CLINICAL STUDY

Power spectral analysis of heart rate in hypothyroidism

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Abstract

Objective: The aim of the present study was to evaluate the impact of hypothyroidism on the autonomic regulation of the cardiovascular system by analysing separately sympathetic and parasympathetic influences on the heart.

Design: In seven newly diagnosed untreated hypothyroid patients we analysed power spectral density of heart rate cyclic variations at rest, while lying, and while standing. The same protocol was repeated after the induction of stable euthyroidism by levothyroxine (L-T₄) treatment. The results were also compared with those obtained from seven age-, sex- and body mass index-matched control subjects.

Methods: Heart rate variability was evaluated by autoregressive power spectral analysis (PSA). This method allows reliable quantification of low frequency (LF) and high frequency (HF) components of the heart rate power spectral density. These are considered to be under mainly sympathetic and purely parasympathetic control respectively. In addition, heart rate variations during deep breathing, lying to standing, and Valsalva's manoeuvre were assessed.

Results: PSA showed a sharp reduction in the HF (parasympathetic) component in hypothyroid subjects compared with controls (lying, 29.4 ± 5.4 vs 47.7 ± 6.3 normalized units (NU) (means $\pm$ S.E.M.), $P < 0.05$; standing, 14.0 ± 3.5 vs 32.1 ± 3.6 NU, $P < 0.005$). Conversely, the LF (mainly sympathetic) component was higher in hypothyroid subjects than in controls (lying, 61.6 ± 6.4 vs 45.4 ± 6.7 NU; standing, 71.7 ± 8.0 vs 53.1 ± 5.6 NU), this difference being significant in the standing position. Hence, the LF/HF ratio, which is considered an index of sympathovagal balance, was increased in hypothyroid subjects while both lying (2.75 ± 0.6 vs 1.16 ± 0.3 ; $P < 0.05$) and standing (10.0 ± 3.7 vs 1.85 ± 0.3 ; $P < 0.02$). Total heart rate variability, expressed as total power spectral density, was lower in hypothyroid patients than in control subjects, this difference being significant in the lying position (574 ± 126 vs 2302 ± 994 ms², $P < 0.05$). In patients re-examined after L-T₄ therapy, complete normalization of cardiovascular parameters was observed (LF/HF ratio, lying, 1.26 ± 0.4 ; standing, 2.56 ± 0.8 , both $P < 0.01$ vs baseline values). The response to conventional cardiovascular autonomic tests was not significantly different between hypothyroid patients and healthy controls, and did not change in patients after therapy.

Conclusions: These results suggest that, contrary to the clinical picture, thyroid hormone deficiency is associated with an increased sympathetic influence on the autonomic cardiovascular system. The changes in sympathetic function could be explained by a secondary adaptation to an altered cardiovascular responsiveness.

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Introduction

Thyroid hormones have prominent effects on the heart and the peripheral vascular system by direct action on these tissues and by indirect influences, at least in part due to changes at the autonomic nervous system level (1, 2). It is generally considered that hypothyroidism basically influences the sympathetic nervous system in a direction opposite to that of thyrotoxicosis. This is indicated by clinical features suggesting that the

sympathetic system is overactive in hyperthyroidism and hypoactive in hypothyroidism. However, studies examining production, release, degradation and plasma levels of catecholamines have established that catecholamine secretion is normal or even reduced in hyperthyroidism (3, 4). In hypothyroidism, in contrast to the overall depression of adrenergic responses at cardiac and peripheral level, plasma noradrenaline concentrations are increased (5, 6). On the other hand, cardiovascular homeostasis is also influenced

by the modulatory effect of the autonomic nervous system and abnormalities of cardiac parasympathetic nervous system activity have also been shown to be associated with thyroid hormone deficiency (7). Other data also suggest an enhanced central sympathetic output in hypothyroidism, reaching virtually every tissue (8–11). Elevation of the diastolic blood pressure is a common feature in patients with hypothyroidism, even though the mechanism of increased blood pressure is not known (12). Alterations in autonomic nervous functions, as well as an acceleration in the structural change of vascular tissue or extracellular fluid volume expansion, have been proposed as possible mechanisms (13).

