CLINICS

CLINICAL SCIENCE

The diagnostic significance of NT-proBNP and troponin I in emergency department patients presenting with palpitations

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OBJECTIVE: This prospective study investigated the diagnostic significance of the N-terminal pro-brain natriuretic (NT-proBNP) and troponin I peptides in emergency department patients presenting with palpitations.

METHODS: Two groups of patients with palpitations but without documented supraventricular tachycardia were compared: a group with supraventricular tachycardia (n = 49) and a control group (n = 47). Both groups were diagnosed using electrophysiological studies during the study period. Blood samples were obtained from all of the patients to determine the NT-proBNP and troponin I levels within the first hour following arrival in the emergency department.

RESULT: The mean NT-proBNP levels were 207.74 ± 197.11 in supraventricular tachyarrhythmia group and 39.99 ± 32.83 pg/mL in control group ($p<0.001$). To predict supraventricular tachycardia, the optimum NT-proBNP threshold was 61.15 pg/mL, as defined by the receiver operating characteristic (ROC) curve, with a non-significant area under the ROC curve of 0.920 (95% CI, 0.86-0.97, $p<0.001$). The NT-proBNP cut-off for diagnosing supraventricular tachycardia had 81.6% sensitivity and 91.5% specificity. Supraventricular tachycardia was significantly more frequent in the patients with NT-proBNP levels ≥61.15 pg/mL (n = 44, 90.9%, $p>0.001$). The mean troponin I levels were 0.17 ± 0.56 and 0.01 ± 0.06 pg/mL for the patients with and without supraventricular tachycardia, respectively ($p<0.05$). Of the 96 patients, 21 (21.87%) had troponin I levels ≥0.01: 2 (4.25%) in the control group and 19 (38.77%) in the supraventricular tachycardia group ($p<0.001$).

CONCLUSION: Troponin I and, in particular, NT-proBNP peptide were helpful for differentiating supraventricular tachycardia from non- supraventricular tachycardia palpitations. Further randomized, large, multicenter trials are needed to define the benefit and diagnostic role of NT-proBNP and troponin I in the management algorithm of patients presenting with palpitations in emergency departments.

KEYWORDS: N-terminal of Brain Natriuretic Peptide; Troponin I; Palpitations; Supraventricular Tachycardia.

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INTRODUCTION

Palpitations, a common symptom of patients presenting to the emergency department, can be linked to serious (but treatable) cardiac arrhythmias (1). Many patients with this symptom arrive at the emergency department with or without documented supraventricular tachyarrhythmia (SVT). Diagnosing palpitations can be difficult in the emergency department, and the waiting period for a first appointment with an arrhythmia clinic can be long. A detailed history, physical examination, and electrocardiograph are of limited value in the differential diagnosis because most rhythm disturbances are paroxysmal in nature; therefore, in many cases, the etiology of palpitations remains unclear in the emergency department. The majority of these patients have anxiety or panic disorders (2,3). The most important problem faced by emergency department physicians is determining which patients to send to arrhythmia clinics.

The literature contains only limited data from small-scale studies assessing the diagnostic values of N-terminal of

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brain natriuretic peptide (NT-proBNP) and troponin I in patients presenting to the emergency department with palpitations (4-6). Consequently, this prospective study investigated the diagnostic significance of the NT-proBNP and troponin I peptides in emergency department patients presenting with palpitations.

