

EVEN MILD CHANGES IN FREE THYROXINE COULD INFLUENCE THE DEGREE OF HEART FAILURE MEASURED BY ITS BIOLOGICAL SURROGATES

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running title: Mild changes in free thyroxine and heart failure

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Summary

Both, severe hypo- or hyperthyroidism may alter hemodynamic parameters. The aim of our study was to ascertain, whether also distinct changes within normal range of free thyroxine (fT4) would be associated with an impairment of left ventricle function in patients with chronic heart failure. Hundred-forty-eight patients (m121, f27, mean age 63.8 ± 1.14) with chronic heart failure, fT4 levels within the normal range (9-22 pmol/l) and without thyrostatics or substitution treatment. Degree of heart failure was quantified by plasma B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP). Patients with fT4 in the range 11.9-14.6 pmol/l [optimal, 2nd-3th quintile] had significantly lower NT-proBNP (718 ± 70.4 pg/ml), than those with $fT4 \leq 11.8$ [low-normal, bottom quintile] (1236 ± 223.6 pg/ml; $p < 0.03$) and those with fT4 over 14.6 pmol/l [high-normal, top two quintiles] (1192 ± 114.9 pg/ml; $p < 0.0002$). These differences remain significant, also if adjusted for age, gender and other confounders; adjusted odds ratio was 1.30 (1.05-1.59) for optimal vs. low-normal and 1.27(1.04-1.55) for optimal vs. high-normal. Similar statistical differences were also found in BNP, but only when optimal and high-normal fT4 ranges were compared. In conclusion, the severity of heart failure seems to be also influenced by only mild deviations of fT4 concentrations from optimal levels.

Key-words: thyroxine ; high-normal; low-normal; heart failure; natriuretic peptides

Introduction

Thyroid hormones have many effects on the cardiovascular system. It is evident, that thyroid dysfunction may accelerate atherosclerosis through some conventional cardiovascular risk factors (dyslipidemia, hypertension, etc.) however thyroid status also has a close link to several hemodynamic parameters (Biondi *et al* 2002, Klein *et al* 1990, Feldman *et al* 1986, Bengel *et al* 2000, Ripoli *et al* 2005). Triiodthyronine plays a direct role in the modulation myocardial contractile status by up-regulation of heavy alpha and beta chains of myosin, regulation of the activity of Na/K/ATPase, calcium-activated ATPase in sarcoplasmic reticulum (SERCA II) and voltage-regulated calcium channels. Moreover, it regulates the activity of beta receptors as well (Biondi *et al* 2002, Klein *et al* 1990). Triiodthyronine decreases peripheral vascular resistance, increases peripheral oxygen consumption and oxygen demand of myocardial tissue, especially under stress condition (Biondi *et al* 2002, Bengel *et al* 2000, Ripoli *et al* 2005). Pathophysiologically, thyroid dysfunction leads to an impairment of the isovolemic relaxation and filling of the left ventricle, and to an impairment of the myocardial contractility, decrease of stroke volume and ejection fraction (Biondi *et al* 2002, Feldman *et al* 1986, Ripoli *et al* 2005). Clinical consequences of all these pathophysiological processes may be the heart failure. Impairment of cardiac function has been already observed in patients with clinically manifest hypo- or hyperthyroidism, however, inconsistencies of findings exist in subclinical thyroid dysfunctions. The aim of this study was to ascertain whether mild changes of free thyroxine concentration (fT4) were associated with an impairment of left ventricle function quantified by respective biological markers, in patients with clinically manifest chronic heart failure (CHF).

