Elevation of NT-pro-BNP levels in high fever patients without heart failure

Kalp yetmezliği olmayan yüksek ateşli hastalarda NT-proBNP düzeylerinin yüksekliği

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ABSTRACT

Objective: We aimed to investigate the NT-proBNP levels in high fever patients without heart failure, to contribute to the proper request and interpretation of the test.

Methods: Patients group included 31 patients who admitted with a body temperature ≥38ºC and showed no signs of heart failure on their echocardiograms. Patients were internalized in the Infectious Diseases Clinic. The control group included 31 healthy subjects. NT-pro-BNP, Procalcitonin (Cobas e 601 Roche Diagnostics, Germany), Complete Blood Count (Beckman Coulter LH 780, USA) and CRP (Siemens BN II Nephelometer, Germany) levels were evaluated.

Results: Median (2.5-97.5 % percentiles) body temperature values of the patients and controls were 38.4 (38.0 - 39.8) and 36.1 (36-36.6) C° respectively ($p < 0.0001$). Median (2.5-97.5 % percentiles) NT-proBNP levels of the patients and control groups were; 240 (48.3- 2637) and 34.8 (5.35-86) ng/L respectively ($p < 0.0001$). NT-proBNP levels correlated significantly with body temperature, CRP, and PCT (r=0.761, 0.726 and 0.727 respectively, all p's < 0.0001). We observed recovery at 8 patients (at least 48 hours without fever), and median (2.5-97.5 % percentiles) NT-proBNP levels at time of fever and without fever were 378.3 (80.2- 1642) and 183 (9- 419.8) ng/L, respectively (p=0.007). In multiple regression analyses; body temperature, leucocyte count and PCT were found predictive for NT-proBNP levels. (R^2=0,456, F=11.987, P<0,001)

Conclusion: Despite to the normal cardiac functions, elevated NT- proBNP levels are observed in patients with fever. This situation should be considered in the interpretation of high NT- proBNP levels.

Keywords: CRP, Fever, NT-proBNP, Procalcitonin, Heart failure

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ÖZET

Amaç: Kalp yetmezliği olmayan yüksek ateşli hastalarda NT-proBNP düzeylerini değerlendirip testin doğru istem ve yorumuna katkı sağlamayı amaçladık.

Yöntem: Çalışma grubu hastaneye ≥ 38 π C ateş nedeniyle başvuran ve ekokardiyografide kalp yetmezliği saptanmayan 31 hastadan oluşmaktadır. Hastalar enfeksiyon hastalıkları kliniğine tedavi ve ileri araştırma amaçlı yatırıldı. Kontrol grubu 31 sağlıklıdan oluşmaktadır. NT-proBNP ve PCT düzeyleri, Cobas e 601 (Roche Diagnostics, Mannheim, Almanya), tam kan sayımı Beckman Coulter LH 780 (Miami-Florida, ABD), CRP ise Siemens BN II Nephelometre (Siemens, Almanya) cihazlarında çalışıldı.

Bulgular: Hasta ve kontrol grubunun vücut ısı medyan (2.5-97.5 % persentil) değerleri sırasıyla 38.4 (38.0 - 39.8) ve 36.1 (36-36.6) C° bulundu (p < 0.0001). Medyan (2.5-97.5 % persentil) NT-proBNP düzeyleri hasta ve kontrol grubunda sırasıyla 240(48.3- 2637) ve 34.8(5.35-86) ng/L (p < 0.0001) bulundu. NT-proBNP düzeyleri ile vücut ısısı, CRP ve PCT arasında anlamlı düzeyde korelasyon saptandı (sırasıyla r=0.761, 0.726 ve 0.727, p'ler < 0.0001). Sekiz hastada iyilişme (en az 48 saat ateşsiz dönem) gözlendi ve ateşli dönem ve ateşsiz dönem medyan (2.5-97.5 % persentil) NT-proBNP düzeyleri sırasıyla 378.3 (80.2- 1642) ve 183 (9- 419.8) ng/L bulundu (p=0.007). Çoklu regresyon analizinde vücut ısısı, lökosit sayısı ve PCT NT-proBNP düzeyleri üzerinde etkili bulundu. (R^2=0,456, F=11.987, P<0,001)

Sonuç: Normal kardiyak fonksiyona rağmen yüksek ateşli hastalarda artmış NT-proBNP düzeyleri gözlendi. Bu durum yüksek NT-proBNP düzeylerini değerlendirirken göz önüne alınmalıdır.

