ORIGINAL RESEARCH

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Association among tenascin-C and NT-proBNP levels and arrhythmia prevalence in heart failure

Abstract

Purpose: Tenascin-C (TN-C) and amino-terminal fragment of the B-type natriuretic peptide (NT-proBNP) are the important predictors in prognosis of heart failure (HF). The aim of this study was to analyze the relationship of TN-C and NT-proBNP levels with the frequency and severity of ventricular arrhythmia.

Materials and Methods: Our study included 107 HF patients with EF < 45%. According to Holter analysis, the patients were divided into two groups as malignant arrhythmia group (n=29) with Lown Class 4a and 4b arrhythmia and benign arrhythmia group (n=78) with Lown Class 0-3b arrhythmia. The groups were compared with respect to levels of TN-C and NT-proBNP. The relationship of TN-C and NT-proBNP levels with frequency of ventricular premature beat (VPB) was also analyzed.

Findings: NT-proBNP (5042.1±1626 versus 1417.1±1711.6 pg/ml) and TN-C (1089±348.6 versus 758.5±423.9 ng/ml) levels were significantly higher in the malignant arrhythmia group than that of the benign arrhythmia group (p<0.001). A significantly strong positive correlation (r=0.741, p<0.001) was found between the NT-proBNP levels and VPB numbers of the patients, whereas a significantly weak positive correlation was detected between the TN-C levels and VPB numbers of the patients (r=0.347, p<0.001).

Conclusion: This study has shown that NT-proBNP and TN-C levels increase in the HF patients with malignant arrhythmia. In the HF patients; the frequency of ventricular arrhythmias also increases as NT-proBNP and TN-C levels increase. However, in this study, the old NT-pro BNP seems better than the TN-C.

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Heart failure (HF) is a complex syndrome accompanied by systemic hypoperfusion, pulmonary and/or systemic congestion [1]. In patients with HF, ventricular arrhythmias may lead to symptoms and/or sudden cardiac death [2]. In patients with congestive HF, serum levels of amino-terminal fragment of the B-type natriuretic peptide (NT-proBNP) have been shown to have prognostic importance [3]. NT-proBNP is mostly released from the ventricles as a response to increased intraventricular pressure and myocardial tension [3]. Increased intraventricular pressure and myocardial strain cause electrophysiological impairments, such as slowed intraventricular conduction, afterdepolarization and triggered ventricular ectopic beats, which lead to increased arrhythmogenesis [4]. In cardiac pathologies, tenascin-C (TN-C) is associated with macrophage infiltration and inflammation [5]. Expression of TN-C increases in HF patients with varying degrees of myocardial inflammation. Myocardial inflammation is known to be an arrhythmia trigger [6]. TN-C and NT-proBNP levels are better indicators of prognosis of patients with HF when they are tested together in the patients with dilated cardiomyopathy (DCMP) [7].

Increased levels of NT-proBNP and TN-C are serum indicators of elevated intraventricular pressure, myocardial strain and inflammation resulting in ventricular arrhythmias; thus, we aimed to investigate the relationship among these serum indicators and the occurrence of severe ventricular arrhythmia in HF patients.

Materials and Methods

Patients

This study included 107 HF patients with left ventricular ejection fraction (EF) <45% who had been admitted to our clinic. Following a detailed physical examination, 12-lead electrocardiography, echocardiography, fasting blood glucose, lipid profile and kidney functions were tested. Patients' medications were recorded. Venous blood samples for TN-C and NT-proBNP measurement were obtained from all the patients and 24-hour Holter ECG recordings were performed. This study was conducted in accordance with criteria of Helsinki Declaration and approved by the Ethics Committee of the Çukurova University Medical Faculty. Informed consent was obtained from all of the participants involved in the study.

Patients who were pregnant or had infection and inflammatory disease, malignancy, collagen tissue diseases, serum creatine level >2.5 mg/dl, acute decompensated heart

failure, atrial fibrillation, CRT and ICD implanted and under 18 years old were excluded from the study.

All the patients included in the study underwent transthoracic echocardiographic examinations. The transthoracic echocardiographic examinations were performed using Vivid s5[®] Cardiovascular ultrasound system (3S 1.5- 3.6 MHz probTransthoracic GE Medical System, Buckinghamshire, UK). The procedure was conducted by giving the patients left lateral decubitus position following 5-minutes resting period. The procedure was applied as recommended by The American Society of Echocardiography; left ventricular end-diastolic and end-systolic diameters, EF were measured by M-mode echocardiography from the parasternal long-axis view.