To date, few clinical studies are available dealing with the potential impact of hypothyroidism on cardiovascular autonomic balance. In the present study, we achieved a detailed evaluation of cardiovascular autonomic function in hypothyroid subjects before and after the restoration of euthyroidism by synthetic thyroxine (L-T₄) treatment. Traditional cardiovascular autonomic tests were combined with a more advanced approach based on the power spectral analysis (PSA) of heart rate variations.

Methods

Subjects

The study sample comprised seven newly diagnosed, untreated hypothyroid female subjects (mean age $\pm$ S.E.M., 52.1 ± 5.3 years) with a body mass index ranging from 21.3 to 24.1 kg/m² (23.1 ± 0.9). Hypothyroidism was diagnosed clinically and confirmed by high serum thyrotrophin (TSH) levels and low thyroid hormone levels (TSH, 55.5 ± 9.5 mU/l, free T₄ (FT₄), 3.1 ± 0.4 pmol/l). All patients were affected by autoimmune thyroid disease, as indicated by the measurement of thyroid antibodies. These patients were studied both at baseline and after 12–18 months of L-T₄ treatment to achieve stable euthyroidism; this was confirmed by the normalization of thyroid hormone levels (TSH, 1.59 ± 0.2 mU/l, free T₄, 15.0 ± 0.3 pmol/l).

None of the subjects had a history, signs, or symptoms of pre-existing cardiovascular diseases or evidence of electrocardiogram alterations. Patients were free of other diseases and were not taking any medications. Seven healthy control subjects, matched by age (52.0 ± 5.2), sex and body mass index (23.3 ± 0.8), were also examined.

Experimental procedures

The autonomic cardiovascular function was assessed by a computerized system as previously described (14). Cardiovascular reflex tests were performed following Ewing's criteria (15). A personal computer collected,

stored and processed RR intervals and blood pressure (systolic, diastolic and mean) analysing heart rate and blood pressure variations during (1) lying to standing, (2) deep breathing and (3) Valsalva's manoeuvre. The results are expressed as the mean values from three successive tests.

PSA was carried out during 10-min periods of RR interval acquisition. Patients with ectopic beats (>1 per min) were excluded. Both supine and standing readings were taken after at least 5 min of rest in each posture. All studies were carried out early in the morning in a quiet room.

The evaluation of the heart rate PSA was calculated using an autoregressive mathematical model. The conceptual step of autoregressive modelling for PSA and the interpretation of spectral components have been described elsewhere (14). Briefly, this model allows calculation during a relatively short sequence of RR intervals, giving an estimation of the main power densities and eliminating irrelevant factors and negligible components. The RR interval series in normal subjects can be broken down, in terms of cyclic variations around the mean, into three major spectral components that characteristically fall into three principal frequency bands. The low frequency band (LF), between 0.03 and 0.17 Hz, normally has a mean central frequency around 0.12 Hz, and is thought to represent mainly sympathetic activity and, to a much lesser extent, parasympathetic activity, as well as probably other physiological reflex mechanisms, such as baroreceptor activity and peripheral vasomotor tone; it is strongly inhibited by beta-blockers and enhanced in many situations that stimulate sympathetic activity (standing, exercise and mental stress) (16). The high frequency band (HF), between 0.17 and 0.36 Hz, is synchronized with breathing phases and closely associated with vagal activity; it is enhanced by vagomimetic drugs and is totally abolished by atropine (17–19). Finally, the very low frequency band (<0.02 Hz) is not under autonomic control, but probably under the influence of the renin–angiotensin system or other possible hormonal mechanisms (19). This component was not taken into account in this study because our evaluation focused on efferent vagal–sympathetic components.

PSA of heart rate variations was carried out in both lying and standing positions to highlight the influence of parasympathetic and sympathetic pathways respectively (18). In normal subjects, passive tilt or, more simply, standing up, is accompanied by an increase in the LF and a decrease in the HF component of RR variability (16–18). The power of each component was measured in normalized units (NU), as these give a better estimation of the balance between the various components. These were obtained by dividing the absolute power of each spectral component by the total variance of the RR intervals, from which the power of the continuous component (here defined as the

power density with a frequency between 0 and 0.02 Hz) was removed (16).

