Brain natriuretic peptide as a diagnostic marker for heart failure in hyperthyroid patients with ischemic heart disease

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Objective
The aim of the study was to evaluate the value of the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) as an early diagnostic marker for chronic heart failure (CHF) in hypothyroid patients with ischemic heart disease (IHD).
Materials and methods
A total of 120 patients with an age range between 42 and 64 years participated in the study. All patients were classified into four groups: the master first group includes 30 patients with IHD, CHF functional class II–III and hyperthyroidism; the second group includes 30 patients with IHD and CHF functional class II–III, but with normal thyroid function; the third group includes 30 hyperthyroid patients without CHF or IHD; and the fourth group includes 30 hyperthyroid patients with IHD, without CHF. All patients were subjected to the following: full clinical and functional assessment, measurement of NT-proBNP, echocardiography, and the 6-min walk test.
Results
NT-proBNP levels were high in all studied groups. NT-proBNP levels showed no significant difference between patients of second and fourth group. The master first group had the highest significant NT-proBNP concentrations than other studied groups. Thyroid hyperfunction in patients with IHD appears to stimulate the natriuretic peptides secretion at a level exceeding what is recommended for the initial diagnosis of CHF.
Conclusion
The highest NT-proBNP level in hyperthyroid patients with IHD apparently is caused by stimulation of natriuretic peptide secretion by both thyroid hyperfunction and myocardial ischemic changes, which determine the need to check out the cut-off value of NT-proBNP level as a serological marker for the initial diagnosis of heart failure of such patients' category.

Keywords:
brain natriuretic peptide, chronic heart failure, hyperthyroidism, ischemic heart disease

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Introduction

An estimated 37.7 million individuals are living with heart failure (HF) worldwide [1]. The worldwide incidence of HF ranges from 100 to 900 patients for each 100 000 individual per year, relying on the criteria of diagnosis used and community studied [2]. Epidemiological studies carried out in developing countries have determined the risk factors and etiologies for HF, but no further detailed epidemiological data were available [3,4]. Ischemic heart disease (IHD) is one of the most important risk factor for HF [5,6]. One of the most urgent problems at present is the combination of cardiovascular pathology with other diseases. The number of patients with multimorbidity significantly increases with age, reaching up to 78% in people 80 years of age and older [7]. Often in patients of middle and older age groups, there is a combination of IHD and thyroid hyperfunction, with the prevalence of the thyrotoxicosis range from 0.5 to 3.9%, which is most often in women [8–10]. Considering the mutual influence of hyperthyroidism and cardiovascular pathology such as chronic heart failure (CHF) and IHD, it is necessary to take into account their combination when choosing methods for diagnosis and treatment tactics. According to the recommendations of the European Society of Cardiology (ESC) (2016), the most important early diagnosis of CHF is the defining the level of brain natriuretic peptide (BNP) or N-terminal fragment of the precursor BNP (NT-proBNP), especially in HF patients with persistent and midrange ejection fraction (HFmrEF) of the left ventricle (LV) [11]. BNP and NT-proBNP are strong prognostic markers of IHD [12] or HF [13]. The maximum limit of normal in chronic settings for NT-proBNP is 125 pg/ml. Plasma levels of NT-proBNP less than

125 pg/ml make the diagnosis of HF unlikely [11]. The literature data show that the level of NT-proBNP is affected by changes in thyroid hormone levels. A number of researchers noted that an increase in thyroid hormone levels in the serum provoked an increased production of natriuretic peptides, in particular NT-proBNP [14]. Serum level of NT-proBNP may increase with thyrotoxicosis, regardless of the presence of HF, which is probably related to direct stimulating action of thyroid hormones [15]. On the contrary, thyrotoxicosis can lead to structural changes in the heart, undetectable with conventional echocardiography, and these changes may be responsible for raising the level of NT-proBNP [14]. Many studies have reported on the efficacy of using NT-proBNP level as a diagnostic marker for detection of CHF [16–18]. The controversial judgments about the effect of thyroid hormones on the level of NT-proBNP determine the need for further studies for the causes of its increase in the serum of hyperthyroid patients with IHD. It is of interest to estimate the effect of increased level of thyroid hormones for secretion of NT-proBNP and the possibility of using this marker for the diagnosis of CHF on the background of IHD and hyperthyroidism. The aim of this study was to evaluate the value of the BNP as an early marker for the diagnosis of HF in patients with IHD and hyperthyroidism.

