CLINICAL STUDY

Haemodynamic changes following treatment of subclinical and overt hyperthyroidism

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Abstract

Objective: Hyperthyroidism has profound effects on the cardiovascular system, including reduced systemic vascular resistance (SVR) due to relaxation of vascular smooth muscle cells, enhanced heart rate (HR) and cardiac output (CO) due to an increase in cardiac diastolic relaxation, contractility and heart rate. Subclinical hyperthyroidism is characterised by reduced serum TSH levels despite free thyroxine (T₄) and tri-iodothyronine (T₃) estimates within the reference range, in subjects with no obvious symptoms of hyperthyroidism. We measured haemodynamic changes (using impedance cardiography) in subjects with endogenous subclinical hyperthyroidism in order to elucidate whether these patients had signs of excess thyroid hormone at the tissue level.

Design: The patients were otherwise healthy women with a multinodular goitre ($n = 6$; age 47–81 years; serum TSH 0.006–0.090 mU/l and normal free T₄ and T₃ estimates), studied before and after normalisation of TSH (0.280–1.120 mU/l) by means of radioiodine treatment, and they were compared with 9 overt hyperthyroid patients (2 with multinodular goitre and 7 with Graves' disease) in the untreated state and after euthyroidism had been obtained.

Results: Treatment of the subclinical hyperthyroid women resulted in 11% reduction in HR ($P < 0.02$), 19% reduction in CO from (means $\pm$ s.d.) 6.93 ± 2.15 l/min to 5.58 ± 1.94 l/min ($P < 0.05$), and 30% increase in SVR ($P < 0.02$). Similar but more pronounced changes were seen in the hyperthyroid group: 17% reduction in HR, 25% reduction in CO and 46% increase in SVR (all at least $P < 0.05$). Taking all 15 patients together, thyroid function (as measured by free T₃ index (FT3I) or TSH) correlated significantly to the haemodynamic parameters as follows: the higher the thyroid function the lower the mean arterial pressure and SVR, and the higher the CO and central aortic compliance (stroke volume/pulse pressure) ($P < 0.05$). Plasma norepinephrine increased significantly after treatment of the overt hyperthyroid patients, whereas epinephrine did not change, and no changes were seen among subclinical hyperthyroid patients.

Conclusion: Treatment of endogenous subclinical hyperthyroidism resulted in significant changes in several haemodynamic parameters regarding the heart and the vascular system, compatible with some degree of excess tissue exposure to thyroid hormones in the untreated state. Our data favour more aggressive treatment of these patients, and endogenous subclinical hyperthyroidism might be regarded as a mild form of hyperthyroidism.

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Introduction

Subclinical hyperthyroidism is characterised by reduced serum thyrotrophin (TSH) levels despite free thyroxine (T₄) and tri-iodothyronine (T₃) estimates within the reference range, in subjects with no obvious symptoms of hyperthyroidism. This syndrome has emerged in the last 5–10 years with the availability of increasingly sensitive TSH assays, making it possible to measure reduced TSH levels in hyperthyroidism. It is currently debated whether this is solely the pituitary sensing slightly increased amounts of thyroid hormones at the tissue level (resulting in reduced TSH

secretion), or whether this is a more widespread phenomenon. If so, discrete organ dysfunction due to mild thyroid hyperfunction might lead to premature precipitation of other diseases.

Several studies have been performed recently addressing this question, but when interpreting the results one must realise that two distinct entities of subclinical hyperthyroidism exist, endogenous and exogenous. The latter is due to deliberate treatment with TSH-suppressive doses of exogenous levothyroxine (L-T₄), typically in patients with thyroid cancer or goitre. However, L-T₄ suppressive treatment most often results in raised serum free T₄ estimates, and more seldom

raised serum free T_3 estimates as well, and the patients often suffer mild hyperthyroid symptoms. Therefore, many of these patients on $L-T_4$ suppressive treatment are in fact mildly hyperthyroid, and do not fulfil the criteria of subclinical hyperthyroidism.