Anahtar Sözcükler: CRP, Ateş, NT-proBNP, Prokalsitonin, Kalp yetmezliği

INTRODUCTION

Natriuretic peptides (NP's) play a key role in the maintenance of cardiovascular homeostasis as regulatory hormones against volume and pressure overload (1). Brain natriuretic peptide (BNP) is the most widely used NP in clinical practice; it is measured either as a biologically active form of 32 amino acids, BNP1-32 or inactive amino terminal part of 76 amino acids, NT-proBNP. BNP plasma levels are low in healthy individuals but it is drastically increased in congestive heart failure (CHF). In CHF, both BNP and NT-proBNP are directly synthesized in response to the myocardial wall stress caused by the volume and pressure overload (2, 3, 4). The biological function of BNP is to reduce the preload and afterload of the heart via natriuresis, diuresis, and vasodilatation. The increased plasma NP levels in heart failure (HF) patients are found directly proportional to the severity of the CHF according to the New York Heart Association classification (4). Both are useful in the differential diagnosis of cardiac dyspnea from other origins of dyspnea (5). NP measurement as an initial diagnostic tool is especially beneficial in the absence of echocardiography (ECHO); the increased values indicate further examination and the normal values exclude the necessity of ECHO. The probability of CHF development in patients with normal plasma NP levels is very low (6). BNP and NT-proBNP are prognostic predictors in acute heart failure(4) and hypertension (7). The serial measurements of NPs help monitor CHF therapy since there are well-documented correlations between NP's levels and simultaneous hemodynamic and left ventricular function indicators (8).

Factors such as age and sex affect BNP and NT-proBNP levels; NP's levels rise with age (9) and are higher in women in every age group (10). On the other hand, lower NP levels are detected in obese individuals (1). Although BNP/NT-proBNP are widely used in the diagnosis and exclusion of CHF, their plasma levels are also increased in other diseases. These diseases may be of cardiac origins such as myocardial, cardiac valve diseases and atrial fibrillation or non-cardiac origins such as primary pulmonary diseases, anemia, stroke, subarachnoidal hemorrhage, hyperthyroidism, renal failure and septic shock (4,11,12,13,14).According to the animal and tissue culture experiments, there is significant evidence that the production and secretion of NPs are activated by endotoxins and inflammatory mediators (15).

The synthesis of NP's has stimulated ba various growth factors and cytokines including interleukin-1®, TNF-ζ, leukemia inhibitor factor (16, 17, 18). It is also shown that IL-6 induces ANP and BNP gene expression in rat ventricular myocytes (19). NP's are also shown to be expressed in specific immune tissues and cells such as timus, spleen, lymph nodes, tonsils; BNP plays a role in inflammation (20, 21).Based on this knowledge on the association of NP's with the inflammatory process, BNP levels were investigated in inflammatory and infectious diseases, sepsis, or critical illness (22, 23, 24) and high BNP levels were observed in infected patients without severe sepsis or septic shock.(25).

In this study; we aimed to investigate the NT-proBNP levels in high fever patients without heart failure, to contribute to the proper request and interpretation of the test.

METHODS

Study design and subjects

A total of 38 patients (males; 47.3 %, females; 52.7 %) attending to the emergency department (ED) of the hospital with fever (≥38°C) between October 2017-January 2018 were evaluated in this prospective observational study. All the patientswere conscious, oriented, non-pregnant, and normotensive with no-cardiacdisease history. Body temperatures were measured at the tympanic membrane by infrared technology with Covidien Genius2 (Mansfield, USA) thermometer (Accuracy +/-0.1˚C, given by the manufacturer) by trained nurses at the time of admission to ED. Blood culture, urine culture, complete blood cell count,C-reactive protein (CRP), procalcitonin (PCT), and NT-proBNP analyses were performed without delay from the patients whose body temperatures ≥38ºC. Urinalysis, complementary diagnostic serological and microbiological tests, and additional cultures were performed if required. To exclude comorbid CHF and cardiac valve disease, ECHO was performed in the first 24 hours by the same cardiology specialist, and 7 patients (4 females, 3 males) were excluded because of cardiac pathologies such as diastolic dysfunction, valve disease, infective endocarditis or pulmonary hypertension. Thus; 31 patients (48.3% males, 51.7% females) with normal ECHO signs who were internalized in infectious Diseases Clinic for further evaluation and therapy were included in the study. Median (2.5-97.5 percentiles) values for age was 44 (19-62.7) years. The control group consisted of 31healthy hospital staff volunteers (45.2% males, 54.8 % females) and median (2.5-97.5 percentiles) values for age was 41.7 (19-61) years.