Assays

Serum fT₄ and TSH were measured by an immuno-enzymatic fluorescent revelation method (Baxter Diagnostic, Miami, FL, USA).

Statistical analysis

Differences between hypothyroid patients before and after L-T₄ treatment were analysed using the Wilcoxon test for paired samples; the Mann–Whitney U-test and the linear correlation test were used for all other analyses. $P < 0.05$ or less was considered to indicate significance. Data are expressed as the mean $\pm$ S.E.M.

Results

In the 10-min electrocardiogram recordings, both lying and standing, mean RR interval values were similar in hypothyroid subjects before and after treatment as well as in controls (Table 1).

Total heart rate variability, expressed as total power spectral density (PSD), was significantly lower, in the lying position, in hypothyroid patients compared with control subjects (Table 1). HF component, expressed in normalized units, was significantly lower for both lying and standing in hypothyroid patients compared with control subjects. Conversely, the LF component was higher in hypothyroid subjects than in controls, this difference being significant in standing position. Moreover, in hypothyroid patients re-examined after achieving stable euthyroidism, HF showed, in the standing position, a significant increase and LF showed, both in lying and standing positions, a significant decrease over

pre-treatment; in re-evaluated patients, density band values were similar to control subjects (Table 1, Figs 1 and 2).

Hence, the LF/HF ratio, which is thought to express the sympathetic vs parasympathetic balance, was higher in hypothyroid subjects compared with controls, both on lying (2.75 ± 0.6 vs 1.16 ± 0.3 , $P < 0.05$) and on standing (10.0 ± 3.7 vs 1.85 ± 0.3 , $P < 0.02$). In patients re-examined after T₄ therapy, complete normalization of LF/HF ratio was observed (2.75 ± 0.6 vs 1.26 ± 0.4 , $P < 0.01$ and 10.0 ± 3.7 vs 2.56 ± 0.8 , $P < 0.01$ respectively) (Table 1, Figs 1 and 2). Mean systolic and diastolic blood pressure values were slightly higher (albeit with no statistical significance) in hypothyroid subjects compared with controls and the re-examined patients (147 ± 10 vs 130 ± 9 and 133 ± 7 ; 85 ± 5 vs 79 ± 6 and 85 ± 3 mmHg respectively). The response to conventional cardiovascular autonomic tests did not show significant differences between hypothyroid patients, healthy controls and re-examined patients after therapy (Table 2).

Discussion

Clinical characteristics of hypothyroidism are essentially diametrically opposed to those associated with hyperthyroidism. Resting heart rate is either normal or slightly low, cardiac output is decreased and systemic vascular resistance is high (1, 2). Thyroid hormone replacement therapy is generally effective and beneficial in relieving symptoms and signs. This evidence supports the hypothesis that thyroid hormone deficiency causes decreased sympatho-adrenergic activity. However, contrary to the clinical picture and in contrast to the overall depression of adrenergic response at the peripheral level, evidence suggests that the sympathetic neural out-flow tends to be elevated in many tissues

Table 1 Mean values ($\pm$ S.E.M.) of lying and standing heart rate power densities in hypothyroid patients (before and after treatment) and control subjects.

	RR intervals (ms)	Total PSD (ms ²)	LF (ms ²)	LF (NU%)	HF (ms ²)	HF (NU%)	LF/HF (NU ratio)
<i>Lying</i>							
Normal (N) ($n = 7$)	865 ± 10	2302 ± 994	476 ± 178	45.4 ± 6.7	852 ± 488	47.7 ± 6.3	1.16 ± 0.3
Hypothyroid (H) ($n = 7$)	856 ± 36	574 ± 126	164 ± 27.4	61.6 ± 6.4	92 ± 25.6	29.4 ± 5.4	2.75 ± 0.6
Euthyroid (E) after therapy ($n = 7$)	817 ± 38	952 ± 406	211 ± 105	36.3 ± 9.1	267 ± 168	34.6 ± 4.8	1.26 ± 0.4
N vs H, P	NS	<0.05	NS	NS	<0.05	<0.05	<0.05
H vs E, P	NS	NS	NS	NS	NS	NS	<0.01
N vs E, P	NS	NS	NS	NS	NS	NS	NS
<i>Standing</i>							
Normal (N) ($n = 7$)	755 ± 24	1754 ± 636	558 ± 215	53.1 ± 5.6	279 ± 124	32.1 ± 3.6	1.85 ± 0.3
Hypothyroid (H) ($n = 7$)	754 ± 21	477 ± 97	142 ± 29.8	71.7 ± 8.0	46 ± 22.4	14.0 ± 3.5	10.0 ± 3.7
Euthyroid (E) after therapy ($n = 7$)	743 ± 27	689 ± 222	136 ± 49.7	45.8 ± 6.9	116 ± 46.3	28.3 ± 6.0	2.56 ± 0.8
N vs H, P	NS	NS	<0.02	<0.05	<0.01	<0.005	<0.02
H vs E, P	NS	NS	NS	<0.01	<0.05	<0.01	<0.01
N vs E, P	NS	NS	<0.05	NS	NS	NS	NS