Cardiac function and cardiovascular haemodynamics have been studied extensively in overt hyperthyroidism (1, 2). One of the earliest cardiovascular responses to thyroid hormone administration in humans is a decrease in systemic vascular resistance (SVR) (1, 2), and SVR is typically reduced by more than 50% in overt hyperthyroid patients (3). This is probably due to a direct effect of thyroid hormones on vascular smooth muscle cells causing relaxation (2, 4), and an effect mediated by adrenergic receptors, since beta-adrenergic blockade blunts the thyroid hormone-mediated decrease in SVR (5). Cardiac output (CO) increases in hyperthyroid patients, secondary to the reduction in SVR, but also due to a direct inotropic and chronotropic effect of thyroid hormones on the heart (1, 2, 6). This is probably due to thyroid hormone-mediated effects on cardiac myocyte gene expression, including the beta-adrenergic receptor (1, 2), as well as a direct non-genome effect of thyroid hormones on the cells (7, 8). The results are increased diastolic relaxation, increased contractility and increased heart rate (5, 8) causing an elevation in cardiac output.

Endogenous subclinical hyperthyroidism is typically seen in patients with a multinodular goitre, and the natural history is that of slow progression towards overt hyperthyroidism, with a rate of approximately 4–5% per year (10). At present, there is no consensus as to when to treat these patients, since in general they feel well.

We have evaluated several haemodynamic parameters and the plasma levels of catecholamines in subjects with endogenous subclinical hyperthyroidism and in a group of overt hyperthyroid patients. The study was performed before and after treatment (aiming at normalisation of serum TSH in the subclinical group and euthyroidism in the hyperthyroid group).

Materials and methods

Two groups of patients were studied. The first group consisted of six women with endogenous subclinical hyperthyroidism. They all, by definition, had repeated levels of TSH below 0.15 mU/l and free T_4 and T_3 indices (serum T_4 multiplied by the T_3 -uptake test, FT4I and FT3I respectively) within the reference range: FT4I: 55–150 arbitrary units; FT3I: 0.80–2.40 arbitrary units. Their mean age was 64 years (47–81 years). All presented with a multinodular goitre (as evaluated by scintigraphy and ultrasound) with mild compression symptoms, but were otherwise healthy, and received no medicine. They were treated with

radioiodine (^{131}I) (296–740 MBq) on an outpatient basis, with the aim of reducing thyroid volume and thus compression symptoms. Studies were performed before treatment, and when TSH had normalised, after a mean interval of 224 days (range 131–443 days).

The second group consisted of nine patients (eight women and one man; mean age 45 years (range 26–65 years)) with overt hyperthyroidism. Based on scintigraphy and ultrasound, two had a multinodular goitre and seven a diffuse goitre. Six of the patients with diffuse goitre were treated with carbimazole, whereas the other three were treated with radioiodine (222–296 MBq).

The second evaluation was performed after a mean interval of 276 days (range 132–481 days), when the patients were euthyroid.

All subjects were studied between 0900 and 1000 h in the post-absorptive state, after half-an-hour rest in the supine position. Blood samples were drawn at the end of the study period. The subjects were studied in the supine position, and after three min in the 60 degrees head-up tilted position (11, 12). Blood pressure was measured by a Dinamap 1845 oscillometry sphygmomanometer (13).

Stroke volume (SV) was measured by impedance cardiography (Medis impedance cardiograph; Medis GmbH, Ilmenau, Germany) (14). This method is based on the assumption that the rate of changes in thoracic impedance to alternating high frequency current reflects dynamic changes in blood volume of the ascending aorta (15, 16). An empirical equation has been derived relating the maximal rate of change in the transthoracic impedance to the left ventricular stroke volume (17), and the validity of this equation has been verified by several studies (for review see 11).

