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Plasma levels of NT-pro-brain natriuretic peptide in patients with overt and subclinical hyperthyroidism and hypothyroidism

Ocena stężenia mózgowego peptydu natriuretycznego (NT-pro-BNP) w osoczu chorych z czynnościowymi zaburzeniami tarczycy

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Abstract

Background: Several studies have assessed natriuretic peptides in patients with thyroid disorders, and these studies have provided contrasting results. This difference may be partially explained by the presence of concomitant disorders of the cardiovascular system in participants.
Material and methods: The study included 101 patients free of any cardiovascular disorder, who, on the basis of plasma levels of TSH and thyroid hormones, were divided into patients with overt hyperthyroidism, patients with subclinical hyperthyroidism, patients with overt hypothyroidism, patients with subclinical hypothyroidism, and control subjects with normal thyroid profile. Hyperthyroidism was induced either by nodular thyroid disease or by Graves' disease, while hypothyroidism was secondary to autoimmune thyroiditis or surgery.
Results: Compared to control subjects, hyperthyroid patients were characterised by higher plasma levels of NT-pro-BNP. This increase was particularly pronounced in cases of overt disease. On the other hand, neither clinical nor subclinical hypothyroidism was associated with any significant changes in this peptide. Plasma levels of NT-pro-BNP did not differ between patients with Graves' disease and toxic nodular goitre nor between patients with autoimmune hypothyroidism and hypothyroidism secondary to thyroidectomy. Only L-thyroxine substitutions, but not hyperthyroidism treatment, caused changes in plasma concentration of NT-pro-BNP.
Conclusions: Hyperthyroidism and hypothyroidism induce changes of the plasma concentration of NT-pro-BNP. Although both exogenous L-thyroxine and antithyroid drugs restored thyroid function, only the former drug changed plasma NT-pro-BNP content. The thyrometabolic state of a patient should always be taken into consideration when NT-pro-BNP is assessed as a marker of cardiac dysfunction. **(Pol J Endocrinol 2011; 62 (6): 523–528)**

Key words: *hyperthyroidism, hypothyroidism, L-thyroxine, brain natriuretic peptide, BNP, NT-pro-BNP*

Streszczenie

Wstęp: W dotychczas przeprowadzonych badaniach oceniano stężenia peptydów natriuretycznych u osób z chorobami tarczycy, dostarczyły one jednak rozbieżnych wyników. Różnice te można częściowo tłumaczyć obecnością współistniejących schorzeń układu sercowo-naczyniowego.
Materiał i metody: Badaniem objęto 101 pacjentów, u których nie stwierdzono schorzeń układu sercowo-naczyniowego. Na podstawie wyników oznaczeń stężeń w osoczu TSH i wolnych hormonów tarczycy uczestników badania podzielono na chorych z klinicznie jawną nadczynnością tarczycy, chorych z subkliniczną nadczynnością tarczycy, pacjentów z klinicznie jawną niedoczynnością tarczycy, pacjentów z subkliniczną niedoczynnością tarczycy i osoby bez zaburzeń funkcji gruczołu tarczowego. U podłoża nadczynności tarczycy leżała choroba Gravesa-Basedowa lub wole guzowate, podczas gdy niedoczynność miała charakter autoimmunologiczny lub była konsekwencją tyreoidektomii.
Wyniki: W porównaniu z grupą kontrolną u osób z nadczynnością tarczycy stwierdzono wyższe stężenia w osoczu NT-pro-BNP. Wzrost ten był szczególnie wyrażony w przypadku klinicznie jawnej nadczynności tarczycy. W klinicznie jawnej oraz w subklinicznej niedoczynności tarczycy nie obserwowano zmienionych stężeń tego peptydu. Stężenie NT-pro-BNP w osoczu nie różniło się pomiędzy osobami z chorobą Gravesa-Basedowa i chorymi z wolem guzkowym nadczynnym, jak również pomiędzy osobami z niedoczynnością tarczycy o podłożu autoimmunologicznym i pozabiegowym. Obserwowano, iż jedynie leczenie niedoczynności tarczycy wiązało się ze zmianami stężeń badanego białka we krwi.
Wnioski: Nadczynność i niedoczynność tarczycy w różny sposób wpływają na stężenie NT-pro-BNP w osoczu krwi. Mimo iż zarówno egzogenna L-tyroksyna, jak i leczenie tyreostatykiem przywracają prawidłową funkcję tarczycy, jedynie L-tyroksyna wpływa na stężenie NT-pro-BNP. Stan tyreometaboliczny chorego powinien być zawsze uwzględniany przy ocenie stężenia NT-pro-BNP jako markera dysfunkcji serca. **(Endokrynol Pol 2011; 62 (6): 523–528)**