Sampling

Antecubital vein area was wiped with 70% alcohol and 2% chlorhexidine and oneset of blood culture specimens (1 aerobe, 1 anaerobe) were taken in BD BACTEC (Becton Dickinson, New Jersey, USA; lot no:7297961) culture bottles. Blood was collected in BD (Beckton Dickonson, New Jersey, USA; lot no: 7275502) vacutainer tubes with pure gel for NT-proBNP, PCT, and CRP tests, and in BD (Beckton Dickonson, New Jersey, USA; lot no: 7142798) vacutainer tube with dipotassium ethylenediaminetetraacetic acid for complete blood count. The second set of blood cultures were taken from the other antecubital vein after 5-30 minutes. Blood samples were centrifuged at 1500 g for 10 min and studied without delay The patient was informed about the urine culture and requested towash the hands and wipe the genital area from front to back with a soapy gauze then take mid-flow urine into the sterile urine container Firatmed (Ankara, Turkey; lot:1703).

Methods

NT-proBNP (lot no22774806) and PCT (lot no 27885702) was measured by Cobas e 601 (Roche Diagnostics, Mannheim, Germany) with the electrochemiluminescence method. CRP was measured with the nephelometric method by Siemens BN II Nephelometer (Siemens, Germany). with Siemens Cardio Phase hsCRP kit (Marburg, Germany; lot no: 167561D). Complete blood cell count was measured by Beckman Coulter LH 780 analyzer (Miami-Florida, USA).

Statistical Analysis

The distribution of data was assessed by the Kolmogorov–Smirnov test, and since the data were abnormally distributed, results

were expressed as median (2.5–97.5 percentiles). The non-parametric data were compared using theMann-Whitney U test for independent samples and the Wilcoxon test for paired samples. The correlation of NT-proBNP levels with body temperature, CRP, PCT and leucocyte count was measured by Spearman correlation. MedCalc Statistical Software (version 12,Med- CalcSoftware, Mariakerke, Belgium) was used. To investigate the impact of body temperature, CRP, and PCT on patients' NT-proBNP levels, multiple regression analysis was performed using SPSS program (Statistical Package for Social Science, version 25;Chicago, IL). The level of significance was set at $p < 0.05$.

Informed consent of the patients was obtained and the study was approved by theethical committee of our institution. Decision number: 2017/514/114/5

RESULTS

A total of 62 participants (53.2% female) with a median age of 42.8 years were included in the study. The summary statistics of the patient and the control group was shown in Table 1. Comparisons of NT-proBNP levels for the patients and control groups were shown by Box and Whisker graphs as median, 25-75% percentiles, lower-upper limit, and extreme values (Figure 1). The diagnosis and characteristics of the patients among age, gender, body temperature, and NT-proBNP levels were summarized in Table 2.

NT-proBNP levels correlated significantly with body temperature, CRP, and PCT (p's <0.0001, r=0.761, 0.726 and 0.727 respectively) but there was no significant correlation between NT-proBNP and leukocyte count.In multiple regression analyses with NT-proBNP as dependent variable and body temperature, CRP, leucocyte count and PCT as independent variables; body temperature, leucocyte count and PCT were predictive variables for NT-proBNP (R^2=0,456, F=11.987 P<0,001 (Table 3).The patient group was divided into subgroups as culture-positive andculture-negative and although culture-positive patients had higher NT-proBNP levels; there was no significant difference between the two groups. (P=0.058) (Figure 2). During hospitalization body temperatures of 8 patients decreased to the normal levels thus second blood samples were taken to compare NT-proBNP levels with the timeof fever and without fever. There was a significant difference betweenNT-proBNP levels of two periods (P=0.0078). NT-proBNP levels and change % at the time of fever and without fever were shown in Table 4.

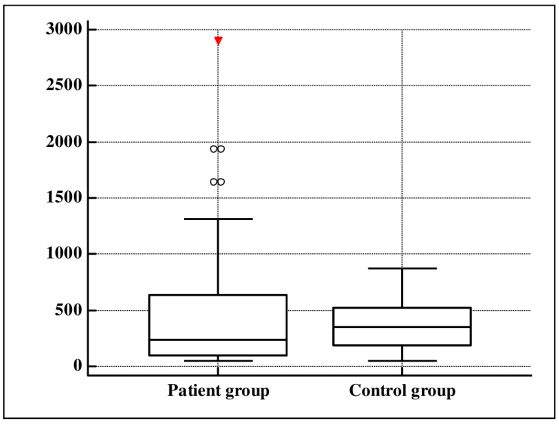

Figure 1. Box and Whisker plot of NT-proBNP levels in patient and control groups.(The values of the control group are multiplied by 10.)