Materials and methods

The study included 120 patients who were admitted at Cardiology and Endocrinology Departments of the University Hospital, Egypt. All patients were classified into four groups: the master first group: 30 patients with hyperthyroidism, IHD, and CHF functional class (FC) II–III; the second group: 30 patients with IHD and CHF FC II–III, but without thyroid dysfunction; the third group: 30 patients with hyperthyroidism but without IHD or CHF; and the fourth group: 30 patients with hyperthyroidism and IHD, without CHF. Patients with IHD FC II–III were selected according to the Canadian Cardiovascular Society grading of angina pectoris [19]. Diagnosis and treatment of IHD and CHF were conducted in accordance with modern standards and recommendations [11,20]. Hypertensive patients were classified according to 2013 ESH/ESC guidelines for the management of arterial hypertension [21]. Patients with CHF FC II–III were selected according to the New York Heart Association Functional Classification [22]; in addition, full clinical and functional assessments were carried out to determine the tolerability of physical load used in 6-min walk test [23]. The indices of free tri-iodothyronine (FT3), free tetraiodothyronine (FT4), and Thyroid stimulating hormone (TSH) were determined by radioimmunological method. The NT-proBNP level was determined by an enzyme immunoassay for quantifying NT-proBNP in human serum on the automatic enzyme immunoassay analyzer. The exclusion criteria for the study were hemodynamically significant heart diseases (congenital, acquired), pericarditis, myocarditis, acute myocardial infarction or acute cerebral infarction, advanced diseases of the liver or kidneys (glomerular filtration rate <30 ml/min/1.73 m^2), and the presence of artificial pacemaker, inflammatory or infectious diseases, and malignant neoplasms.

All patients signed an informed consent to participate in the study. Statistical processing of receiving data was conducted using the program (SPSS V.20; SPPS Inc., Chicago, Illinois, USA). *P* value less than 0.05 was considered significant.

Results and discussion

The results of the study showed that the BMI and age in the group of patients with hyperthyroidism without CHF or IHD (third group) were significantly lower ($P<0.05$) in comparison with the master first group, the second group, and the fourth group. This finding is concurrent with the literature studies, which confirm that overweight, obesity, and advanced aging are directly related to the development and progression of cardiovascular diseases including IHD and CHF [24–29]. Clinical characteristics and parameters of the thyroid hormonal profile for all participants are presented in Table 1. When analyzing the level of thyroid hormones in patients of the master first, third, and fourth group, there were no significant differences between them. However, the duration of hyperthyroidism was the longest in patients of the master first group 6.7±0.45 months, exceeding by 2.4 and 2.5 times than in the third and fourth group, respectively. It can be assumed that the reason was the severity of the clinical picture on the background of cardiovascular morbidity of the master first group, prompting initially to seek medical consultation with early diagnosis of the hyperthyroid status. The heart rate in the master first group as well as in the third and fourth group (i.e. patients with hyperthyroidism) was significantly higher ($P<0.05$) than in the second group, which was probably a consequence of the stimulating effect of thyroid hormones on the sympathetic nervous system. It is important to

Table 1 Clinical characteristics and parameters of the thyroid hormonal spectrum for all groups (*n*=120)