We have previously compared this method with both the isotope and thermodilution techniques (11). Absolute values of CO using these techniques correlated closely having a regression equation $y = 0.68x + 1.48$ (CO measured by impedance cardiography (y), and by thermodilution (x)). This means that impedance cardiography slightly overestimates low absolute values of CO and slightly underestimates high values. In hyperthyroid patients, we were looking for increased values of CO, a task made more difficult due to the tendency to underestimate high CO values. In contrast, changes over time correlated closely between the two methods ($y = 1.00x + 0.003$) (11), and the precision of the measured CO using impedance cardiography was high, within-day and day-to-day variation being 5% and 7% respectively (11). Furthermore, the method is observer independent. Thus, since the method is non-invasive it is well suited for repeated measurements. Consequently, the present study is primarily comparative, i.e. looking at changes due to treatment, and we did not include a control group.

Simultaneous tracings of ECG and the first derivative of the transthoracic impedance (dZ/dt) were obtained.

The ECG and dZ/dt were obtained by eight ordinary, self-adhesive, low-resistance ECG electrodes as described by Kubicek *et al.* (17). The electrodes were placed in pairs on the lateral part of the body, one pair on the root of the neck, another pair approximately five cm more proximal, a third pair on the lower part of the thorax, at a level corresponding to processus xiphoidaeus, and finally a fourth pair approximately five cm more distal. The pairs of electrodes most proximal and distal (outer electrodes) delivered alternating current of 4 mA and 100 kHz, whereas the inner electrodes picked up the voltage change across the thorax and this signal was processed by the impedance cardiography calculating dZ/dt . Stroke volume was calculated from the dZ/dt signal using the formula derived by Kubicek *et al.* (17):

$$SV = (dZ/dt) \cdot r \cdot (L/Z_0)^2 \cdot T$$

where dZ/dt is the height of the maximal (negative) deflection of the first derivative of transthoracic impedance (in $\text{ohm} \cdot \text{s}^{-1}$), r is the specific resistivity of the blood ($150 \text{ ohm} \cdot \text{cm}$), L is the distance (cm) between the inner pair of electrodes, Z_0 is the mean transthoracic impedance (ohm) and T is the left ventricular ejection time (s) as measured from the intersection between the upstroke of dZ/dt and the baseline to the high frequency vibrations of the aortic component of the second heart sound. SV was calculated as the mean of 500 consecutive measurements.

SV was measured both in the supine position and in the head-up tilted position. At the same time continuous blood pressure (BP) and heart rate (HR) recording took place using oscillometry. CO was calculated as $CO = SV \cdot HR$, and the cardiac index (CI) as CO/m^2 surface area (as calculated from height and weight). Mean arterial pressure (MAP) was measured by the oscillometric BP measurement (13). Systemic vascular resistance (SVR) was then calculated as $SVR = MAP/CO$ ($\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}$). Pulse pressure (PP) was calculated as $PP = (\text{systolic} - \text{diastolic BP})$, and finally SV/PP was calculated as an index of central (aortic) compliance.

Blood samples were obtained before and during L-T₄ treatment and both samples from each patient were measured in the same assays. Serum levels of T₄, T₃,

and TSH were measured by methods from Wallac Oy, Helsinki, Finland (AutoDelphia T₄, T₃ and human TSH), whereas T₃-uptake test was measured by the Coat-a-Count T₃ Uptake test (Diagnostic Product Corporation, Los Angeles, CA, USA). The analytical sensitivity of the TSH assay was 0.001 mU/l, whereas the functional sensitivity (i.e. the lowest level of serum TSH having an interassay coefficient of variation of 20% or less) was 0.005 mU/l. Thus, the lowest measurable TSH concentration was defined as 0.005 mU/l. Plasma norepinephrine and epinephrine were measured by HPLC (18, 19). Intra-assay coefficients of variation were 6% and 14% respectively.

Informed consent was obtained from all patients under study, and the study protocol was approved by the local ethical committee.

Statistical analysis

A paired *t*-test was used for comparing data before and during L-T₄ substitution, Spearman's Rank correlation was used for correlating data to serum TSH levels, whereas linear regression was used for other tests for covariance. Significance was accepted when $P < 0.05$.

