (0.19)	2.19 (0.18)	2.6 (0.29)	2.49 (0.22)	2.7 (0.18)	2.83 (0.22)
After treatment	2.24 (0.21)	2.75 (0.38)	3.22 (0.48)	3.44 (0.5)	3.43 (0.4)	3.4 (0.32)
p	NS	NS	NS	< 0.01	< 0.05	< 0.05
Δ sGaw						
Before treatment		0 (0.08)	0.41 (0.13)	0.29 (0.1)	0.51 (0.11)	0.63 (0.09)
After treatment		0.51 (0.23)	0.98 (0.34)	1.19 (0.36)	1.19 (0.22)	1.12 (0.19)
p		NS	< 0.05	< 0.05	< 0.05	< 0.05
Hypothyroid patients						
sGaw						
Before treatment	2.57 (0.5)	3.46 (0.38)	3.77 (0.26)	4.04 (0.38)	3.59 (0.28)	4.38 (0.65)
After treatment	2.16 (0.2)	2.54 (0.18)	3.42 (0.26)	2.97 (0.15)	3.42 (0.34)	3.49 (0.33)
p	NS	< 0.05	NS	< 0.05	NS	NS
Δ sGaw						
Before treatment		0.9 (0.39)	1.1 (0.43)	1.47 (0.67)	1.02 (0.54)	1.81 (0.69)
After treatment		0.39 (0.1)	1.26 (0.19)	0.81 (0.16)	1.26 (0.25)	1.33 (0.28)
p		NS	NS	NS	NS	NS

NS—not significant.

Fig 2 Area under the salbutamol dose response curve (AUC) in 10 hyperthyroid subjects (hyper) and six hypothyroid subjects (hypo) before and after treatment.

inverse relationship between AUC and thyroxine values in the 16 patients before treatment ($n = 16$, $r = -0.62$, $p < 0.025$). This relationship remained when values from both visits for each subject were included (fig 3).

Discussion

In this study FEV_1 , FVC, and sGaw tended to increase after treatment in the hyperthyroid patients and to decrease in the hypothyroid patients. The differences were small, however, and the only significant change was the increase in FVC in the hyperthyroid patients. This is in keeping with the results of three previous studies of thyrotoxic patients, which found a small increase in vital capacity after treatment.^{13,23,24} The reduction in vital capacity in thyrotoxicosis has been attributed to pulmonary congestion due to early thyrotoxic heart failure¹³ and to respiratory muscle weakness, present in almost one third of thyrotoxic patients in one study.²⁵ These changes are unlikely, however, to account for the deterioration in asthma and the

Fig 3 Relationship of the area under the salbutamol dose response curve (AUC) to total serum thyroxine (T_4) concentrations in all 16 subjects before and after treatment ($n = 32$, $r = -0.46$, $p < 0.05$). □ Hyperthyroid subjects before treatment; ■ hyperthyroid after treatment; △ hypothyroid before treatment; ▲ hypothyroid after treatment).

increased bronchodilator requirements observed with thyrotoxicosis. This study was therefore designed to look at the airway responsiveness to a β agonist in hyperthyroid and hypothyroid patients before and after treatment. Hyperthyroid and hypothyroid patients are not easy to study in the body plethysmograph and several hyperthyroid patients could not be included because they were unable to tolerate being in a confined space. The scatter of results was therefore slightly greater than is seen in normal trained subjects.

The time course of bronchodilatation was similar in the thyrotoxic subjects to that seen previously in normal subjects after the same dose of salbutamol.²⁶ The peak response was slightly later, 60 minutes compared with 15–30 minutes in normal subjects; but the differences were not significant. A delayed action would not explain the reduced response on the plateau of the dose response curve seen in the thyrotoxic patients.

The results from this study suggest that there is an inverse relationship between airway adrenergic responsiveness and the level of thyroid function. The airway response to salbutamol (sGaw, Δ sGaw, and AUC) was reduced in the thyrotoxic subjects before treatment. Findings in the hypothyroid subjects were less clearcut and possibly obscured by the fall of 17% in baseline sGaw after treatment. The changes were, however, in the opposite direction to

those seen in the thyrotoxic patients, with significantly higher values for AUC and for two doses of salbutamol before treatment. After treatment the mean dose response curves of the two groups moved in opposite directions to occupy a similar intermediate position, showing that airway responsiveness in the two groups was similar when thyroid function was normal. The negative correlation between serum thyroxine levels and the area under the salbutamol dose response curves for all subjects again supports an inverse relationship between thyroid function and airway adrenergic responsiveness.

Our findings in the thyrotoxic subjects are similar to the findings in tracheal preparations from guineapigs treated with thyroxine, where the dose response curve for terbutaline induced relaxation was flatter than in control animals.²⁷ This suggests that our findings are likely to be due to a specific effect of thyroxine on airway smooth muscle at or beyond the airway β adrenoceptor. Beta adrenoceptor numbers are influenced by ambient catecholamine concentrations and by other hormones such as hydrocortisone. Recent studies in thyrotoxic patients suggest that circulating catecholamine concentrations and catecholamine secretion rates are normal or low.¹⁴⁻¹⁷ Despite early reports to the contrary,^{28,29} the number of β_2 adrenoceptor binding sites and the cyclic AMP response to isoprenaline also appear to be normal, at least in circulating lymphocytes from thyrotoxic patients and in lung tissue from animals exposed to thyroxine.^{20,30} There is therefore at present no strong evidence for a direct effect of thyroxine on the β adrenoceptor.

An interaction between corticosteroid metabolism and adrenergic responsiveness has been described in animal models of thyroid disease. An increased response to noradrenaline was seen in rats given hydrocortisone and in hypothyroid rats with high circulating hydrocortisone concentrations.³¹ In thyrotoxic patients hydrocortisone clearance and metabolism is increased but circulating hydrocortisone concentrations appear to be normal, suggesting that adrenal compensation may be occurring.³²

Changes distal to the β adrenoceptor are perhaps the most likely explanation for our findings. In hyperthyroid rat hearts the maximum contractile response to isoprenaline was reduced despite normal maximum protein kinase activation.³³ Thyroxine may therefore be acting at a point distal to protein kinase. The flattening of the salbutamol dose response curve in thyrotoxic patients in this study and of the terbutaline dose response curve of the trachea from thyrotoxic guineapigs is compatible with a similar mechanism in airway smooth muscle.

This study strongly suggests an inverse relationship between airway adrenergic responsiveness and the level of thyroid function. The mechanism underlying the relationship is obscure but the observation is supported by recent in vitro work and is the probable explanation for the deterioration seen in patients with asthma when they develop thyrotoxicosis.

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