SUBJECTS AND METHODS

Study Design and Patients

This prospective cohort study was performed in the ED of Abant İzzet Baysal University, School of Medicine Hospital, between 2011 and 2012. The study was approved by the local ethics committee. During the study period, 326 consecutive patients with palpitations were treated in the emergency department. All of the patients' baseline electrocardiograms (ECGs) were normal. Blood samples were obtained from all of the patients within the first hour following arrival in the emergency department. After providing pre-hospital care, we excluded 175 patients who met the exclusion criteria described below. A total of 151 patients were directed to the Cardiology Arrhythmia Clinic to undergo an electrophysiological study. Some of these 151 patients underwent this study based on their 12-lead ECGs, but some patients were diagnosed based on their histories, symptoms, and physical examinations. In addition, 55 patients were excluded from the study for other reasons, including failing to provide informed consent forms (n = 38), presenting with atrial fibrillation (n = 7), and failing to undergo an electrophysiological study (n = 10). Ninety-six patients met the inclusion criteria and were included in the study. Two patient groups were compared: an SVT group (n = 49) and a control group (n = 47). During the study period, both groups were diagnosed using electrophysiology studies. The recruitment, exclusion, and subsequent grouping of all patients are also shown in the flowchart (Figure 1). We used blood samples from the SVT and control groups to determine the NT-proBNP and troponin I levels.

Data on baseline demographic characteristics, clinical history, and clinical signs were gathered by trained research personnel in the emergency department. Electrocardiographs were obtained and interpreted by the attending physician in the emergency department. The exclusion criteria were age <16 years, a history of renal insufficiency, trauma, severe coronary artery disease, right and/or left systolic dysfunction, pneumonia, pulmonary embolism, carcinoma, pneumothorax, pleural effusion, intoxication (drugs), anaphylactic reactions, asthma exacerbation, chronic renal failure requiring hemodialysis, diabetes mellitus, hypertension, atrial fibrillation (paroxysmal or sustained in both conditions), ventricular tachycardia (paroxysmal or sustained in both conditions), and other causes of elevated NT-proBNP and troponin I levels. Patients with a myocardial infarction or acute renal failure were also excluded, as these conditions are known to increase NT-proBNP and troponin I levels.

Measurement of NT-proBNP and Troponin I Levels

Blood samples were obtained from all of the patients to determine the NT-proBNP and troponin I levels within the