Figure 1 Individual values of lying and standing low frequency (LF) and high frequency (HF) components, as well as of the LF/HF ratio, in control and hypothyroid subjects (before and after L-T₄ treatment). The horizontal bars indicate the respective mean values. (○) Control subjects, (●) hypothyroid patients.

in hypothyroidism (8–11). Moreover, high plasma noradrenaline levels, which are considered to be the expression of an increased sympathetic tone, are an almost universal finding in hypothyroid patients. On the other hand, the responsiveness to endogenous catecholamines is reduced, suggesting a desensitization at the receptor and/or post-receptor level (20, 21). In addition, it is of interest to note that as in hypothyroid cardiomyopathy, hypertrophic cardiomyopathy (22), although a different disorder, shows some similarities regarding autonomic imbalance associated with pre-synaptic and possible post-synaptic impairment. For example, evidence suggests that both are characterized by hypersympathetic tone and high catecholamine levels, suggesting possible catecholaminergic desensitization.

Recently, the study of heart rate variability has been considered a useful tool in the detection of autonomic activity in the cardiovascular system in both experimental and clinical settings. PSA of RR length variations has been shown to be a good approach in the attempt to quantify sympathetic and parasympathetic

components in the autonomic regulation of the heart. Although no difference in basal heart rate was observed, as often reported in hypothyroidism (1), using this method we found that our hypothyroid patients, compared with control subjects, showed a reduction in HF values and, moreover, an increase in LF component, resulting in an increased LF/HF ratio. As the HF power is considered to be strictly under vagal activity, our findings are in keeping with previous observations by Inukai *et al.* (7), who found significant reductions in RR interval variations during breathing cycles in patients with severe hypothyroidism, suggesting abnormalities of cardiac parasympathetic nervous activity. It is of interest that in our previous report (23), we found that in the opposite clinical condition (i.e. hyperthyroidism), a hypersympathetic tone occurs as well to some extent. In the latter, however, it appears to be wholly due to reduced vagal activity, which is responsible for a shift in the sympathovagal balance towards sympathetic predominance. In this context, we hypothesize that the decreased vagal activity found in hyperthyroidism could be attributed to a reduction

Figure 2 Power spectral density of the cyclic variations of heart rate in a hypothyroid patient before (above) and after (below) L-T₄ treatment. Note the reduction in the LF band (0.03–0.17 Hz) and the increase in the HF band (0.17–0.36 Hz).

Table 2 Mean values ($\pm$ S.E.M.) of responses to cardiovascular autonomic tests in hypothyroid patients (before and after treatment) and control subjects.

	Deep breathing (beats/min)	Valsalva's manoeuvre (Valsava ratio)	Lying to standing (RR 30/15)
Normal (N) ($n = 7$)	24.5 ± 2.1	1.69 ± 0.03	1.19 ± 0.04
Hypothyroid (H) ($n = 7$)	17.6 ± 3.1	1.60 ± 0.02	1.16 ± 0.03
Euthyroid (E) after therapy ($n = 7$)	20.0 ± 3.5	1.62 ± 0.03	1.18 ± 0.03
N vs H, P	NS	NS	NS
H vs E, P	NS	NS	NS
N vs E, P	NS	NS	NS