Results

Thyroid parameters (Table 1)

By definition, all patients with subclinical hyperthyroidism had serum TSH levels below 0.15 mU/l, and FT4I and FT3I within the normal range. TSH concentrations were measurable in sera from all subjects with subclinical hyperthyroidism (range 0.006–0.090 mU/l), whereas TSH was low and unmeasurable in 4/9 patients with overt hyperthyroidism (range <0.005–0.024 mU/l). After treatment, TSH levels normalised, and FT4I and FT3I decreased 23 and 13% respectively ($P < 0.05$).

Haemodynamic parameters – subclinical hyperthyroidism (Table 2)

Treatment of the patients resulted in the following statistically significant changes: 19% reduction in CO

Table 1 Serum levels of thyroid hormone parameters in subclinical and overt hyperthyroidism before and after treatment. Results are means $\pm$ s.d. (range).

	Subclinical hyperthyroidism ($n = 6$)		Overt hyperthyroidism ($n = 9$)	
	Before	After	Before	After
TSH (mU/l)	0.027 $\pm$ 0.036 (0.006–0.090)	0.660 $\pm$ 0.294** (0.280–1.120)	0.011 $\pm$ 0.007	1.112 $\pm$ 1.456
FT4I (arbitrary units)	111 $\pm$ 21	86 $\pm$ 16*	301 $\pm$ 108	98 $\pm$ 39
FT3I (arbitrary units)	2.08 $\pm$ 0.19	1.81 $\pm$ 0.31*	9.03 $\pm$ 6.06	1.96 $\pm$ 0.53

* $P < 0.05$, ** $P < 0.01$, values before compared with after treatment.

Table 2 Haemodynamic parameters in patients with subclinical hyperthyroidism. Results are means $\pm$ s.d., $n = 6$.

	Supine		Upright	
	Before	After	Before	After
HR (beats/min)	74 $\pm$ 8	66 $\pm$ 8**	82 $\pm$ 5†	73 $\pm$ 8*
CO (l/min)	6.93 $\pm$ 2.15	5.58 $\pm$ 1.94*	5.32 $\pm$ 1.41†††	4.37 $\pm$ 0.89
CI (l/min/m ²)	4.05 $\pm$ 1.34	3.23 $\pm$ 1.22**	3.08 $\pm$ 0.97†††	2.55 $\pm$ 0.60
MAP (mmHg)	96.9 $\pm$ 4.0	98.9 $\pm$ 7.4	102.0 $\pm$ 10.4	102.7 $\pm$ 10.3
SVR (dyn*s*cm ⁻⁵)	1223 $\pm$ 400	1585 $\pm$ 594**	1653 $\pm$ 591††	1972 $\pm$ 542
SV/PP (ml/mmHg)	1.55 $\pm$ 0.62	1.37 $\pm$ 0.49	1.29 $\pm$ 0.48	1.13 $\pm$ 0.35

* $P < 0.05$, ** $P < 0.02$, values before compared with values after treatment.

† $P < 0.05$, †† $P < 0.02$, ††† $P < 0.01$, values before in the upright position compared to values before in the supine position.

($P < 0.05$), 11% reduction in HR ($P < 0.02$), and 30% increase in SVR ($P < 0.02$) in the supine position, whereas in the upright position only HR changed significantly due to treatment ($P < 0.05$). MAP and SV/PP did not change. Head-up tilting resulted in 11% increase in HR ($P < 0.05$), 23% reduction in CO ($P < 0.01$), and a 35% increase in SVR before treatment ($P < 0.02$), with no change in this pattern after treatment. Neither TSH nor free thyroid hormone estimates correlated to any of the haemodynamic parameters, nor to changes induced by treatment.

Haemodynamic parameters – overt hyperthyroidism (Table 3)

Treatment of the hyperthyroid state resulted in pronounced and statistically significant changes: 17% reduction in HR, 25% reduction in CO, and 46% increase in SVR in the supine position, with no change in MAP or SV/PP. Similar trends were seen in the upright position. Head-up tilting only resulted in one statistically significant change – 8% increase in MAP. Neither TSH nor free thyroid hormone estimates correlated to any of the haemodynamic parameters, nor to changes induced by treatment.