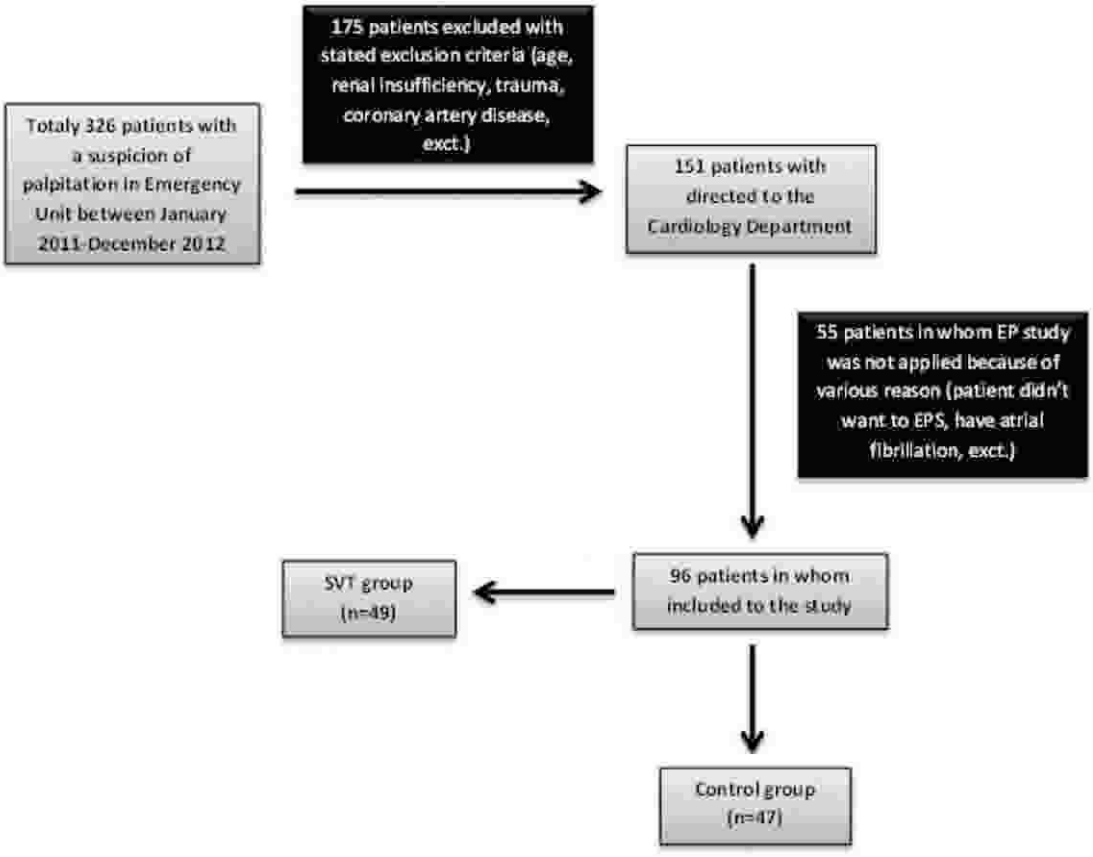

Figure 1 - Recruitment, exclusion, and subsequent grouping of all patients.

first hour after arriving in the emergency department. During the initial evaluations, a 5-mL blood sample was collected in tubes containing potassium ethylenediaminetetraacetic acid (1 mg/mL blood). The samples were centrifuged at 4 ℃, and the plasma was then separated and frozen at −80 ℃ before analysis. Samples were analyzed using the Roche NT-proBNP electrochemiluminescent assay, and testing was performed on an Elecsys 1010 analyzer (Roche Diagnostics, Mannheim, Germany). The assay precision, analytical sensitivity, interferences, and stability have all been described previously (6). The troponin I level was analyzed in samples using ELISA kits (Roche Diagnostics), and the results were evaluated according to the manufacturer's instructions (with a 99th percentile cutoff point of 0.1 pg/mL).

Electrophysiological Study Protocol

The patients selected to undergo an electrophysiological study had already undergone extensive negative workups, including risk factor analysis, patient history, physical examination, elimination of postural hypotension or hypoglycemia, baseline ECG, carotid sinus massage, 24-h ambulatory monitoring, and echocardiogram. The electrophysiological study was performed in the case of either an absent evident etiology or a clinically suspected cardiac cause. An echocardiogram and a complete electrophysiological study were performed. The electrophysiological study included measuring the sinus node recovery time, HV interval at baseline and under stress by incremental pacing, inducibility of ventricular arrhythmia by programmed ventricular pacing (with three cycles and three extra stimuli), and inducibility of supraventricular arrhythmia using an atrial pacing protocol. The electrophysiological study results were considered positive with the induction of a rapid supraventricular arrhythmia with symptoms similar to the patient-reported symptoms.

Statistical Analysis

The baseline characteristics were reported as counts and proportions or means ± standard deviations, as appropriate. Continuous variables were compared between the groups using nonparametric rank tests (Mann-Whitney U-test and Kruskal-Wallis test), and qualitative variables were compared using Pearson's chi-square test. The diagnostic value of NT-proBNP was assessed using receiver operating characteristic (ROC) curve analysis. Logistic regression models were fitted to calculate the risk (odds ratio [OR] and 95% confidence interval [CI]) for SVT. All models were evaluated for interactions, and none were found. *p*-values <0.05 were considered statistically significant. The SPSS ver. 15.0 (SPSS, Chicago, IL) statistical software was used.

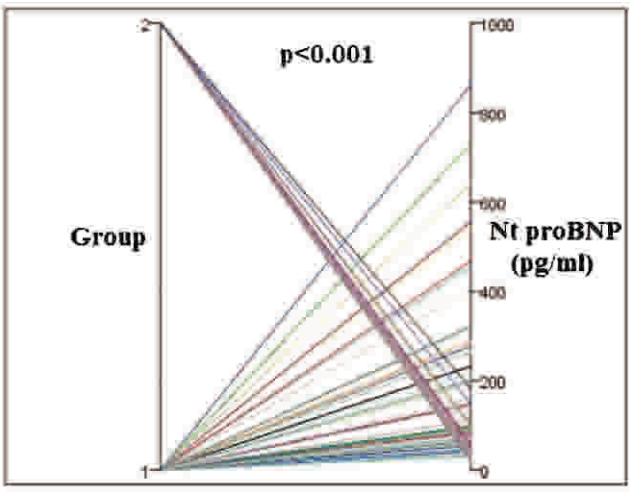

Figure 2 - The mean NT-proBNP levels of the two groups (SVT and control).