Methods

The study sample consisted from patients with clinically manifest, chronic congestive heart failure, examined in the course of EuroHeart Failure survey. Selection criteria and standard examination protocol of this multicentric program were in detail described elsewhere (Cleland

et al 2000, Rosolova *et al* 2005). Briefly, patients consecutively hospitalized during a time-span of 12 months for congestive heart failure or at discharge treated for this condition, were selected. Only patients from the Pilsen center of EuroHeart Failure survey were included into the present analysis (they represents about 30% of the Czech sample of EuroHeart Failure survey). Patients with free thyroxin concentration outside normal limits (9-22pmol/L) and /or on thyrostatics or L-thyroxin substitution were excluded. Information of personal and demographic characteristics, personal and family history of coronary heart disease, life-style and current pharmacotherapy were obtained at interview. Following standardized examinations were performed: Height and weight were measured in light indoor clothes without shoes using SECA 707 scales and measuring stick. Blood pressure was measured twice in the sitting position on the right arm, using standard mercury sphygmomanometers, with precision of 2mm of mercury. All used devices (i.e. scale and sphygmomanometer) were calibrated at the start of survey using appropriate standard procedures and by manufacturer reference. Venous blood samples were drawn after minimally 12 hour overnight fast. Estimation of total , HDL and LDL cholesterol as well as triglycerides and glycaemia was done in fresh blood specimens by use of commercial kits (Unimate, Roche Diagnostics, Mannheim, Germany) on Cobas Mira S Autoanalyser (Roche Diagnostics). Blood concentrations of thyroid stimulating hormone (TSH), FT4, total homocysteine (tHcy) and B-type natriuretic peptide (BNP) were estimated from frozen specimens (-80° C) by use of commercial FPIA kits (Abbott Diagnostics ,Wiesbaden, Germany) on AxSYM analyser. Intra-individual variability of these estimations was less than 2%. N-terminal pro-BNP (NT-proBNP) was estimated using ELISA by commercial kits (Biomedica, Vienna, Austria), with coefficients of variation less than 6%. For statistic evaluation STRATA 6 software was used. Mann-Whitney U test, Spearman correlation, Fisher Chi square and multiple logistic regression were calculated when necessary. All procedures were done according to Good Clinical Practice regulation and were approved by

the local Ethical Committee. The Informed consent was obtained from all subjects and all personal data were stored under the provisions of the Czech Data Protection Act.

Results

A total of 148 patients, 121 males and 27 females were included into this analysis. Personal and medical history, anthropometrical and biochemical characteristics of the study sample are given in table 1. Correlations between fT4 concentrations and natriuretic peptides are given in figure 1. Free thyroxine concentration was in continuous manner significantly positively associated with NT-proBNP and BNP (Fig.1).

The study sample was divided into three categories according to fT4 concentrations: low-normal fT4 (9-11.8pmol/L, i.e. 1st quintile), optimal fT4 (11.9-14.6 pmol/L, i.e. 2nd and 3rd quintile) and high-normal fT4 (14.7-22 pmol/L i.e. 4th and 5th quintile). Patients with low-normal fT4 were statistically significantly younger than those with optimal fT4 concentration (58.5 versus 64.9 years, resp.; $p=0.03$), while patients with high-normal fT4 significantly lower body mass index (26.3 versus 31.0 kg/m², resp.; $p=0.003$) and higher TSH level (1.15 versus 1.66 mU/L, resp; $p=0.003$). In terms of other characteristics (table 1), except natriuretic peptides we did not find any statistically significant differences. Differences in BNP and NT-proBNP among these defined fT4 categories are given in figure 2. Patients with low-normal fT4 showed significantly higher levels of NT-proBNP, as compared with subjects with optimal fT4. On the other hand, high-normal fT4 patients were observed to have a statistically significant increase in both, NT-proBNP and BNP (Fig 2), when compared with patients with optimal fT4. The significance of these differences also remains, if adjusted for potential confounders (age, gender, body mass index, systolic blood pressure, total cholesterol, glycaemia and homocysteine; table 2) by multiple logistic regression. Taking the relative risk of increase in natriuretic peptides in patients with optimal fT4 equal to 1, patients with low-normal fT4 showed a significant 30% risk of increased NT-proBNP. Similarly, patients with

high-normal fT4 showed significant odds ratio of increased NT-proBNP and BNP (1.27 and 1.26, resp.).

