Cardiovascular and Sympathetic Nervous Responses to Mental Stress in Hyperthyroid Patients

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We measured the cardiovascular and sympathetic nervous responses to mental stress in subjects with hyperthyroidism. Ten hyperthyroid subjects and 10 age- and sex-matched normal subjects performed mental arithmetic. At rest, the heart rate was higher in hyperthyroid subjects than in normal subjects, but systolic blood pressure, plasma norepinephrine, and epinephrine concentrations did not differ between the two groups. Systolic blood pressure and heart rate during stress, and the changes in blood pressure and in plasma epinephrine concentration from rest to stress, were higher in hyperthyroid subjects than in normal subjects. Therefore, cardiovascular and adrenal responses to mental stress were abnormally high in subjects with hyperthyroidism.

(Internal Medicine 31: 1175–1178, 1992)

Key words: mental arithmetic, plasma norepinephrine concentration, plasma epinephrine concentration

Introduction

Thyroid hormones have profound effects on the metabolism of many tissues in the body, including the heart. Many hyperthyroid patients are in a hyperdynamic cardiovascular state, as reflected by palpitations, dyspnea, tachycardia, and abnormally high systolic blood pressure. There are clinical similarities between the effects of excessive sympathoadrenal activity and those of hyperthyroidism, but the roles of thyroid hormones and catecholamines in the hyperdynamic cardiovascular state are complex (1–4). There have been several reports on the cardiovascular responses to dynamic exercise in hyperthyroid patients (2, 5–8), but none regarding cardiovascular responses to mental stress. In normal subjects, the effects of mental stress on plasma catecholamines are different from the effects of dynamic exercise (9). In this study, we examined cardiovascular and sympathetic nervous responses to mental arithmetic in hyperthyroidism.

Methods

Ten untreated hyperthyroid subjects and 10 age- and sex-matched normal subjects were studied. Patients with

coronary artery disease, hypertension, valvular heart disease, or cardiomyopathy were not included. There were 7 women and 3 men, aged 15 to 64 years (35 ± 17). All of them had at least moderate symptoms and signs of hyperthyroidism and diffuse goiters. Serum free T_3 concentration was high (16.2 ± 5.9 pg/ml, normal: 2.2 to 5.2), as was serum free T_4 concentration (6.0 ± 2.4 ng/dl, normal: 0.70 to 1.96). For the normal control subjects, we examined 7 women and 3 men aged 20 to 64 years (36 ± 16).

Subjects arrived in the laboratory between 9:00 and 10:00 AM after a light breakfast, having avoided tea, coffee, and cigarettes. There were no other dietary restrictions. A 19-gauge catheter was placed in the antecubital vein of the right arm and a small amount of physiological saline was continuously infused. Subjects remained supine for 30 minutes. Blood (3 ml) was drawn to measure plasma catecholamine concentrations, as an index of sympathetic nervous activity. Blood pressure was measured with an automatic sphygmomanometer (Nippon Colin, STBT-680) on the left arm. Blood pressure and a 12-lead electrocardiogram were recorded. The subjects were told to continuously subtract 7 starting from 1013 as quickly as possible, for a period of 3 minutes. During this time, they were distracted by the

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Received for publication February 10, 1992; Accepted for publication August 6, 1992

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rhythmic beats of metronome. Blood pressure and the 12-lead electrocardiogram were recorded every minute during, immediately after, and 1, 2, 3, 5, 7, and 10 minutes after the mental arithmetic. A blood sample was obtained during the last 20 seconds of the mental arithmetic.

The purpose and nature of the protocol were explained to all subjects when they were recruited, and again on the morning of the study, when informed consent was obtained. Permission for these investigations was granted by the Hospital Ethics Committee.

Blood samples were kept in ice water. After centrifugation, plasma samples were kept frozen at -40°C . Plasma norepinephrine and epinephrine concentrations were measured by the THI (tri-hydroxyindole) method, with a high performance liquid chromatograph.

The results are expressed as mean $\pm$ standard deviation. For statistical analysis, we used the paired t-test to compare data collected at rest with that collected during mental arithmetic, and used the unpaired t-test to compare data collected from normal subjects with that from hyperthyroid subjects. A *p* value of less than 0.05 was taken to indicate a significant difference.

Results

In both groups systolic blood pressure (SBP), diastolic

blood pressure (DBP), and heart rate (HR) were all significantly higher during mental arithmetic than at rest ($p < 0.01$, Fig. 1). There were no differences in SBP between the two groups either at rest or after mental arithmetic. However, during the mental arithmetic, SBP was significantly higher in hyperthyroid subjects than in normal subjects ($p < 0.01$, Fig. 1A). At rest and after mental arithmetic, DBP was significantly lower in hyperthyroid subjects than in normal subjects ($p < 0.01$). During mental arithmetic, there were no differences in DBP between the two groups (Fig. 1B). HR was significantly higher in hyperthyroid subjects than in normal subjects at rest, and both during and after the mental arithmetic ($p < 0.01$, Fig. 1C).

We compared the changes in SBP, DBP, and HR measured at rest and during mental arithmetic. The change in SBP was significantly higher in hyperthyroid subjects than in normal subjects 1 minute into the mental arithmetic (19 ± 7 vs. 11 ± 9 mmHg, $p < 0.05$). The change in DBP was significantly higher in hyperthyroid subjects than in normal subjects at 1 minute (19 ± 9 vs. 7 ± 7 mmHg, $p < 0.01$) and 2 minutes (20 ± 10 vs. 12 ± 7 mmHg, $p < 0.05$) into the mental arithmetic. The change in HR did not differ between the two groups.