Słowa kluczowe: *nadczynność tarczycy, niedoczynność tarczycy, L-tyroksyna, mózgowy peptyd natriuretyczny, BNP, NT-pro-BNP*

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Introduction

The natriuretic peptides constitute a group of peptide hormones which play important roles in the regulation of renal and cardiovascular homeostasis [1]. Brain natriuretic peptide (BNP), or B-type natriuretic peptide, is a 32 amino acid polypeptide secreted by the ventricles and, to a lesser extent, by the atria of the heart in response to volume expansion, pressure overload, and other kinds of myocardial stress associated with increased endocardial pressure and excessive stretching of cardiomyocytes [2, 3]. This cardioprotective peptide is believed to be involved in the regulation of blood pressure, blood volume, and sodium balance [4, 5]. After binding to its receptors, BNP reduces systemic vascular resistance and central venous pressure, leading to an increase in diuresis and natriuresis, and to vascular relaxation [2]. During its synthesis, a 108 amino acid precursor moiety (pro-BNP) is split at a ratio of 1:1 into the physiologically active BNP, corresponding to the C-terminal fragment, and the biologically inactive N-terminal fragment (NT-pro-BNP), consisting of 76 amino acids [5, 6]. The half-life of NT-pro-BNP is several times longer than that of BNP (1–2 hours *vs.* 15–20 min) [2, 3]. Measurement of plasma levels of BNP or NT-pro-BNP has been recommended in the diagnosis and prognosis of patients with symptoms of left ventricular dysfunction and for stratification of risk in patients with acute coronary syndromes [4, 7, 8]. Apart from heart failure and acute coronary syndromes, the release of BNP is enhanced in patients with other disorders, including atrial fibrillation, arterial hypertension, pulmonary hypertension, dyspnoea or hypertrophic cardiomyopathy [1, 9, 10]. Because of its greater stability and longer half-life, it is assumed that NT-pro-BNP is also a useful marker of cardiac dysfunction, playing a role in the diagnosis, management, and prognosis of patients with congestive heart failure.

Although some previous studies assessed BNP and/or NT-pro-BNP levels in patients with thyroid dysfunction [11–17], the value of the obtained results was limited by the fact that these studies either included patients with heart failure, atrial fibrillation, hypertension or other cardiovascular disorders, or excluded patients only on the basis of clinical history. This study, which assessed echocardiographically diameters of cardiac cavities, left ventricle mass and the left ventricle ejection fraction, determined NT-pro-BNP in patients free from any cardiovascular disorders.

Material and methods

Subjects

The study included 101 patients, without any changes in the cardiovascular system, who on the basis of plasma levels of TSH, free thyroxine (fT_4) and free triiodothyronine (fT_3) were allotted into one of five groups: (A) patients with overt hyperthyroidism (n = 47); (B) patients with subclinical hyperthyroidism (n = 16); (C) patients with overt hypothyroidism (n = 24); (D) patients with subclinical hypothyroidism (n =14); and control subjects with normal thyroid profile (n = 30). Overt hyperthyroid patients suffered from either nodular thyroid disease (n = 21) or from Graves' disease (n = 26). In turn, overt hypothyroidism was induced by either autoimmune thyroiditis (n = 19) or surgery (n = 5). We excluded all patients with any autoimmune disorder (with the exception of thyroid autoimmune disorders) or suffering from heart failure, coronary artery disease, atrial fibrillation, cardiomyopathy or any other cardiovascular disorder. The remaining exclusion criteria were: decompensated diabetes, hepatic cirrhosis, severe renal insufficiency, any organ transplantation in the past, any present or previous psychotic disorders, depression. alcoholism or drug addiction.

Study protocol

The study protocol was approved by the local bioethical committee and written informed consent was obtained from each patient. Patients with thyroid dysfunction were observed in both baseline conditions (before treatment) and after euthyroidism had been restored. The mean daily dose and the mean period of treatment to restore euthyroidism were, respectively, 100 μg and 39 days for L-thyroxine, and 30 mg and 14 days for methimazole. Echocardiography, performed using a standard ultrasound system (Vingmed System Five Advantage, General Electric, USA), measured left ventricular end-diastolic diameter, interventricular septum and posterior wall diastolic diameter. Next, left ventricular mass was calculated by the Devereaux formula and then indexed to the body surface area. Left ventricular ejection fraction was measured based on the biplane Simpson method.