Groups	Index			
	Master first group (*n*=30)	Second group (*n*=30)	Third group (*n*=30)	Fourth group (*n*=30)
BMI (kg/m^2) (mean±SD)	27.38±2.75; P_2>0.05; P_3<0.05; P_4>0.05	27.62±2.28	23.24±1.80; P_2=0.01	26.92±3.11; P_2>0.05; P_3<0.05
Male [*n* (%)]	13 (43.3)	14 (46.6)	12 (40.0)	11 (36.6)
Female [*n* (%)]	17 (56.6)	16 (53.3)	18 (60.0)	19 (63.3)
Age (years) (mean±SD)	58.74±3.22; P_2>0.05; P_3<0.05; P_4>0.05	57.33±3.61	44.9±2.72; P_2<0.05	58.88±3.14; P_2>0.05; P_3<0.05
Mean heart rate (bpm) (mean±SD)	91±9; P_2<0.05; P_3>0.05; P_4>0.05	72±9	94±8; P_2<0.05	95±8; P_2<0.05; P_3>0.05
AH [*n* (%)]	26 (86.6)	19 (63.3)	12 (40)	18 (60)
Grade 1	7 (26.9)	6 (31.5)	9 (75)	10 (55.5)
Grade 2	14 (53.8)	11 (57.8)	3 (25)	6 (33.3)
Grade 3	5 (19.2)	2 (10.5)	–	2 (11.1)
AH duration (years) (mean±SD)	4.26±0.51	4.2±0.42	First detected	3.25±0.54
IHD (CCS) [*n* (%)]				
FC I	–	–	–	–
FC II	8 (26.6)	10 (30)	–	11 (36.6)
FC III	22 (73.3)	20 (70)	–	19 (63.3)
FC IV	–	–	–	–
IHD duration, (years) (mean±SD)	5.3±1.2; P_2>0.05; P_4>0.05	5.5±0.67	–	4.29±0.93; P_2>0.05
Previous MI [*n* (%)]	16 (53.3)	22 (73.3)	–	7 (23.3)
CHF (NYHA) [*n* (%)]				
FC II	16 (53.3)	20 (66.6)		–
FC III	14 (46.6)	10 (33.3)	–	–
TSH (mIU/l) (mean±SD)	0.02±0.09; P_2<0.05; P_3>0.05; P_4>0.05	1.64±0.95	0.02±0.06; P_2<0.05	0.03±0.05; P_2<0.05; P_3>0.05
FT4 (pmol/l) (mean±SD)	41.8±12.6; P_2<0.05; P_3>0.05; P_4>0.05	14.8±2.7	42.5±18.3; P_2<0.05	43.6±16.2; P_2<0.05; P_3>0.05
FT3 (pmol/l) (mean±SD)	7.2±1.4; P_2<0.05; P_3>0.05; P_4>0.05	3.9±1.3	7.7±2.1; P_2<0.05	6.9±1.9; P_2<0.05; P_3>0.05
HT duration (months) (mean±SD)	6.7±0.45; P_3<0.05; P_4<0.05	–	2.75±0.37	2.68±0.26; P_3>0.05

AH, arterial hypertension; CCS, Canadian Cardiovascular Society grading; CHF, chronic heart failure; FC, functional class; FT3, free triiodothyronine; FT4, free tetraiodothyronine; HT, hyperthyroidism; IHD, ischemic heart disease; MI, myocardial infarction; NYHA, New York Heart Association; P_2, comparison with the second group; P_3, comparison with the third group; P_4, comparison with the fourth group; TSH, thyroid stimulating hormone. P<0.05, significant.

Table 2 Six-minute walking results in patients with chronic heart failure

Groups	Index	
	Master first group (*n*=30)	Second group (*n*=30)
6MWT (m) (mean±SD)	255.93±15.84 P<0.05	302.35±20.13

6MWT, 6-minute walk test. P<0.05, significant.