Discussion

In this study we found, that even mild changes of fT4, still within normal clinically accepted levels, may influence the burden of heart failure, quantified by its biological surrogates (ie. natriuretic peptides). This relationship between fT4 and natriuretic peptides had a J shape distribution. Lowest degree of heart failure was observed in the range of fT4 11.9-14.6pmol/L (2nd and 3rd quintile). Concentration of fT4 outside both ends of these limits (ie higher or lower) were associated with increased concentrations of heart failure surrogates, in spite that still remained within accepted normal ranges of fT4. This association was more evident at high-normal fT4 levels, than at low normal, where only increase of probably more sensitive marker (NT-proBNP) was observed.

Impairment of the left ventricular function is well-evident in patients with overt hypo- or hyperthyroidism, however, any evidence is lacking or not verified in patients with mild (subclinical) forms of thyroid dysfunction. Hemodynamic alteration measured by echocardiography or MRI, in patients after total thyroidectomy for thyroid cancer having not been substituted with thyroid hormones and development of a severe secondary hypothyroidism was observed (Bengel *et al* 2000). In comparison to controls, decreased left ventricular end-diastolic volume, cardiac index and increased vascular resistance were reported in subjects with still normal fT4, but already increased TSH, measured by MRI (Ripoli *et al* 2005).

Left ventricular dysfunction was also commonly observed in patients with overt hyperthyroidism. Elevation of T hormones in a short time-span resulted in an increase in myocardial contractility and cardiac output, partly because of tachycardia, moreover, long-term

elevation resulted again into heart failure. It was reported (Wei *et al* 2005) that patients with overt hyperthyroidism have six times higher BNP levels, than controls. Several case-reports observed left ventricle dilatation and low ejection fraction in patients with active Graves-Basedow thyreotoxicosis (Boccalandro *et al* 2003). Important pathophysiological mechanism of heart failure in chronic overt hyperthyroidism are probably associated with histological changes in myocardium and left ventricle hypertrophy. Overt hyperthyroidism was reported to produce focal necrosis and fibrosis of myocardial cells (Callas *et al* 1974). Recent experimental study observed in hamsters an increase of left ventricular diameter and decrease of ejection fraction only after 2 months of application of T hormones. Similarly, several clinical studies reported, that an excessive increase of T hormones, usually present in clinically manifest thyreotoxicosis, produces left ventricular hypertrophy and dilatation (Kuzman *et al* 2005, Ching *et al* 1996).

There is rather limited or non-existing evidence, whether normalization of thyroid status by T-hormones or thyrostatics also improve hemodynamic parameters, namely in patients with less serious forms of thyroid dysfunction. Virtually only a range of single case-reports observed, that thyrostatics produced not only decrease in fT4 in patient with severe thyreotoxicosis (before thyroidectomy were done as a final solution), but also increase in ejection fraction and decrease of left ventricular dilatation (Boccalandro *et al* 2003)

It is difficult to quantify cardiac dysfunction by only clinical methods. In our study we used the estimation of natriuretic peptides, which are now routinely available. B-type of natriuretic peptide is produced in the left ventricle on challenge of increase wall stress. It enables to quantify heart failure in a continuous manner and has an evident prognostic potential (Cowie *et al* 1997, Bettencourt *et al* 2000, Hobbs *et al* 2003).

The present study had several limitations. Beside relatively small sample size, the echocardiography was not routinely performed in the course of our study. Therefore, we cannot to analyze the association between free thyroxine and ejection fraction.

In conclusion, in the present study we observed that patients with clinically manifest chronic heart failure relatively have lower concentrations of natriuretic peptides, if their fT4 concentration ranges in a narrow optimal level (by definition used). Nevertheless, our study is limited by its retrospective, observational design. Therefore, it only allowed us to speculate on potential benefit of thyrostatics or Thormone supplementation in patients with heart failure and fT4 outside these optimal limits be treated or not. On the other hand, for the present, these patients should deserve particular attention and a very careful standard therapeutic management of heart failure.