Laboratory assays

Blood samples were collected from the antecubital vein at 8 am after overnight fasting (12 hours) and collected into tubes containing serum. Patients were required to refrain from smoking or taking vigorous exercise prior to blood sampling. The samples were centrifuged within 15 min of venipuncture. The plasma samples were then separated and stored at –70°C until analysis. Plasma levels of TSH and free thyroid hormones were assayed immunoenzymatically (MEIA), by routine laboratory techniques (Abbot AxSYM, Abbot Laboratories, USA). Thyroperoxidise antibodies (TPOAb) and thyrotropin receptor antibodies (TRAb) were measured, respectively, by an enzyme-linked immunosorbent assay (ELISA) method and by a radioimmune assay (RIA) method.

Reference ranges were as follows: TSH — 0.4–4.0 mU/L, fT_4 — 0.93–1.7 ng/dL, fT_3 — 2.0–4.4 pg/mL, thyroid peroxidise antibodies: 12 IU/L, thyroid receptor antibodies: < 2 IU/mL. Plasma levels of NT-pro-BNP were determined by an immunoenzymatic method using polyclonal antibodies, which recognise epitopes located in the N-terminal part (ECLIA, Roche Elecsys 2010, USA) (1–76).

Statistical analysis

Results are shown as the mean ± standard deviation (SD). Statistical analysis was performed using Statistica 7.1 package (StatSoft, Inc. Tulsa, OK, USA). Pretreatment and post-treatment data within the same group were compared with Student's paired t-test. A p of less than 0.05 was regarded as statistically significant.

Results

Marked differences in plasma levels of TSH and free thyroid hormones were observed between patients belonging to various studied groups (Table I). Individuals with clinically overt hyperthyroidism were statistically younger than healthy subjects (52.8 ± 13. years *vs.* 59.9 ± 12.8 years, $p < 0.001$) and had a lower body mass index (BMI) (23.8 ± 3.9 kg/m^2 *vs.* 28.3 ± 3.7 kg/m^2, $p < 0.001$). No differences in age or BMI were observed between control subjects and patients with other thyroid disorders. There were no differences in left ventricular mass index. All subjects had this parameter in the normal range.

Compared to control subjects, patients with both overt and subclinical hyperthyroidism had higher plasma levels of NT-pro-BNP (overt hyperthyroidism: 1,129.7 ± 1,119.8 pg/ml *vs.* 138.9 ± 173.3 pg/ml, $p < 0.001$; subclinical hyperthyroidism: 598.1 ± 639.2 pg/ml *vs.* 138.9 ± 173.3 pg/ml, $p < 0.001$) (Figure 1). Plasma levels of NT-pro-BNP were significantly higher in subjects with overt hyperthyroidism than in patients with subclinical hyperthyroidism ($p < 0.05$). No differences in NT-pro-BNP were observed between subjects with toxic nodular goitre (1,244.0 ± 2,096.9 pg/ml) and Graves' disease (1,037.3 ± 1,598.8 pg/ml) (data not shown). Plasma levels of NT-pro-BNP did not differ between patients with overt hypothyroidism (190.0 ± 161.2 pg/ml), subclinical hypothyroidism (234.1 ± 180.1 pg/ml) and control subjects (138.9 ± 173.3 pg/ml) (Figure 1). Plasma levels of NT-pro-BNP in subjects with autoimmune hypothyroidism (569.1 ± 1,651.8 pg/ml) were similar to those observed in patients with post-surgery hypothyroidism (239.9 ± 136.7 pg/ml) (data not shown).

Hyperthyroidism treatment did not affect plasma levels of NT-pro-BNP (pretreatment: 1,129.7 ± 1,819.8 pg/ml, post-treatment: 1,059.3 ± 1,598.1 pg/ml) (Figure 2). No effect of treatment was observed either in patients with Graves' disease (1,037.3 ± 1,598.8 pg/ml *vs.* 741.2 ± 773.8 pg/ml) or subjects with toxic nodular goitre (1,244.0 ± 2,096.9 pg/ml *vs.* 1,453.1 ± 2,198.0 pg/ml). L-thyroxine treatment increased plasma levels of NT-pro-BNP from 190.0 ± 161.2 pg/ml to 313.3 ± 238.5 pg/ml ($p < 0.05$) when all hypothyroid patients were assessed together (Figure 3). When both subgroups of overt hypothyroid patients were assessed separately, L-thyroxine produced no significant effect in patients with autoimmune hypothyroidism (569.1 ± 1,651.8 pg/ml *vs.* 591.3 ± 1313.7 pg/ml) or in post-surgery hypothyroidism: 239.9 ± 136.7 pg/ml *vs.* 355.3 ± 251.6 pg/ml).