emphasize that patients of the master first group, second group, and fourth group were dominated by the FCIII of angina pectoris (73, 70, and 63, respectively), but the duration of IHD being comparable in all three compared groups. Exercise tolerance was at the lowest level in the master first group, as the mean average distance walked with this group was 255.93±15.84, which is 1.18 times less than in the second group (P<0.05). Lower tolerance to exercise apparently is owing to the presence of concomitant hyperthyroidism in patients of the master first group. Hyperthyroidism is associated with exercise intolerance due to insufficient increase in cardiac output during effort [30–33]. Six-minute walk test results in patients with CHF are presented in Table 2. The mean left ventricular ejection fraction (LVEF) in the patients of the third and fourth group was within the normal range (66 and 55%, respectively), but it should be noted that a higher value of LVEF was present in the group of patients with hyperthyroidism (third group) compared with other groups (P<0.05), which is known to be a characteristic of the hyperkinetic stage of thyrotoxic heart disease. Hyperthyroidism promotes an increase in myocardial contractility and LV hypertrophy and may develop a 'high-output HF'

Table 3 The N-terminal prohormone of brain natriuretic peptide level and left ventricular ejection fraction for all groups

Groups	Index			
	Master first group (n=30)	Second group (n=30)	Third group (n=30)	Fourth group (n=30)
Mean NT-proBNP (pg/ml)	713.13 (432.25–894.92); $P_2<0.05$; $P_3<0.05$; $P_4<0.05$	325.61 (254.72–455.67)	254.46 (181.14–37.13); $P_2=0.01$	346.28 (264.75–421.65); $P_2>0.05$; $P_3<0.05$
Mean LVEF (%)	40.0 (36.0–43.0); $P_2<0.05$; $P_3<0.05$; $P_4<0.05$	46.0 (41.0–47.0)	66.0 (61.0–69.0); $P_2<0.05$	55.0 (52.0–60.0); $P_2<0.05$; $P_3<0.05$

LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; P_2, comparison with the second group; P_3, comparison with the third group; P_4, comparison with the fourth group. $P<0.05$, significant.

[34–36]. However, the risk of developing HF with a low ejection fraction increases in elderly hyperthyroid patients with concomitant IHD and arterial hypertension [32]. Analysis of indices of LVEF in patients of the second group and the master first group indicates a decrease in contractility of the LV in the conditions of development and progression of CHF. In patients of the second group who have IHD and CHF, LVEF was significantly lower (46%), than in the third and fourth group ($P<0.05$), but within LVEF range from 40 to 49%, which corresponds to HF with midrange EF (HFmrEF) type of cardiac insufficiency (ESC guidelines, 2016) [11]. Patients with CHF associated with IHD and hyperthyroidism (the master first group) have the lowest significant LVEF, 40.0% (36.0–43) in relation to the other studied groups ($P<0.05$). The NT-proBNP level and LVEF for all studied groups are presented in Table 3. There was an elevated level of NT-proBNP in all groups included in the study. The level of NT-proBNP in the group of patients with hyperthyroidism without CHF and IHD (third group) was 2.8 times lower than in patients of the master first group, but it exceeded the established cut-off value of 125 pg/ml for NT-proBNP as an initial diagnostic test according to the recommendations of ESC (2016) [11]. No significant difference was found between patients with IHD and CHF (second group) and those with IHD and hyperthyroidism but without CHF (fourth group) regarding the level of NT-proBNP ($P>0.05$), but both groups were 2.19 and 2.06 times, respectively, significantly lower in comparison with the master first group ($P<0.05$), which allows one to think about the additive effects of morphological and functional changes of the LV and hyperproduction of thyroid hormones on the mean level of NT-proBNP, which was at the highest concentration in patients of the master first group, 713.13 pg/ml (432.25–894), probably owing to the influence of both factors together on the secretion of the NT-proBNP.The study confirms the importance of determining the diagnostic level of NT-proBNP for the detection of CHF in case of patients with IHD with thyroid hyperfunction.

Conclusion

In patients with IHD and hyperthyroidism, the recommended plasma level of NT-proBNP (125 pg/ml) cannot be used as an initial diagnostic criterion of CHF, and further studies are needed for determining the optimal level of initial diagnosis in such group of patients.

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Conflicts of interest

There are no conflicts of interest.

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