in diastolic arterial pressure related to the peripheral vasodilatation and probably reflects vagal withdrawal without concurrent sympathetic excitation. On the other hand, hypothyroid subjects showed both a reduction in HF and an absolute increase in the LF component of PSA. The notion that LF RR interval spectral power is related quantitatively to sympathetic–cardiac nerve traffic and tracks baroreflex-mediated changes in sympathetic nerve activity, however, has recently been the subject of heated discussion (24). Some studies suggest that the LF component is a quantitative marker of sympathetic modulation (especially when expressed in normalized units) (16, 25), others that it is a parameter that includes both sympathetic and vagal influences (19, 26). Consequently, the LF/HF ratio, rather than the LF power *per se*, is considered by some investigators to reflect the sympathetic modulation and mirror sympathetic vagal balance (18). In our patients we showed that the LF/HF ratio, in addition to the LF component, was higher in the hypothyroid state, in particular when patients are in the standing position, i.e. when the sympathetic drive is more activated. Moreover, the evidence that thyroxine therapy in our hypothyroid patients appears to restore the efferent vagal activity and reduces (rather than increases as generally supposed) the sympathetic drive on the heart, also supports the view of an increased ratio of sympathetic to vagus nerve traffic to the heart in hypothyroidism. Furthermore, it has long been known that the thyroid hormone has profound effects on systemic vascular resistance and may act as a vasodilator agent with a direct effect on the contractility of the vascular smooth muscle or endothelial cells, either alone or in concert with adrenergic, cholinergic and other vasoactive agents (27). In this case it could be argued that the increased vasomotor tone occurring in hypothyroidism influences, through baroreceptor modulation, the heart rate variability. Consistent with hypersympathetic tone on peripheral vasculature in these subjects (9, 11, 28), striking skin and subcutaneous tissue vasoconstriction were reported in hypothyroid patients (11, 27). Our findings are also consistent with the previous observations of Fagius *et al.*, who reported a higher level of muscle nerve sympathetic activity (MSA) in hypothyroidism (9). In this respect, it is of interest that the simultaneous evaluation of spectral measures of MSA and RR interval variability have recently been put forward as common central mechanisms governing both parasympathetic and sympathetic cardiovascular modulation (29). Moreover, it is interesting to note that although LF/HF values did not differ statistically between hypothyroid patients after treatment and controls, these latter showed higher total power values. This suggests that hypothyroid patients, although adequately treated with L-T₄, are still potentially subject to vagal failure of the heart, as a possible pharmacological effect. In hypothyroidism, as a result of reduced responsiveness

to catecholamines, the contractility and functional reserve of the heart are severely compromised (1, 2, 30). In a previous study, Christensen suggested that the reduced cardiac output in hypothyroid individuals initially causes a tendency to hypotension leading to a compensatory increase in noradrenaline release (31). In this context, the evidence of increased sympathetic stimulation of the heart in hypothyroidism, in spite of the clinical impression of a low adrenergic function, appears to confirm an adaptation to the altered cardiovascular (central and peripheral) responsiveness.

Among traditional autonomic tests, hypothyroid and control subjects did not differ in terms of reflex responses. On the other hand, previous reports showed normal response of muscle nerve sympathetic activity to manoeuvres such as Valsalva and deep-breathing in hypothyroidism, providing evidence that dynamic cardiovascular coupling is unaffected (9). Furthermore, we would like to underline the fact that PSA appears to be a more sensitive test for autonomic imbalance as compared with cardiovascular tests (14). Hence, it is not surprising to note differences in PSA between controls and hypothyroid patients which have not been revealed by cardiovascular tests, especially when such differences are found (as could be the case) in only a small number of patients. The lack of differences in basal heart rate values between controls and hypothyroid patients can also be explained in the same way, although this latter is well known to be prone to bradycardia. In addition, it is interesting to note how PSA can detect differences in autonomic regulation in classes of patients with similar mean heart rate values. In conclusion, our data suggest that, contrary to the clinical picture, hypothyroid patients have increased sympathetic influence on the cardiac pacemaker. The changes in sympathetic activity might represent an adaptation to altered adrenergic responsiveness at cardiac and peripheral level.

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