Discussion

Our study has shown that among clinical conditions associated with thyroid dysfunction, only hyperthyroidism was accompanied by higher plasma levels of NT-pro-BNP. Increased NT-pro-BNP levels were observed in patients with subclinical hyperthyroidism, most of whom were asymptomatic and did not have any abnormalities on echocardiography. These hyperthyroidism-related changes in NT-pro-BNP probably reflect a hypermetabolic condition associated with hyperthyroidism rather than being characteristic of any particular clinical entity. This hypothesis, which is in line with the observations by Schultz et al. [18], is supported by the fact that plasma NT-pro-BNP levels were clearly higher in patients with overt hyperthyroidism than in subjects with subclinical hyperthyroidism, while no differences in plasma levels of this peptide were observed between patients with toxic nodular goitre and subjects with Graves' disease, causing the same degree of thyroid dysfunction. The latter finding is in agreement with the observations by other authors [11, 12] who noticed similar plasma levels of BNP, irrespective of the disorder leading to hyperthyroidism (Graves' disease, nodular and multinodular goitre, painless thyroiditis, or subacute thyroiditis). Although increased plasma levels of BNP and/or NT-pro-BNP have been observed by other authors [11–17], most these studies included subjects with heart failure and other cardiovascular disorders known to elevate plasma BNP and NT-pro-BNP, and were limited to overt hyperthyroidism.

The strength of our report is its very strict inclusion and exclusion criteria, which made it possible to link the obtained results to hyperthyroidism, and to exclude their association with cardiovascular disorders, particularly heart failure and atrial fibrillation. Although our overt hyperthyroidism patients differed from healthy subjects in age and BMI, they do not seem to be the factors responsible for higher NT-pro-BNP levels. We think this because the levels of these markers were elevated even in subjects with subclinical hyperthyroidism, who were of a similar age, and had similar BMI and left ventricular mass index, as compared with control patients.

Table I. *Baseline characteristics of patients*
Tabela I. *Wyjściowa charakterystyka pacjentów*

Group		Age [years]	BMI [kg/m^2]	fT3 [pg/ml]	fT4 [ng/dl]	TSH [μIU/ml]	LVMI [g/m^2]	LVmass [g]
Control subjects (n = 30)	Mean ± SD	59.96 ± 12.82	28.35 ± 3.65	2.76 ± 0.72	1.297 ± 0.28	1.808 ± 1.036	107.12 ± 22.13	210.08 ± 40.96
Overt hyperthyroidism (n = 47)	Mean ± SD	52.79 ± 13.74	23.79 ± 3.93	11.49 ± 7.01	4.434 ± 2.107	0.047 ± 0.122	109.23 ± 20.51	182.04 ± 35.25
Overt hypothyroidism (n = 24)	Mean ± SD	57.46 ± 15.24	28.98 ± 4.45	1.89 ± 0.89	0.625 ± 0.381	29.901 ± 21.902	110.16 ± 25.58	206.29 ± 59.74
Subclinical hyperthyroidism (n = 16)	Mean ± SD	59.37 ± 16.03	26.32 ± 4.24	3.11 ± 0.94	1.335 ± 0.518	0.079 ± 0.153	111.34 ± 39.37	199.04 ± 74.13
Subclinical hypothyroidism (n = 14)	Mean ± SD	54.71 ± 18.71	28.83 ± 8.52	2.29 ± 0.75	1.306 ± 0.724	7.012 ± 2.287	101.16 ± 28.22	193.31 ± 68.98
Statistical analysis								
Control subjects *vs.* overt hyperthyroidism		p = 0.0096 S	p ≤ 0.001 S	p ≤ 0.001 S	p ≤ 0.001 S	p ≤ 0.001 S	p = 0.8182 NS	p = 0.0396 S
Control subjects *vs.* overt hypothyroidism		p = 0.7606 NS	p = 0.9514 NS	p = 0.0003 S	p ≤ 0.001 S	p ≤ 0.001 S	p = 0.9455 NS	p = 0.3653 NS
Control subjects *vs.* subclinical hyperthyroidism		p = 0.9265 NS	p = 0.0945 NS	p = 0.2005 NS	p = 0.8356 NS	p ≤ 0.001 S	p = 0.8717 NS	p = 0.181 NS
Control subjects *vs.* subclinical hypothyroidism		p = 0.4649 NS	p = 0.371 NS	p = 0.0716 NS	p = 0.1697 NS	p ≤ 0.001 S	p = 0.2730 NS	p = 0.1509 NS

