

Atrial Fibrillation, Heart Failure with Impaired Ejection Fraction and Natriuretic Peptides

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Abstract

Objectives: Atrial fibrillation (AF) is frequent in clinical practice and its relationship with heart failure (HF) is well known. The present study investigated clinical and biochemical characteristics and N-terminal pro-B type natriuretic peptide (NT-proBNP) levels of patients with AF and HF with impaired left ventricle ejection fraction in a closed cohort.

Materials and Methods: Patients who had AF, left ventricle ejection fraction (LVEF) <50% and who had a NT-proBNP measurement in the stable phase of HF, who applied to the İzmir Kemalpaşa State Hospital's cardiology clinic between January and June 2018 were enrolled. Characteristics of 137 patients and the correlation of the change in creatine, glomerular filtration rate (GFR), and NT-proBNP to the clinical factors were investigated.

Results: Mean age, LVEF, CHA₂DS₂ and CHA₂DS₂VASc scores were 71.8±9.1 years, 46.9±5.3%, 3.2±1.3 and 4.7±1.3 respectively in the study group. The median NT-proBNP was 1553.00 pg/mL in stable phase of HF. Elevated

NT-proBNP in decompensated phase was present in 32 patients and the median was 2944.50 pg/mL. Initial GFR was correlated positively with hemoglobin but strongly negatively with age, CHA₂DS₂ and CHA₂DS₂VASc scores. NT-proBNP was correlated strongly positively with CHA₂DS₂VASc and systolic pulmonary artery pressure and negatively with LVEF as expected.

Conclusion: Both of AF and HF are related to an increase of NT-proBNP level. Present study suggests a median 92.05% increase compared to stable phase level in NT-proBNP is related to decompensation. This finding emphasizes the importance of level of stable phase-NT-proBNP in patients with AF for the diagnosis of decompensation, because of no consensus on upper limit of NT-proBNP in patients with AF while the knowledge of higher levels is not new. Also, the relationship between GFR and CHA₂DS₂, CHA₂DS₂VASc scores implicates careful GFR monitoring in patients with higher scores to avoid improper drug doses such as NOAC's.

Keywords: Atrial fibrillation, heart failure, NT-proBNP



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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in cardiology practice. In Europe and United States of America, one of four adults is to be expected to develop AF in lifetime. The predicted boost of patients with AF is multifactorial. The increase of AF-related diseases such as hypertension (HT), heart failure (HF), coronary artery disease (CAD) and improved life expectancy are important factors but increased clinical sensibility to diagnose and treat AF has an outstanding value. Hence, AF is related to all-cause mortality and morbidity such as HF and stroke in both genders, a great effort is given to prevent undesirable events⁽¹⁾. Another important issue is the cost of AF, which rises depending on AF-related complications such as stroke if AF is not treated properly⁽²⁾. Many patients have both AF and HF and these diseases can augment each other in multi different ways. AF is related to an increased mortality and worse prognosis in both HF with impaired left ventricle ejection fraction (LVEF) and preserved LVEF. Although natriuretic peptides (NP) are essential in the diagnosis and follow-up of HF, to interpret their levels in the presence of AF may be challenging because of their elevated levels even in the absence of HF. Yet, there is no consensus for the upper normal limit in the presence of AF^(3,4). In the present study, we aimed to investigate characteristics and NT-proBNP levels in stable HF patients who have AF with impaired LVEF in our closed cohort.

Material and Methods

Outpatient data of İzmir Kemalpaşa State Hospital's Clinic of Cardiology was reviewed retrospectively for a given time through the hospital record system (HRS) PROBEL. Patients were selected through their diagnostic ICD-10 codes. Patients diagnosed with AF were searched. The diagnosis of AF was made with an electrocardiogram, which demonstrates the typical pattern of AF in accord to European recommendations. After that, the patient records about their history, laboratory and imaging results were reviewed. Since the hospital was the only healthcare facility in a cohort with more than 100,000 people and AF

was considered as a chronic disease, data were interpreted as closed cohort data. AF-patients with a LVEF <50% and having a NT-proBNP measurement during stable phase of HF were included. Stable phase of HF was defined according to European guideline as a treated patient with symptoms and signs of HF, who remained unchanged for a minimum one-month period. Prosthetic heart valves, moderate to severe mitral stenosis and end stage renal disease requiring hemodialysis were considered as the exclusion criteria. Medications such as oral anticoagulant (OAC) agents and treatment adherence were controlled via social security system through the Internet. LVEF measurements were made with 2D transthoracic echocardiogram with the modified Simpson's rule according to European recommendations.