Continuous 24-h ECG recordings were obtained using Holter recorders (DMS, Hunfelden-Dauborn, Germany). Cardioscan II Premier (DMS) Software was used in obtaining data. Holter data were evaluated based on ACC/AHA ECG and ambulatory ECG Clinical Evaluation Report [8]. Mean 24-hour heart rate, SDNN (standard deviation of all R-R intervals where R is the peak of a QRS complex), SDANN (standard deviation of the 5-min mean R-R intervals where R is the peak of a QRS complex), arrhythmias, conduction disturbances were recorded for each cases. Artifacts were analyzed automatically and manually, and all artifacts were eliminated.

Ventricular arrhythmias were classified according to the Lown Criteria [9]: Class 0: no ventricular premature beat; Class 1: ventricular premature beats (VPB) <30 beat/hour; Class 2: VPB >30 beats/hour; Class 3a: multifocal VPB; Class 3b: ventricular bigeminy or trigeminy; Class 4a: two consecutive VPB; and Class 4b: three or more consecutive VPB/nonsustained ventricular tachycardia (VT). In our study, the Lown Class 4a and 4b patients were evaluated as the malignant arrhythmia group. The Lown Class 0-3b patients were evaluated as benign arrhythmia group. Since our study included only patients with heart failure, and because the number of patients with class 0 of the Lown classification is very low in heart failure patients as well, class 0 group was not considered as a separate control group.

VPB were counted in numbers according to the result of the 24-hour Holter monitoring. Peripheral venous blood samples were collected from the patients and centrifuged at 15,000 g for 15 minutes. Serum samples were stored at -80°C until the day of analysis. TN-C level was measured by enzyme linked immunosorbent assay (ELISA) method using a TN-C kit (ELISA kit for Human Tenascin, catalog no. E91975Hu; USCN Life Science Inc., Wuhan, China). Results were

TABLE 1. Comparison of demographic, clinical and laboratory data of the groups with and without malignant arrhythmia in accordance with Lown Classification.

	Lown Classification		<i>P</i>
	Lown 0-3b N=78	Lown 4a-4b N=29	
Age	61.3±11.8	65.4±14.9	0.135
Male N(%)	56 (% 72)	21 (% 72)	0.949
SBP (mmHg)	114.9±28.2	107.9±27.2	0.253
DBP (mmHg)	77.9±18.4	72.1±15.2	0.134
Dilated CMP N(%)	36 (% 46)	6 (% 21)	0.017
Ischemic CMP N(%)	42 (% 54)	23 (% 79)	0.017
DM N(%)	24 (% 31)	8 (% 28)	0.749
HT N(%)	47 (% 60)	12 (% 41)	0.081
HL N(%)	20 (% 26)	7 (% 24)	0.874
Smoking N(%)	38 (% 49)	13 (% 45)	0.720
NYHA			
Class 2 N(%)	21 (% 27)	2 (% 7)	0.081
Class 3 N(%)	25 (% 32)	12 (% 41)	
Class 4 N(%)	32 (% 41)	15 (% 52)	
ACEI/ARB use N(%)	49 (% 63)	16 (% 55)	0.471
Statin use N(%)	28 (% 36)	11 (% 38)	0.846
Aldosterone use N(%)	25 (% 32)	14 (% 48)	0.121
Beta blocker use N(%)	44 (% 56)	15 (% 52)	0.665
CCB use N(%)	8 (% 10)	1 (% 3)	0.259
Amiodarone use N(%)	8 (% 10)	2 (% 7)	0.596
Digoxin use N(%)	13 (% 17)	6 (% 21)	0.628
Aspirin use N(%)	16 (% 21)	6 (% 21)	0.984
Furosemide use N(%)	17 (% 22)	4 (% 14)	0.354
EF (%)	35.3±6.3	33±7	0.107
Holter time (min)	1358.1±29	1359.8±27	0.795
Mean heart rate (beat/day)	78.5±11	86.3±13	0.003
VPB (beat/day)	419.9±457.2	2,106.7±3,314.3	<0.001
NT-proBNP (pg/ml)	1,417.1±1,711.6	5,042.1±1626	<0.001
TN-C (ng/ml)	758.5±423.9	1,089±348.6	<0.001
K (mEq/L)	4.3±0.6	4.3±0.7	0.787
Ca (mg/dl)	9.3±0.7	9.2±0.8	0.637
Mg (mg/dl)	2.2±0.4	2.1±0.3	0.558
CRP (mg/dl)	1.4±1.8	1.3±1.5	0.716
Cr (mg/dl)	1±0.3	1.1±0.4	0.481
Total cholesterol (mg/dl)	160±40.4	154.3±35.6	0.502
TSH (mIU/l)	2.3±1.2	2.2±1	0.841
SDNN (ms)	111±39.3	72.5±31	<0.001
SDANN (ms)	96.8±36.9	59.3±33.1	<0.001