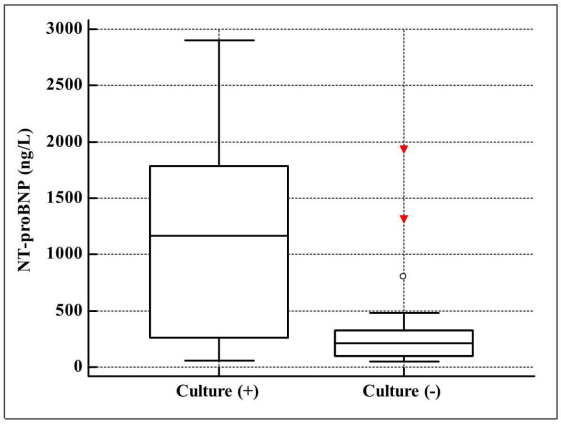

Figure 2. Box and Whisker plot of NT-proBNP levels in culture positive and culture negativepatients

Table 1. Summary statistics of the patient and control groups.

Parameter	Control Group Median (2.5–97.5% Percentile)	Patient Group Median (2.5–97.5% Percentile)	P
Age (year)	44 (19-63)	41.7 (19-61)	0,640
Gender(F/M)	17/14	16/15	0,801
Body temperature (ºC)	36.1(36-36.6)	38.4 (38-39.8)	*0.0001
CRP (mg/ L)	2.8(1.25-3.17)	163(12.3-331)	*0.0001
PCT (μg/L)	0.03(0.01-0.08)	0.30 (0.03-18.5)	*0.0001
NT-proBNP (ng/L)	34.8 (5.35-86)	240 (48.3-2637)	*0.0001

*p<0.05

Table 2. Summary statistics of the patient group

Diagnosis	Age(Years)	Gender	Body Temperature(ºC)	NT-proBNP (ng/L)	Culture
Soft tissue infection	49	Male	38	55.5	Negative
Febrile neutropenia	55	Male	38.9	693	Tissue:Aspergillus Flavus
Urinary tract infection /epididimorşit	60	Male	38.4	322	Negative
Spondylodiscitis	56	Female	38.3	116	Negative
Febrile neutropenia	46	Female	39	95.9	Negative
Fever of unknown origin	34	Female	38.2	186	Negative
Soft tissue infection	60	Male	38	240	Negative
Pneumonia/urinarytract infection	22	Male	38	1936	Negative
Urinary tract infection	52	Male	38	55.7	Negative
Menenjit	44	Male	38.7	209	Negative
Febrile neutropenia/Bacteraemia/ urinary tract infection	53	Female	39	1641	Blood+Urine Escherichia Coli
Urinary tract infection	24	Male	38	309	Negative
Brucella	54	Male	39	434	Blood:Brucella
B Bacteraemia/ urinary tract infection	42	Female	38.3	1935	Blood+Urine Escherichia Coli
Acute retroviral syndrome	26	Male	38.8	75	Negative
Febrile neutropenia/ Tifilitis	34	Male	38	188	Negative
Fever of unknown origin	26	Female	38	478	Negative
Fever of unknown origin	52	Male	38	801	Negative
Upper respiratory tract infection + urinary tract infection	19	Male	38.5	91.4	Urine; Escherichia Coli
Complicated urinary tract infection	46	Female	38.1	211	Negative
Complicated urinary tract infection	35	Female	40.1	1315	Negative
Complicated urinary tract infection /Pneumonia	52	Female	38.2	331	Negative
Diabetic foot infection	63	Male	38.3	2904	Wound: Enterobacter cloacae
Cellulite	54	Female	38.1	80.2	Negative
Upper respiratory tract infection	33	Female	38.8	313	Negative
Febrile neutropenia	41	Male	38.2	46.2	Negative
Spondilodiskit/prosthesis infection	62	Female	38.5	188	Negative
Febrilnötropeni/oral candidiyazis	22	Female	38	196	Negative
Catheter infection	20	Female	39	1642	Blood:Staphylococcus aureus
Oralcandidiasis/lower respiratory tract infection	40	Female	38	54	Sputum:Haemophilus influenzae
Still disease	19	Female	38.7	424	Negative

Table 3. Multiple Lineer Regression analyses using body temperature, CRP, PCT and leucoyte count as independent variables.

Variables	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	b	Std.Error	Beta		
(Constant)	-8725.7	2587.4		-3.372	0.001
Body Temperature	233.9	70.1	0.49	3.339	0.001
CRP	-1.21	1.02	-0.225	-1.184	0.214
Leucocyte Count	0.04	0.01	0.316	3.687	0.001
PCT	45.9	17.5	0.447	2.621	0.01

(R^2=0.457, F= 11.987, ANOVA p<0.0001)

Table 4. NT-proBNP levels of 8 patients at time of fever and without fever.