The ethic approval of the present the study was obtained on 14.11.2018 from the University of Health Sciences Turkey, İzmir Tepecik Health Practice and Research Center, with the decision number: 2018/13-13. All the authors had no conflict of interest.

NT-proBNP was the choice of natriuretic peptide because of its more stable profile and the measurements were made with Cobas® system using Elecsys proBNP II from Roche Diagnostics GmbH.

Statistical Analysis

In the statistical analysis, data were given as mean \pm standard deviation when the variables distributed normally and as median if they did not in the statistical analysis. Categorical variables were defined with frequencies and percentages. IBM SPSS-22 program was used for analysis.

Results

After screening the patient-data between January and June 2018, 137 patients with AF and LVEF <50% with NT-proBNP measurement during stable phase of HF were included. The mean age was 71.8 \pm 9.1 years. Gender pattern was slightly female dominant (n=79 female (57.7%) vs n=58 male (42.3%)). Comorbid diseases such as CAD, 34.3% (n=47), Diabetes Mellitus, 31.4% (n=43),

HT, 89.8% (n=123), cerebrovascular event (CVE), 21.9% (n=30) and embolic event (peripheral arterial or venous), 2.9% (n=4) were present in the study group in given frequencies. Other diseases such as malignancy, dementia, other neurological disorders (Parkinson's or epilepsy) and thyroid disease were present at the rates of 5.1% (n=7), 3.6% (n=5), 5.1% (n=7) and 11.7% (n=16), respectively. AF diagnosis was paroxysmal in 12 patients (8.8%) and persistent in 125 patients (91.2%) while only eight patients were in sinus rhythm during recruiting. The mean follow-up duration of the study group in the clinic was 2.50 ± 1.23 years. OAC treatment was present in 135 of 137 (98.5%) patients while 36.8% of patients were taking OAC treatment for more than 3 years. Only 8.7% of the study group was taking warfarin hence remaining 91.3% was on non-vitamin K antagonist OAC (NOAC) treatment. Any bleeding was reported in 32 patients (23.4%), which was defined minor in 20 (62.5%) patients and major (a drop more than 2 g/dL in haemoglobin or any bleeding required transfusion) in 12 patients (37.5%) in accord to International Society of Thrombosis and Haemostasis (ISTH), but there was no report on life-threatening or critical organ bleeding or death. Through the HRS PROBEL, the initial creatine and glomerular filtration rates (GFR) before OAC therapy and the actual (last) creatine and GFR measurements were found. GRF was calculated via the Cockcroft-Gault method. While all of patients had NT-proBNP level in stable phase of HF, 32 patients had also NT-proBNP measurement in decompensated phase of HF. Descriptive demographics of study group are given in Table 1.

The study group consisted of elderly patients with impaired LVEF and high $\text{CHA}_2\text{DS}_2\text{VASc}$ score as seen in Table 1. The mean GFR of the group was <60 mL/min, which is also another high-risk predictor. The initial and actual creatine and GFR, stable and decompensated NT-proBNP levels and their alterations are given in Table 2. There was a decrease in GFR during the follow-up with a mean duration of 2.50 ± 1.23 years, which is attributed to aging and sarcopenia related to the HF, while creatine

levels stayed similar. The median NT-proBNP level of AF patients with impaired LVEF in stable phase was 1553.00 pg/mL, which may be considered very high for a stable patient, while median NT-proBNP was 2944.50 pg/mL in decompensation, which is almost twice as high according to the latest recommendations. Lastly, the correlation between some important clinical parameters and creatine, GFR, NT-proBNP and their changes were investigated. The correlation for baseline GFR and haemoglobin was positive, while for age, CHA_2DS_2 and $\text{CHA}_2\text{DS}_2\text{VASc}$ scores negative. NT-proBNP was correlated with