RESULTS

The majority of the patients were female, less than 35 years of age, and presented with a history of more than five palpitation episodes. The mean patient age was 34±21 years (71% females, 29% males). The baseline and clinical characteristics are shown in Table 1.

The mean ± SD NT-proBNP levels were 207.74±197.11 and 39.99±32.83 pg/mL for the patients with and without SVT, respectively ($p<0.001$; Figure 2). To predict SVT, the optimum NT-proBNP threshold was 61.15 pg/mL, as defined by the ROC curve, with a significant area under the ROC curve of 0.920 (95% CI 0.86-0.97, $p<0.001$; Figure 3). An NT-proBNP cut-off level ≥61.15 pg/mL for diagnosing SVT had 81.6% sensitivity and 91.5% specificity. SVT was significantly more frequent in the patients with NT-proBNP levels ≥61.15 pg/mL (n = 44; 90.9%, $p<0.001$). The mean ± SD troponin I values were 0.17±0.56 and 0.01±0.06 pg/mL for the patients with and without SVT, respectively ($p = 0.018$). Of these 96 patients, 21 (4.25%) had troponin I levels ≤0.001 pg/mL. Two of these 21 patients (4.25%) were in the control group, and 19 (38.77%) were in the SVT group ($p<0.001$). To predict SVT, the optimum threshold of

Table 1 - Baseline patient characteristics.

	SVT group (n = 49)	Control group (n = 47)	*p*-value
Gender (female)	71.4%	65.9%	0.102
Age (years)*	34 (17/54)	33 (18/57)	0.138
Smoking	36.1%	41.2%	0.192
First episode	24.5%	34.9%	0.041
Systolic blood pressure * (mm Hg)	118 (107/127)	116 (109/129)	0.651
Diastolic blood pressure * (mm Hg)	75 (67/86)	73 (66/89)	0.721
Heart rate * (beats per minute)	88 (64/92)	84 (61/95)	0.292
Left ventricular ejection fraction * (%)	62 (58/72)	60 (59/70)	0.271
Left atrial diameter* (mm)	3.0 (2.4/3.3)	2.8 (2.4/3.1)	0.108
NT-proBNP (pg/mL)	207.74±197.11	39.99±32.83	< 0.001
Troponin I	0.17±0.56	0.01±0.06	0.018

*(median - min/max).

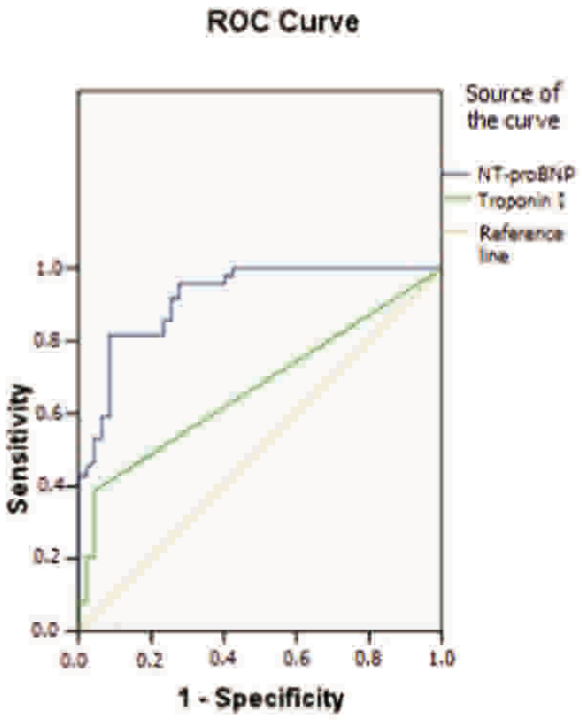

Figure 3 - ROC curve analysis of NT-proBNP and troponin I.