NT-proBNP (ng/L)		(%) Change	p
With Fever	Without fever		
186	107.9	41.9	*0.0078
693.4	222	67.9	
322.4	193	40.1	
91.4	24.2	73.5	
434.3	173	60.1	
80.2	9.03	88.7	
801.3	319.1	60.1	
1642	419.8	74.4	

*P<0.005

DISCUSSION

In this study, we investigated the NT-proBNP levels in patients with fever and without heart failure. We determined higher NT-proBNP levels in patients with fever compared to the control group. In 8 patients whose second measurements could be performed and recovery was observed, NT-proBNP levels decreased as the body temperature turned to the normal.

It has been shown that inflammatory cytokines play a role in the pathogenesis of HF. They also affect the natriuretic peptide levels in non-cardiac failure patients. Therefore they have been largely investigated in sepsis or septic shock patients. During response to infection/ inflammation, endothelium-derived substances such as adrenomedullin and endothelin are released. They are both important in vasculer tone regulation. Adrenomedullin causes vasodilation and endothelin is the potent vasoconstrictor. Vila et al. showed an increse in NT-proBNP levels in response to the bacterial endotoxin-induced inflammation in 10 males who received lipopolysaccharide (LPS).There was a correlation between NT-proBNP levels and heart rate, body temperature, CRP and IL1 levels after endotoxin (22). Lipopolysaccharides and pro-inflammatory cytokines stimulated the expression of BNP mRNA and protein secretion via p38 MAP kinase activation depending on dose ın a study conducted in cultered rat myocytes (26).In humans; a series of neuroendocrine and immune changes interact with each other during response to the bacterial endotoxins (27) and mediators of inflammation like IL-1, IL-6, and TNF are assumed as stimulants of BNP secretion (28). Goritsas et al. investigated BNP levels as a prognostic marker in community-acquired infections. They observed that NT-proBNP levels were significantly higher than the control group and the highest levels were observed in lower respiratory tract infection patients. They also found that NT-proBNP was a prognostic marker of the infection (23). Similar to our findings; in a study by Castillo et al, a significant decrease was observed in NT-proBNP levels of 9 patients with septic shock after recovery (24). Piechota et al. found a significant correlation between NT-proBNP, CRP, and PCT levels in 20 patients with sepsis. The correlation was more significant with NT-proBNP and CRP than NT-proBNP and PCT. NT-proBNP levels

were significantly lower in the survivor group than non-survivors (29). Similarly, Rudiger et al. showed a significant positive correlation with NT-proBNP, CRP, and leukocyte count in 12 critically ill patients and concluded that NT-proBNP and BNP levels were influenced by the systemic inflamatuar response(30).We showed significant correlation between NT-proBNP levels and body temperature, CRP and PCT but we couldn't show correlation between NT-proBNP levels and leucocyte count. The discrepancy between studies could arise from the diversity of patient characteristics; this study was performed in critically ill patients with septic shockwhile our study group consisted of patients with fever but without sepsis and heart failure and in generally stable status. Further researches with large populations are needed to show the relation between NT-proBNP levels and parameters showing systemic inflamatuar response. The variety of the diseases inducing fever and inclusion or exclusion of non-infective febrile patients might also cause the difference. In a study by Varpula et al.; a correlation was observed between positive blood culture and NT-proBNP levels in 254 severe sepsis and septic shock patients, and positive blood culture was shown as the predictor on NT-proBNP levels in linear regression analysis (31). In our study, although culture-positive patients had higher NT-proBNP levels; there was no significant difference between the two groups**.** In our study; body temperature, leucocyte count and PCT were found as the predictive variables for NT-proBNP levels.

In our control group; NT-proBNP levels showed great variability. Thus it would be more accurate to evaluate NT-proBNP increase with comparison to individual basal levels and percent differences might correlate better with the pathophysiology of the illness and so with other biochemical parameters. The lack of basal and/or secondary NT-proBNP levels of all patients was one of the limitations of our study. The other limitation was the heterogeneity of the disease for the patients' group. Besides we didn't have a sufficient number of patients to form homogenous subgroups.

We concluded that; despite to the normal cardiac functions, elevated NT- proBNP levels are observed in patients with fever. This situation should be considered in the interpretation of high NT- proBNP levels.

Ethical considerations: The patient gave informed consent and the study was approved by the Ethics Review Committee of Kartal Dr Lütfi Kırdar Research and Training Hospital 2017/514/114/5.

Conflict of interest: Authors declare that there is no conflict of interest.

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