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ca, calcium; CCB, calcium channel blocker; CMP, cardiomyopathy; CRP, C-reactive protein; Cr, creatine; DM, diabetes mellitus; DBP, diastolic blood pressure; EF, ejection fraction; HT, hypertension; HL, hyperlipidemia; K, potassium; Mg, magnesium; NT-proBNP, amino-terminal fragment of the prohormone brain-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SDNN, standard deviation of all R-R intervals; SDANN, standard deviation of the 5-min mean R-R intervals; TN-C, tenascin-C; TSH, thyroid stimulating hormone; VPB, ventricular premature beats

TABLE 2. Correlation between NT-proBNP and TN-C levels of patients and SDNN/SDANN values

	NT-proBNP		TN-C	
	r	P	r	P
SDNN (ms)	-0.535	<0.001	-0.098	0.315
SDANN (ms)	-0.562	<0.001	-0.082	0.403

Abbreviations: NT-proBNP, amino-terminal fragment of the prohormone brain-type natriuretic peptide; SDNN, standard deviation of all R-R intervals; SDANN, standard deviation of the 5-min mean R-R intervals; TN-C, tenascin-C

expressed as ng/mL. NT-proBNP was measured by electro-chemiluminescence immunoanalysis method using Pathfast (Mitsubishi Kagaku Iatron, Inc. Tokyo, Japan) device and Roche kit for NT-proBNP. The results were given in terms of pg/ml. The measurements were performed in The Central Laboratory of Medical Faculty of Çukurova University.

Statistical analysis

SPSS 19.0 software package was used for analysis of data. The categorical measurements were given in number and percentile while numerical measurements were expressed as mean and standard deviation (median and minimum-maximum when required). Kolmogorov-Smirnov test was used to determine whether numerical measurements were normally distributed. Pearson correlation was used if correlation hypotheses were confirmed between numerical measurements obtained by the NT-proBNP, TN-C and Holter measurements, whereas Spearman correlation was used if hypotheses were not confirmed. Kruskal Wallis test was used in comparison of more than two (Lown) independent groups. Bonferroni-corrected Mann-Whitney U test was used in comparison of two subgroups. In all the statistics, statistical significance level was accepted as $P < 0.05$.

Results

Mean age of the patients in our study was 62.4 ± 12.8 years and 72% of the patients were male. When distributed according to the heart failure classification; 21%, 35% and 44% of the patients were classified as New York Heart Association (NYHA) Class 2, NYHA Class 3 and NYHA Class 4, respectively. The use of beta-blockers, calcium channel blockers, amiodarone and digoxin were 55%, 8%, 9% and 18% among the patients, respectively. Mean EF value of the patients was found to be $34.7 \pm 6.5\%$. Mean VPB count was $877.1 \pm 1,902.9$ beats/day in the 24-hour Holter recording of

the patients. According to the Lown Classification; incidence of Class 4a and Class 4b were determined as 15% and 12%, respectively.

When the patients were distributed to groups as malignant arrhythmia group (Class 4a-4b) and benign arrhythmia group (Class 0-3b) according to Lown Classification, the distributions of the groups with respect to age, gender, cardiovascular risk factors and NYHA functional classifications were similar ($P > 0.05$) (Table 1). No differences with respect to blood pressure, medications, blood electrolyte levels and EF were found between the groups ($P > 0.05$). The groups were similar in terms of C-reactive protein (CRP), creatinine, total cholesterol and thyroid-stimulating hormone (TSH) levels ($P > 0.05$). Medical history of ischemic CMP was more frequently encountered in the malignant arrhythmia group (79% versus 54%) ($P = 0.017$). Mean heart rate was found significantly higher in the malignant arrhythmia group (78.5 ± 11 versus 86.3 ± 13 beats/min) ($P = 0.003$). SDNN (111 ± 39.3 versus 72.5 ± 31 ms) and SDANN (96.8 ± 36.9 versus 59.3 ± 33.1 ms) values were found significantly lower in the malignant arrhythmia group ($P < 0.001$, for both). The frequency of VPB was significantly higher in the malignant arrhythmia group (419.9 ± 457.2 versus $2,106.7 \pm 3,314.3$ beats/day) ($P < 0.001$). NT-proBNP (1417.1 ± 1711.6 versus $5,042.1 \pm 1,626$ pg/ml) and TN-C (758.5 ± 423.9 versus $1,089 \pm 348.6$ ng/ml) levels were significantly higher in the malignant arrhythmia group ($P < 0.001$) (Figures 1 and 2). Both Figures 1 and 2 are Box (Whisker) plots. This plot is an exploratory graphic, used to show the distribution of a dataset. Since the distribution of NT-proBNP and TN-C were not normal, we used this plot to show the difference between the groups. We included the outliers in the analysis by using nonparametric approaches (Kruskal Wallis test, Spearman Rank Correlation). A strong positive correlation was detected between the NT-proBNP levels of the patients and VPB counts ($r = 0.741$, $P < 0.001$) (Figure 3). A weak positive correlation was determined between TN-C levels of the patients and VPB counts ($r = 0.347$, $P < 0.001$) (Figure 4). A negative correlation was detected between NT-proBNP levels of the patients and SDNN, SDANN values ($r = -0.535$, $P < 0.001$; $r = -0.562$, $P < 0.001$, respectively) (Table 2). No correlation was found between TN-C levels and SDNN and SDANN values. When all the patients were evaluated, a weak positive correlation was found between the NT-proBNP and TN-C levels ($r = 0.291$, $P = 0.002$).