Haemodynamic parameters – subclinical and overt hyperthyroidism as one group

Taking the two groups together ($n = 15$), the following correlations were found: the lower the pretreatment

TSH level the higher was the CO ($r = -0.64$; $P = 0.030$), the lower was the SVR ($r = 0.54$; $P = 0.048$), and the higher was the SV/PP ($r = -0.83$; $P = 0.0046$), all in the upright position. Further, the higher the FT3I, the higher was the CO ($r = 0.59$; $P = 0.020$), the lower was the MAP ($r = -0.58$; $P = 0.025$), the lower was the SVR ($r = -0.55$; $P = 0.032$), and the higher was the SV/PP ($r = 0.52$; $P = 0.047$) (all in the supine position).

Catecholamines (Table 4)

Plasma epinephrine did not change, whereas norepinephrine increased significantly in the overt hyperthyroid group.

Discussion

Treatment of subclinical hyperthyroidism, in this case by radioiodine resulting in normalised serum TSH levels and thus complete euthyroidism, resulted in a substantial and significant reduction in HR (11%), CO (19%) (and CI), and a concomitant increase in SVR (30%). These changes were qualitatively very similar to those seen in overt hyperthyroidism, although quantitatively less pronounced. We only studied a small patient sample, since we were careful to include only those with free T₄ and T₃ estimates within the normal reference range, and those who were absolutely free of symptoms especially concerning cardiovascular and lung disease. Nevertheless, our data strongly

Table 3 Haemodynamic parameters in patients with overt hyperthyroidism. Results are means $\pm$ s.d., $n = 9$.

	Supine		Upright	
	Before	After	Before	After
HR (beats/min)	90 $\pm$ 10	75 $\pm$ 8***	98 $\pm$ 10	86 $\pm$ 10*
CO (l/min)	11.42 $\pm$ 2.78	8.53 $\pm$ 2.34*	9.79 $\pm$ 1.36	7.26 $\pm$ 1.29***
CI (l/min/m ²)	6.57 $\pm$ 2.04	4.76 $\pm$ 1.09*	5.63 $\pm$ 0.74	4.04 $\pm$ 0.54***
MAP (mmHg)	88.9 $\pm$ 9.0	93.3 $\pm$ 11.8	96.3 $\pm$ 7.9†	98.1 $\pm$ 6.4
SVR (dyn*s*cm ⁻⁵)	664 $\pm$ 207	967 $\pm$ 419**	800 $\pm$ 135	1122 $\pm$ 259***
SV/PP (ml/mmHg)	2.00 $\pm$ 0.38	2.05 $\pm$ 0.70	1.74 $\pm$ 0.50	1.71 $\pm$ 0.47

* $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$, values before compared with values after treatment.

† $P < 0.01$, values before in the upright position compared with values before in the supine position.

Table 4 Plasma catecholamines in subclinical and overt hyperthyroidism, before and after treatment. Results are means $\pm$ s.d.

	Subclinical hyperthyroidism (<i>n</i> = 6)		Overt hyperthyroidism (<i>n</i> = 9)	
	Before	After	Before	After
Epinephrine (nmol/l)	0.344 $\pm$ 0.092	0.348 $\pm$ 0.041	0.357 $\pm$ 0.082	0.430 $\pm$ 0.100
Norepinephrine (nmol/l)	1.88 $\pm$ 1.01	1.86 $\pm$ 0.55	1.23 $\pm$ 0.17	1.79 $\pm$ 0.60*

**P* < 0.05, compared with before treatment.

suggest that patients with endogenous subclinical hyperthyroidism do have some degree of increased HR, CO and decreased SVR, i.e. the cardiovascular system senses some degree of hyperthyroidism at the tissue level.