S — statistically significant; NS — statistically non significant

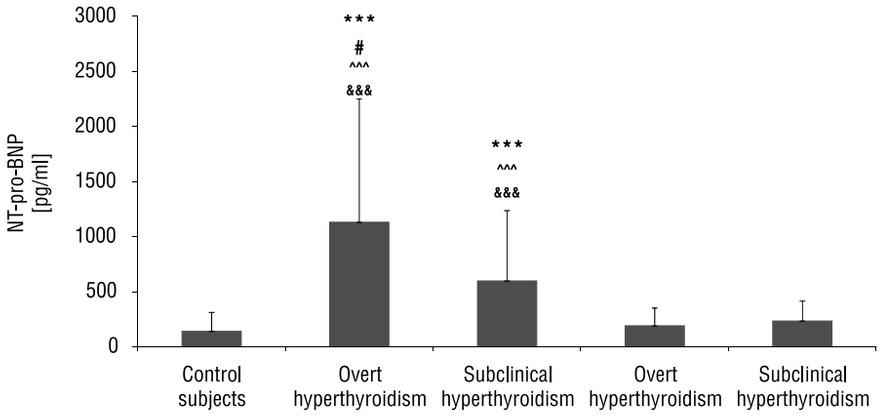

Figure 1. *Plasma levels of NT-pro-BNP in patients with subclinical and clinically overt hyperthyroidism and hypothyroidism. Data represents the mean ± SD. ***P < 0.001* vs. *control subjects. #P < 0.05* vs. *patients with subclinical hyperthyroidism. ^^^P < 0.001* vs. *patients with subclinical hypothyroidism. &&&P < 0.001* vs. *patients with overt hypothyroidism*

Rycina 1. *Stężenie NT-pro-BNP w osoczu chorych na subkliniczne i klinicznie jawne choroby tarczycy. Wyniki przedstawiają średnią ± odchylenie standardowe. ***P < 0.001* vs. *grupa kontrolna. #P < 0.05* vs. *chorzy na subkliniczną nadczynność tarczycy. ^^^P < 0.001* vs. *chorzy na subkliniczną niedoczynność tarczycy. &&&P < 0.001* vs. *chorzy na klinicznie jawną niedoczynność tarczycy*

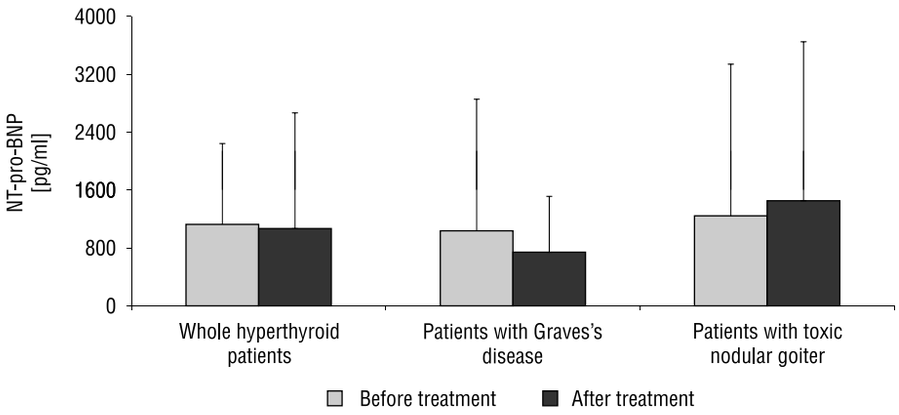

Figure 2. *Effect of methimazole on plasma levels of NT-pro-BNP in hyperthyroid patients. Data represents the mean ± SD*

Rycina 2. *Wpływ metimazolu na stężenie NT-pro-BNP w osoczu chorych na nadczynność tarczycy. Wyniki przedstawiają średnią ± odchylenie standardowe*