FIGURE 1. NT-proBNP levels of the groups with and without malignant arrhythmia in accordance with Lown Classification. The lines below and above the box show the least and the greatest values excluding outliers, respectively. The top and bottom lines of the box show the upper and lower quartiles. The middle line (the thick horizontal line) shows the median of the data; the circles and stars show the outlier values (less than 3/2 times of lower quartile value or more than 3/2 times of upper quartile value).

Discussion

In the recent years, measurement of the serum indicators has gained importance in detection of the patients who carry a high risk of cardiac events. For patients with HF, increased end-diastolic pressure and volume lead to elevation of NT-proBNP levels, while inflammatory processes increase TN-C levels [3,5]. Fujimoto *et al.* noted that TN-C and NT-proBNP levels of the DCM patients, measured at discharge, are very good prognostic markers for detection of HF when evaluated concomitantly [7]. Di Loreto *et al.* encountered higher incidences of sudden cardiac death in he patients with Lown Class 4a and 4b than patients with lower Lown Class [10]. Bigger *et al.* analyzed 400 patients who had acute MI and reported that the higher levels of Lown Classification had significantly higher mortality rates than the next lower levels [9]. In our study, NT-proBNP and TN-C levels were found to be significantly higher in the malignant arrhythmia group (Lown Class 4a-4b) ($5,042.1 \pm 1,626$ versus $1,417.1 \pm 1,711.6$ pg/ml and $1,089 \pm 348.6$ versus 758.5 ± 423.9 ng/ml, respectively) ($P < 0.001$). The detection of higher levels of NT-proBNP and TN-C in the malignant arrhythmia group is consistent with the other literature data since Lown Class 4a-4b is known associated with a poor prognosis [7,9,10].

FIGURE 2. TN-C levels of the groups with and without malignant arrhythmia accordance to the Lown Classification. The middle line (the thick horizontal line) shows the median of the data; the circles show the outlier values.

The relationship between the basal BNP and NT-proBNP levels and development of ventricular arrhythmia in the patients with chronic HF has been investigated in a several studies. A relationship between formation and frequency of VT/VF and increased levels of BNP and NT-proBNP has been reported [6,11-14]. Although Theuns *et al.* did not find such a relationship between basal serum BNP levels and incidence of ventricular arrhythmia that requires treatment of ICD during a 24-week follow-up, they observed this relationship due to the high levels of BNP during follow-up [15]. In our study, we have also detected increased incidence of VPB correlated with increased levels of NT-proBNP, and we have found higher levels of NT-proBNP in the Lown Class 4a-4b patients. This correlation can be explained by the fact that elevated myocardial tension increases ventricular arrhythmias. Increased intraventricular pressure, myocardial tension and scar formation increase the synthesis of NT-proBNP and cause electrophysiological impairments such as slowed intraventricular conduction, reentry, afterdepolarization and triggered ventricular ectopic beats [3,4]. A direct correlation has been reported between left ventricle end-diastolic volume and development of ventricular arrhythmia in the SOLVD study, which involved 311 HF patients [16]. Another study reported that increased left ventricular wall tension evaluated

FIGURE 3. Strong positive correlation was found between NT-proBNP level and VPB count ($r=0.741$, $P<0.001$).

by left ventricular pulmonary capillary wedge pressure increased nonsustained VT [17].