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Table 1. Basic characteristics of the study sample [mean(standard deviation) or prevalence]

n (males/females)	148 (121/27)
age [years]	59.1 (11.58)
current smoking [%]	8.0
current or ex-smoking [%]	70.0
aetiology of heart failure [CHD/HPT/ICMP, %]	66/17/18
heart failure treatment proportion [%]:	
- <i>diuretics</i>	34
- <i>ACE inhibitors or ATII antagonists</i>	93
- <i>betablockers</i>	51
- <i>digoxin</i>	34
- <i>spironolacton</i>	61
lipid-lowering treatment [%]	18
antidiabetics [%]	30
body mass index [kg/m ²]	28.9 (12.16)
systolic blood pressure [mmHg]	120.6 (16.63)
diastolic blood pressure [mmHg]	72.7 (7.24)
total cholesterol [mmol/L]	6.94 (13.57)
HDL cholesterol [mmol/L]	1.34 (1.266)
triglycerides [mmol/L]	1.76 (1.984)
glycaemia [mmol/L]	6.73 (4.92)
total homocysteine [μmol/L]	14.62 (6.31)
thyreostimulating hormone [mU/L]	2.36 (4.47)
free thyroxine [pmol/L]	12.65 (3.34)
N-terminal proBNP [pg/ml]	956.9 (843.80)
BNP [pg/ml]	967.6 (841.88)

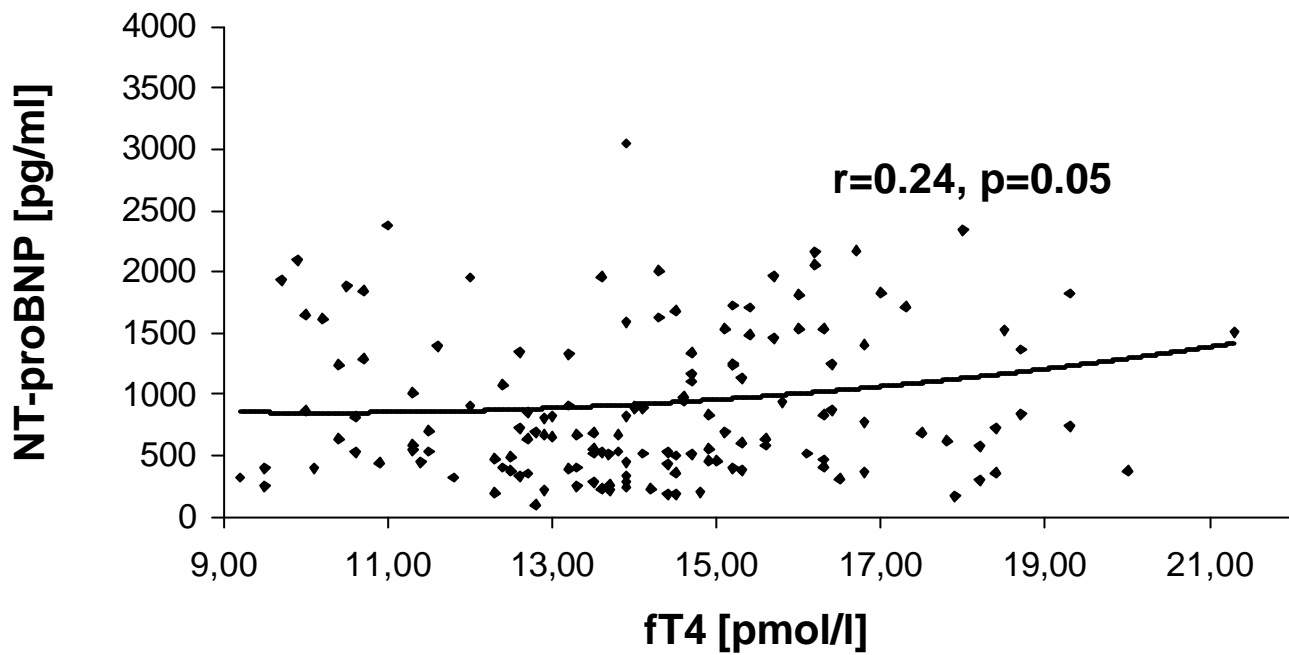
CHD, coronary heart disease; HPT, arterial hypertension; ICMP, idiopathic cardiomyopathy; ACE, angiotensine converting enzyme; ATII, angiotensine II; HDL, high density lipoprotein; BNP, B-type of natriuretic peptide