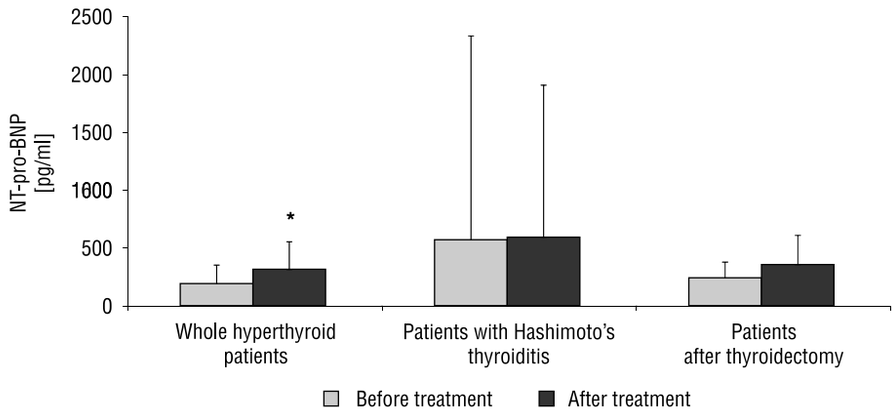

Figure 3. *Effect of L-thyroxine on plasma levels of NT-pro-BNP in hypothyroid patients. Data represents the mean ± SD. *P < 0.05* vs. *baseline value*

Rycina 3. *Wpływ L-tyroksyny na stężenie NT-pro-BNP w osoczu chorych na niedoczynność tarczycy. Wyniki przedstawiają średnią ± odchylenie standardowe. *P < 0.05* vs. *wartość przed leczeniem*

Unlike hyperthyroidism, the presence of hypothyroidism was not associated with any changes in NT-pro-BNP. Although this finding seems at first unexpected, it is, in fact, in line with the results of some [11, 12], but not all [17], studies. There are two possible explanations for our findings. Firstly, the neutral effect of hypothyroidism on NT-pro-BNP is a sum of opposite effects of a hypothyroidism-induced hypometabolic state and increased production of proinflammatory cytokines and endothelins. Both proinflammatory cytokines and endothelins are known stimulators of BNP release [2, 3] and there is some evidence on a proinflammatory state and endothelial dysfunction in the case of hypothyroidism and thyroid autoimmunity [19–21]. Their excess may counterbalance the lack of a stimulatory effect of thyroid hormones on BNP production. A second, although in our opinion less likely, explanation is that BNP release in patients with thyroid disorders only reflects interleukin-6 release. Interestingly, in line with this hypothesis, other authors have observed that only patients with clinical or subclinical hyperthyroidism had increased plasma levels of interleukin-6 [22], while circulating levels of this interleukin in subjects with clinical or subclinical hypothyroidism did not differ from those observed in healthy subjects.

Another interesting finding of our study is that L-thyroxine treatment produced an increase in NT-pro-BNP levels. This finding, being in line with the results of Schultz et al. [17], probably results from a direct effect of exogenous thyroid hormones on the heart. In line with our hypothesis, triiodothyronine was found to enhance BNP gene transcription in animals [23], while thyroxine and triiodothyronine dose-dependently stimulated BNP release from cultures of atrial and ventricular cardiomyocytes [13]. Moreover, induction of an acute hyperthyroid state in healthy subjects by triiodothyronine administration increased plasma levels of NT-pro-BNP [24].

In turn, an unexpected observation, being in contrast with the findings of other authors [17, 25] was that, despite normalisation of plasma levels of TSH and free thyroid hormones, antithyroid drugs did not restore a hyperthyroidism-induced increase in plasma NT-pro-BNP levels. The study protocol does not allow us to explain this finding. It cannot be excluded that the time required to normalise BNP production is much longer than that needed to restore normal thyroid function. Alternatively, antithyroid drugs may produce non-thyroid hormone-related effects, which oppose the effect of a decrease in thyroid hormone reduction on BNP production.

Conclusions

Our study has shown that hyperthyroidism, in both its clinical and subclinical forms, results in a significant increase in serum levels of NT-pro-BNP, while no changes in the production of BNP were induced by hypothyroidism. Although both exogenous L-thyroxine and antithyroid drugs restored thyroid function, only the former drug changed plasma NT-pro-BNP content.

Our results indicate that the thyrometabolic state of a patient should always be taken into consideration when NT-pro-BNP is assessed as a marker of cardiac function.

Acknowledgments

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