The degree of tissue hyperthyroidism as expressed by free thyroid hormone estimates did not correlate to the haemodynamic parameters. This is probably mainly due to small sample size, but taking all 15 patients studied together, FT3I correlated significantly as follows: the more severe the hyperthyroidism the higher the CO, and the lower the MAP and the SVR in the untreated state. Also SV/PP correlated positively to FT3I, suggesting increased central, aortic compliance. Similar correlations were found using TSH instead of FT3I. This demonstrates a close relationship between thyroid function as expressed by both FT3I and TSH, and the cardiovascular response.

Few studies have previously looked at the cardiovascular response in endogenous subclinical hyperthyroidism. Twenty-four-hour Holter-tape registrations have not disclosed increased frequency of arrhythmias but average heart rate has been found increased (20) or unaltered (21). In a recent study by Biondi *et al.* (20) patients with nodular goitre and endogenous subclinical hyperthyroidism had increased left ventricular mass, and systolic function was increased as measured by echocardiography. Finally, Sawin *et al.* (22) suggested that reduced serum TSH levels in otherwise healthy subjects over the age of 60 years (not receiving L-T₄) tripled their risk of developing atrial fibrillation over a period of ten years.

Patients on suppressive L-T₄ therapy due to thyroid cancer or goitre seem to have increased left ventricular mass (23–25), increased heart rate and left ventricular ejection fraction (24). However, a significant proportion of these patients probably had free T₄ estimates above the reference range. Thus several of these patients might, in fact, have been mildly hyperthyroid, therefore not fulfilling the criteria for subclinical hyperthyroidism. In line with this, a recent study performed with careful individual dose tailoring of suppressive L-T₄, resulted in an improvement of several minor haemodynamic changes such as increased left ventricle mass (25).

Subclinical hyperthyroid subjects present with free T₄ and T₃ estimates within the reference range, but

with reductions in TSH levels. The question is whether reduced TSH has any pathophysiological implications. Carr *et al.* (26) studied hypothyroid patients on L-T₄ substitution and demonstrated that serum TSH levels were much more sensitive than serum T₄ and T₃ levels to small increases (and decreases) in the L-T₄ dose (approximately 20%). In our study, treatment of subclinical hyperthyroid patients resulting in a normalisation of TSH levels also caused significant decreases in both FT4I and FT3I, although these were within the normal range. Therefore, reduced TSH levels probably are relevant in terms of signalling enhanced thyroid function, despite free T₄ and T₃ estimates within the normal range.

In line with this, the skeleton also seems to be influenced in patients with endogenous subclinical hyperthyroidism in a way which suggests slight thyroid hormone excess at the tissue level: postmenopausal women with endogenous subclinical hyperthyroidism due to a multinodular goitre have reduced bone mass in comparison to women with normal TSH (27). Furthermore, we have shown that treatment of such patients with radioiodine with the aim of normalising serum TSH, results in increased bone mass as compared with those not treated (28).

The cardiovascular response due to tilting is a counterregulatory phenomenon serving to avoid a dramatic drop in blood pressure and CO, and thereby fainting. No qualitative or quantitative abnormalities were seen before and after treatment in any of the groups studied. This implies that despite the pronounced haemodynamic changes, baroreceptor function remained intact.

Plasma norepinephrine increased due to normalisation of the thyroid function in the group with overt hyperthyroidism, suggesting reduced values in the untreated state. This is in agreement with previous studies, demonstrating slightly reduced levels in hyperthyroidism (29) as well as in patients on suppressive L-T₄ treatment (with exogenous subclinical hyperthyroidism) (25). Thyroid hormones and catecholamines both enhance thermogenesis, and in hyperthyroidism there is less need for the calorogenic action of catecholamines, resulting in reduced production (30). In contrast, epinephrine levels remained unchanged during treatment, which is in accordance with unchanged adrenal medullary activity in hyperthyroidism (30).

We conclude that treatment of endogenous subclinical hyperthyroidism resulting in normalisation of TSH, changes the haemodynamics in ways compatible with some degree of excess tissue exposure to thyroid hormones in the untreated state in the heart and the vascular system. These data favour more aggressive treatment of these patients, and endogenous subclinical hyperthyroidism might rather be regarded as a mild form of hyperthyroidism.

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