Table 2. Adjusted relative risk of increased natriuretic peptides in association with stratified free thyroxine concentrations, ie. optimal fT4 (11.9-14.6 pmol/L), low-normal fT4 (9-11.8 pmol/L) and high-normal fT4 (14.7-22 pmol/L) [Odds ratio (95% confidence intervals)]

	NT-proBNP	BNP
optimal fT4	1	1
low-normal fT4	1.30 (1.05-1.59)	1.12 (0.84-1.41)
high-normal fT4	1.27 (1.04-1.55)	1.26 (1.03-1.53)

multiple logistic regression; particular heart failure surrogates as dependent variables, adjusted for age, gender, body mass index, systolic blood pressure, total cholesterol, glycaemia and homocysteine.

NT-proBNP



BNP

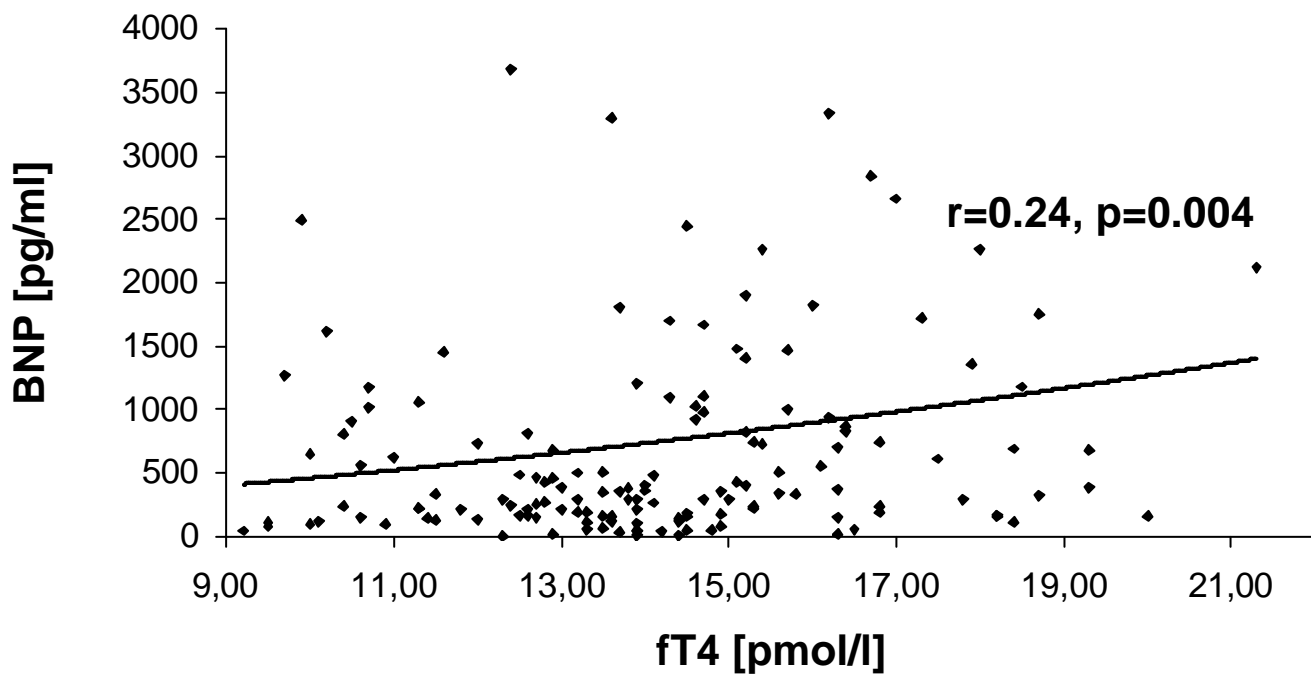


Figure 1. Correlation between free thyroxine concentrations and natriuretic peptides by Spearman's correlation [correlation coefficient, p value]