troponin I was ≥0.005, as defined by the ROC curve, with a significant area under the ROC curve of 0.670 (95% CI, 0.56-0.78, $p = 0.004$; Figure 2). A troponin I cut-off value ≥0.005, which was necessary to diagnose SVT, achieved 38.8% sensitivity and 95.7% specificity.

A Cox proportional logistic regression hazards analysis, which was performed to determine the predictive value of the evaluated parameters (e.g., age, gender, heart rate, mean diastolic pressure, NT-proBNP level, and troponin level), showed that NT-proBNP, but not troponin I, was an independent predictor of SVT (OR 1.130, 95% CI, 0.001-1596.251, $p = 0.000$; OR 0.968, 95% CI, 0.951-0.988, $p = 0.974$, respectively). The addition of echocardiographic parameters to the model did not change the results.

In patients with SVT, the NT-proBNP levels were positively correlated with the heart rate at admission ($r = 0.532$, $p<0.001$), systolic ($r = 0.322$, $p = 0.024$) and diastolic ($r = 0.320$, $p = 0.031$) blood pressures, and white blood cell (WBC) count ($r = 0.318$, $p = 0.019$). There was no significant correlation between the NT-proBNP levels and other laboratory findings ($p>0.05$). In addition, in patients with SVT, the troponin I levels were positively correlated only with the heart rate at admission ($r = 0.418$, $p = 0.021$) and WBC count ($r = 0.323$, $p = 0.031$). There was no significant correlation of the NT-proBNP and troponin I levels with left atrium size in either group ($r = 0.213$, $r = 0.245$, respectively, $p>0.05$).

DISCUSSION

Our study demonstrated that both NT-proBNP and troponin I assessments can potentially improve the sensitivity of the clinician's evaluation of patients presenting to the emergency department with palpitations. In addition, we showed that a NT-proBNP level >61.15 pg/mL was an independent predictor of SVT.

Palpitations are defined as sensations of a rapid or irregular heartbeat (7). Many patients with palpitations have anxiety or panic disorders. Studies have shown that the prevalence of panic disorder in patients with palpitations is 15-31% (8,9). However, palpitations can also be linked to serious, although treatable, cardiac arrhythmias (1). In previous studies, 50% of palpitation cases were traced to cardiac causes (10,11). Diagnosing palpitations can be difficult in the emergency department, and the wait time for a first appointment at an arrhythmia clinic can be long. An important problem faced by emergency department physicians involves determining which patients to refer to arrhythmia clinics. If a cause can be determined in the initial clinical assessment, management decisions are relatively straightforward. In addition, another important problem is that palpitation symptoms recur frequently. A detailed history, physical examination, and ECG can aid the differential diagnosis because most rhythm disturbances are paroxysmal in nature. An ECG obtained during a palpitation episode is the reference standard, but obtaining a valuable ECG is usually impossible (12). Consequently, in many cases, the etiology of palpitations remains unclear in the emergency department. We found that NT-proBNP and troponin I provided important diagnostic information that is useful in the early evaluation of palpitations in emergency departments.