In both groups, plasma norepinephrine and epinephrine concentrations were significantly higher during mental arithmetic than at rest ($p < 0.01$, Table 1). Plasma nor-

Fig. 1. Cardiovascular responses to mental arithmetic in normal and hyperthyroid subjects. R: rest.

Table 1. Plasma Catecholamine Concentrations at Rest and during Mental Arithmetic in Normal and Hyperthyroid Subjects

		Normal	Hyperthyroid	p Value
NE (pg/ml)	Rest	90 ± 56	63 ± 37	<0.05
	MA	124 ± 66**	93 ± 41**	
	Change	34 ± 17	39 ± 31	
E (pg/ml)	Rest	18 ± 14	20 ± 30	
	MA	37 ± 19**	80 ± 78**	
	Change	19 ± 16	50 ± 29	

E: plasma epinephrine concentration, MA: mental arithmetic, NE: plasma norepinephrine concentration. ** $p < 0.01$ vs. rest

epinephrine and epinephrine concentrations did not differ between the two groups either at rest or during mental arithmetic. The change in epinephrine concentration from rest to mental arithmetic was significantly higher in hyperthyroid subjects than in normal subjects ($p < 0.05$).

Discussion

The major manifestations of the hyperdynamic cardiovascular state in hyperthyroid subjects are likely to be increased heart rate, reduced peripheral artery resistance, and increased myocardial contractility (4, 10). The relation between thyroid hormones and catecholamines is complex, since high levels of circulating thyroid hormones cause an increase in the number and activity of beta-adrenergic receptors (11–13).

In the present study, hyperthyroid subjects had high HR and low DBP at rest, and may have been in a hyperdynamic cardiovascular state. Nonetheless, there were no significant differences in plasma norepinephrine concentrations between hyperthyroid subjects and normal subjects. Christensen observed that despite their elevated pulse rate, patients with thyrotoxicosis have significantly lower plasma norepinephrine concentrations than normal subjects, while their plasma epinephrine concentrations are normal (14). Christensen also suggested that sympathetic nervous activity is low in thyrotoxicosis in compensation for the direct effect of thyroid hormones on the cardiovascular system (14). Pharmacologic and physiologic investigations in a variety of experimental animals and in humans have failed to disclose any alteration in the sensitivity of the heart to the inotropic or chronotropic effects of adrenergic stimulation in hyperthyroidism (1, 3). The results of several investigations indicate that thyroid hormone itself has direct inotropic and chronotropic effects on the heart (2–4, 10). In this study, we could not determine whether or not the cardiovascular system was abnormally sensitive to catecholamine stimulation at rest in hyperthyroid subjects.

Iskandrian et al studied cardiac performance at rest

and during dynamic exercise in untreated hyperthyroid subjects (5). There were no significant differences in blood pressure at rest or during exercise between hyperthyroid subjects and normal subjects, but heart rate was significantly higher in the hyperthyroid subjects (5). Left ventricular ejection fraction was normal at rest in hyperthyroid subjects, but during exercise it was significantly lower in hyperthyroid subjects than in normal subjects (5). They concluded that cardiac performance is normal at rest in hyperthyroid subjects, but that some have abnormal left ventricular reserve during exercise (5). In the present study, SBP and HR during mental arithmetic and the increase in SBP from rest to mental arithmetic were significantly higher in hyperthyroid subjects than in normal subjects. Unlike the cardiovascular response to dynamic exercise reported by Iskandrian et al (5), the cardiovascular response to mental arithmetic was abnormally high in hyperthyroid subjects.

According to Nazar et al, the pre-exercise plasma norepinephrine concentration did not differ between hyperthyroid subjects and normal subjects, but the exercise-induced increase in the plasma norepinephrine concentration was significantly greater in hyperthyroid subjects than in normal subjects (6). The plasma catecholamine responses to psychological stress are different from those to physical exercise (9). Dimsdale and Moss reported that during public speaking, epinephrine levels increase two fold, whereas during physical exercise norepinephrine levels increase three fold (9). In the present study, we examined cardiovascular and sympathetic nervous responses in hyperthyroidism. Unlike the changes in plasma norepinephrine concentration caused by physical exercise in the hyperthyroid subjects studied by Nazar et al (6), plasma norepinephrine concentration during mental arithmetic in subjects with hyperthyroidism did not differ from that in normal subjects. The increase in plasma epinephrine concentration from rest to mental arithmetic was greater in hyperthyroid subjects than in normal subjects, which may mean that the adrenal response to mental arithmetic was greater in the former.

Mental arithmetic is thought to raise blood pressure as a consequence mainly of an increase in cardiac output or in total vascular resistance, in both normal subjects and in those with hypertension (15). Because some subjects with hyperthyroidism have low cardiac reserve during dynamic exercise (5, 7, 8), an abnormally high change in total vascular resistance may augment their SBP response during mental arithmetic. In the present study, we could not determine whether or not the abnormal cardiovascular response was due to the increased adrenergic stimulation and the altered sensitivity of the heart to catecholamine stimulation.

However, it can be concluded that cardiovascular and adrenal responses to mental stress are abnormally high in subjects with hyperthyroidism.

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