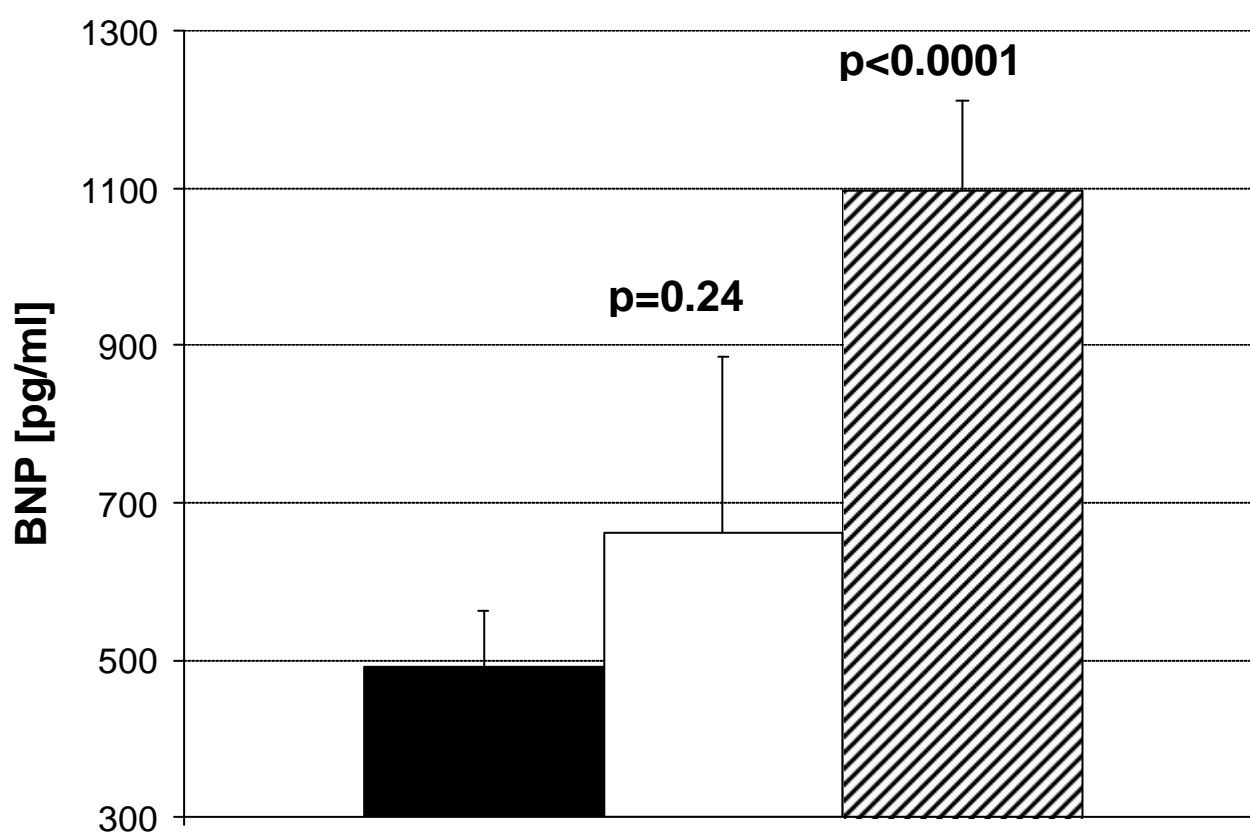
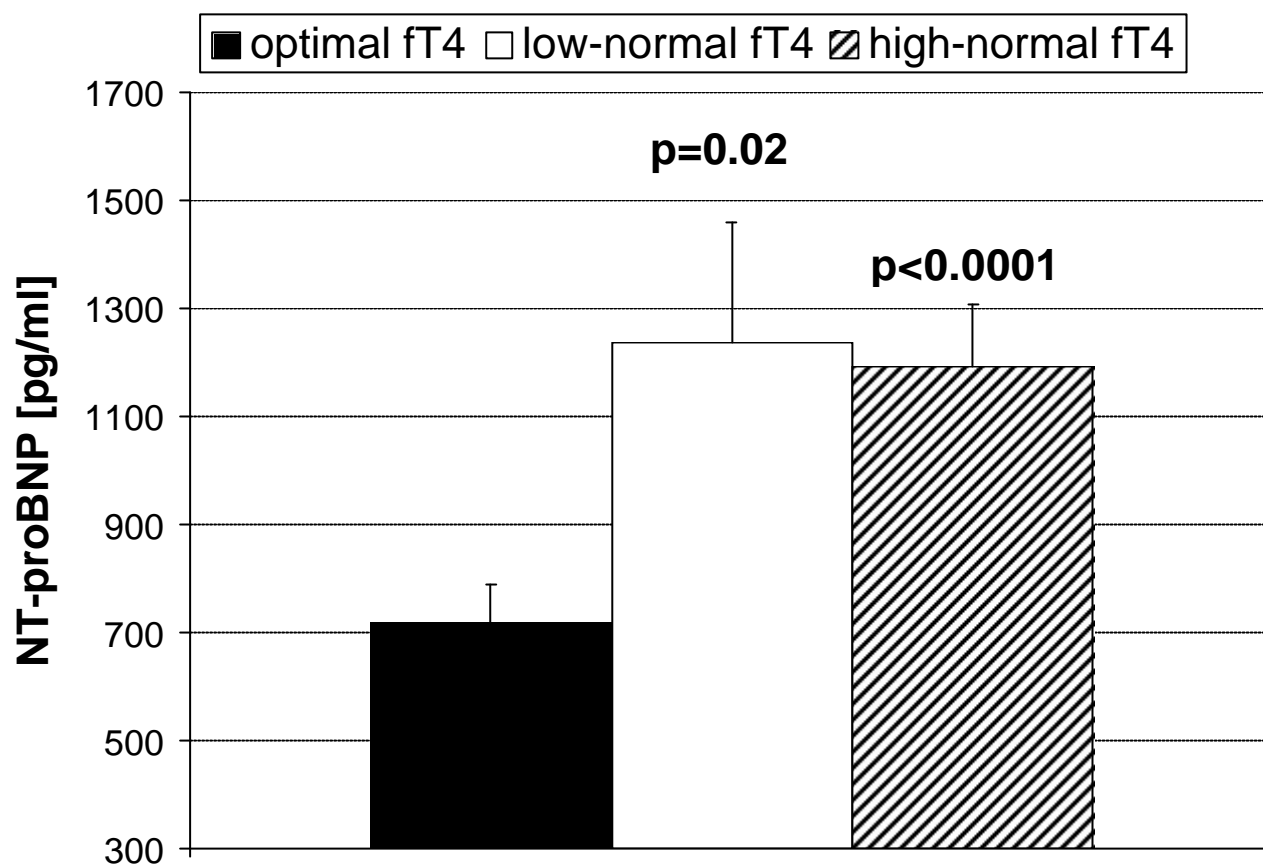


Figure 2: Concentrations of natriuretic peptides according to stratified free thyroxine (optimal, low-normal and high normal by definition) [mean, standard error, p value by Mann-Whitney U test]