Natriuretic peptides (BNP and NT-pro-BNP) are markers of myocardial wall stress and have been used as markers for some types of heart disease (13). Previous studies have concluded that a rapid heart rate resulted from stimulation by natriuretic peptides. Schiebinger et al. showed that increased atrial stimulation from 120-240 beats per minute led to a significant increase in atrial natriuretic peptide secretion in isolated rat hearts (14). Qi et al. observed a significant increase in BNP associated with various tachycardias in an experimental animal study (15). Some studies have shown that natriuretic peptide is increased in plasma during acute attacks of paroxysmal supraventricular tachycardia and falls rapidly after reversion to sinus rhythm (16,17). These studies concluded that stimulation of natriuretic peptide secretion may be responsible for the polyuria and natriuresis associated with SVT. Pecini et al. found a significant increase in atrial and brain natriuretic peptides during atrioventricular nodal reentry tachycardia in peripheral venous blood (18). In another interesting study, Brueckmann et al. determined the time course of NT-proANP levels in patients undergoing radiofrequency catheter ablation for paroxysmal supraventricular tachycardias (19). They observed that NT-proANP levels increased in patients presenting with paroxysmal supraventricular tachycardias and decreased shortly after RF catheter ablation, possibly reflecting a transient reduction in ANP secretion from injured myocardial cells. They concluded that lower NT-proANP levels may serve as a useful laboratory marker with which to determine the long-term success of radiofrequency ablation. Previous studies have shown that NT-proBNP was more sensitive compared with BNP and had an advantage in detecting patients with mild or asymptomatic heart disease because of its longer half-life (20,21). Consistent with these studies, we also preferred NT-proBNP over troponin I as a diagnostic marker. Additionally, we observed that NT-proBNP could be used

as a diagnostic marker with which to identify supraventricular tachycardia patients in the emergency department. A NT-proBNP cut-off ≥61.15 pg/mL to diagnose SVT achieved 81.6% sensitivity and 91.5% specificity. In addition, only NT-proBNP was an independent predictor of SVT in this study.

Similar to our results, there have been a few reports of troponin elevation in patients with various tachyarrhythmias (5,6,22). Kanjwal et al. identified patients with supraventricular tachycardia who had elevated troponin levels without evidence of coronary artery disease (23). All of these patients had elevated troponin I levels and underwent coronary angiography that revealed normal epicardial coronary arteries. In the present study, we observed that the mean troponin I values were significantly higher in the SVT patients compared with the controls. In addition, we excluded patients with coronary artery disease or acute renal failure, as these conditions are known to increase NT-proBNP and troponin I levels (22,23).

Our study showed the significant prognostic value of NT-proBNP and troponin I for diagnosing palpitations in the emergency department. We believe that the exact mechanism for these elevations may be the shortening of diastole with subsequent subendocardial ischemia. Coronary perfusion, particularly to the subendocardium, occurs predominantly during the diastole phase (21). In SVT, the increase in heart rate causes diastole to shorten, with a significant decrease in subendocardial perfusion.

Some limitations of this study should be discussed. First, the main limitation of our study was its relatively small population. This study was performed over a one-year period. Because a small sample size results in low statistical power for equivalency testing, negative results may be simply due to chance. Second, our study had a single-center prospective design. Future prospective studies at larger multicenters are required to confirm our results. The other limitation is that we cannot apply our results to the general population because of the broad exclusion criteria.

To our knowledge, this is the first report of a marker (NT-proBNP and troponin I) strategy aimed at diagnosing SVT based on common palpitations. We have shown that the routine evaluation of NT-proBNP and troponin I may be used to identify supraventricular tachycardia patients in the ED. The results of this study require validation in large, multicenter studies prior to the incorporation of NT-proBNP and troponin I as diagnostic markers in the clinical arena.

AUTHOR CONTRIBUTIONS

Ocak T conceived and designed the study and was responsible for the acquisition of data. Erdem A conceived and designed the study and was responsible for the analysis and interpretation of data, manuscript draft and critical revision of the manuscript. Duran A and Ozlu MF were responsible for the acquisition of data. Tekelioglu UY conceived and designed the study and was responsible for the acquisition of data. Ozturk S conceived and designed the study and was responsible for the analysis and interpretation of data and critical revision of the manuscript. Ayhan SS and Tosun M were responsible for data analysis and interpretation. Koçoglu H was responsible for data acquisition and manuscript draft. Yazici M was responsible for manuscript draft and critical revision of the manuscript.

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