A study investigating the relationship between TN-C levels and development of ventricular arrhythmia in patients with chronic HF has not previously been conducted. In our study, a positive correlation has been observed between TN-C levels and frequency of VPB beside higher detection of TN-C levels in the malignant arrhythmia group ($r=0.347$, $P<0.001$). Albert *et al.* noted that isolated myocardial fibrosis and inflammation fields may form an ideal substrate for fatal arrhythmias [18]. This may be due to the fact that myocardial fibrosis and inflammation with increased expression of TN-C plays a role as an arrhythmogenic factor in the pathogenesis of ventricular arrhythmia. Streitner *et al.* reported an association between increased levels of IL-6 and malignant ventricular arrhythmia [19]. In the MADIT and AVID studies, a reduced incidence of ventricular arrhythmia was attributed to the use of statins in the ICD-implanted patients. This reduced incidence of ventricular arrhythmia may be indirectly associated with anti-inflammatory characteristics of statins [20,21]. In contrast, Konstantino *et al.* found no association between ventricular arrhythmias and inflammatory markers in their study [22]. In the light of these data, more studies to clarify the association between inflammation and ventricular arrhythmia are needed.

It has been reported that increased incidence of VPB via Holter ECG monitoring may be associated with worsening in

FIGURE 4. Weak positive correlation was found between TN-C level and VPB count ($r=0.347$, $P<0.001$).

HF and sudden cardiac death (SCD) [9,23-25]. In our study, the significantly higher frequency of VPB in the group with malignant arrhythmia versus the group without malignant arrhythmia ($2,106.7\pm 3,314.3$ versus 419.9 ± 457.2 beats/day, $P<0.001$) may be a marker of poor prognosis.

It is known that ischemia alters myocardial electrophysiology by affecting automaticity, myocardial refractory state and conduction, and that ischemic CMP is strongly associated with malignant arrhythmias [26]. In our study, higher frequency of the patients with medical history of ischemic CMP in the malignant arrhythmia group (Class 4a-4b) according to Lown Classification supports this data (79% versus 54%) ($P=0.017$).

Increased levels of catecholamines in circulation, resulting from activation of sympathetic nervous system, is associated with a poor prognosis. Increased sympathetic activity results in increased heart rate during resting period and decreased heart rate variability (HRV) [27]. In our study, SDNN (111 ± 39.3 versus 72.5 ± 31 ms, $P<0.001$) and SDANN (96.8 ± 36.9 versus 59.3 ± 33.1 ms, $P<0.001$) values were significantly lower and mean heart rate was significantly higher (86.3 ± 13 versus

78.5±11 beats/min) ($P=0.003$) in the malignant arrhythmia group.

In our study, a significant positive correlation was found between the levels of NT-proBNP and TN-C ($r=0.291$, $P=0.002$). It is known that increased end-diastolic volume and pressure cause activation of proinflammatory cytokines such as TNF- α and IL-6 [28-30].

In the UK-HEART and Multicenter Postinfarction Program (MPIP) studies, decreased SDNN values were reported to be associated with HF-related deaths and SCD [31,32]. SDNN is known to be correlated with SDANN [33]. In our study, a significant negative correlation between HRV indices (SDNN and SDANN) ($r=-0.535$, $P<0.001$) and NT-proBNP values ($r=-0.562$, $P<0.001$) was found. These findings are consistent with those in the literature. In the literature, the relationship between inflammation and HRV is not clear. Aronson *et al.* demonstrated no relationship between TNF- α levels and HRV indexes, but found a negative correlation with IL-6 and SDNN [34]. In our study, a correlation between HRV indexes (SDNN and SDANN) and TN-C, known to be associated with inflammation, was not found. To clarify the relationship between inflammation and HRV, more studies are warranted.

The small number of included patients in the study was an important limitation. In our study, neither the association between NT-proBNP and TN-C levels and clinical endpoints nor the relationship between increased levels of NT-proBNP and TN-C during follow-up period and frequency and severity of arrhythmia were investigated. We found a correlation between the VPB and the NT-proBNP, and a weak correlation with TN-C. Since the levels of these biomarkers would change under other pathological conditions, elevation of these biomarkers by themselves should not be the sole indicators for the prediction of malignant ventricular arrhythmias. The duration of 24-hour Holter monitoring applied to the patients may not be sufficient to detect the frequency and severity accurately in all the patients.

Conclusion

NT-proBNP and TN-C levels were higher in the Lown Class 4a-4b group. Frequency of VPB increased as the levels of NT-proBNP and TN-C increased. Increased levels of NT-proBNP and TN-C may be considered as biomarkers of malignant ventricular arrhythmias, and NT-pro BNP seems to be better a better biomarker than TN-C. These biomarkers may be used for identifying high risk patients in the future.

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