Table 1. Descriptive demographics

	n	Mean \pm SD
Age	137	71.82 \pm 9.17 years
CHA_2DS_2	137	3.23 \pm 1.33
$\text{CHA}_2\text{DS}_2\text{VASc}$	137	4.70 \pm 1.36
Systolic BP	137	143.07 \pm 23.83 mmHg
Diastolic BP	137	84.10 \pm 13.48 mmHg
Heart rate	137	87.12 \pm 19.76 bpm
LVEF	137	46.99 \pm 5.32%
LA diameter	137	51.44 \pm 5.05 mm
Tricuspid Annulus	124	39.76 \pm 4.20 mm
SPAP	137	41.10 \pm 8.46 mmHg
Hemoglobin	137	12.77 \pm 2.15 g/dL
Fasting glucose	137	113.3 \pm 31.5 mg/dL
HDL	135	50.59 \pm 13.13 mg/dL
LDL	135	97.09 \pm 34.25 mg/dL
TG	135	130.30 \pm 80.62 mg/dL
Urea	137	44.98 \pm 17.70 mg/dL
Creatine	137	1.19 \pm 0.29 mg/dL
Na	137	141.66 \pm 3.25 mmol/L
K	136	4.53 \pm 0.50 mmol/L
Uric Acid	110	7.25 \pm 2.03 mg/dL
GFR	137	56.14 \pm 16.34
NT-proBNP	137	1553.00 pg/mL (median)
TSH	137	1.30 mU/L (median)

BP: Blood pressure, LVEF: Left ventricle ejection fraction, LA: Left atrium, SPAP: Systolic pulmonary artery pressure, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride, Na: Sodium, K: Potassium, GFR: Glomerular filtration rate, TSH: Thyroid stimulant hormone, NT-proBNP: N-terminal pro-B type natriuretic peptide, SD: Standard deviation, n: Number
Baseline demographics of study population is given in table1. Median levels of NT-proBNP is used because of its non-normal distribution

CHA₂DS₂VASc and systolic pulmonary artery pressure (SPAP) positively and with LVEF negatively. The change in NT-proBNP showed a positive correlation with systolic blood pressure and SPAP.

Discussion

Patients with AF constitute an increasing part of daily cardiology practice nowadays. Treatment with OAC in AF is crucial to prevent ischemic complications such as embolic stroke anticoagulation management in this population became easier with NOAC in last years. Accompanying HF is another important issue in AF patients for both patients and physicians in decision-

making process. HF may be either with preserved or impaired LVEF. Hence HF classification is made through the LVEF and defined as reduced (LVEF <40%), mildly reduced (LVEF between 40 and 50%) and preserved (LVEF ≥50%) ejection fraction HF, the present study excluded patients with preserved LVEF and focused on group with impaired LVEF⁽³⁾.

The growing experience with AF and HF patients underlined the importance of renal functions. Either relatively nephrotoxic effect of drugs used in the treatment of HF such as diuretics and Renin- Angiotensin System (RAS) inhibitors or progressive nature of HF with a well-known relation with kidneys necessitates to monitor renal functions. Renal functions are crucial in patients with AF taking NOAC because the relation between bleeding and erroneous over-dosed NOACs is well-known⁽⁵⁾. The present study has shown that GFR is decreasing in patients with AF and HF with impaired LVEF within years even creatine levels of these patients stay similar. Decreasing of GFR according to Cockcroft-Gault method may be related to advancing age and decreasing body weight while serum creatine stays similar. Loosing body weight in HF should not be evaluated only as volume loss, but also the catabolic process of HF, known as sarcopenia, should be taken into consideration and weight fluctuation in these patients should be taken seriously. A strong negative correlation between GFR and age is expected but the

Table 2. Changes during follow-up

	n	Mean ± SD
Initial creatine	52	1.19±0.40 mg/dL
Actual creatine	137	1.19±0.29 mg/dL
ΔCreatine	52	-0.01±0.42 mg/dL
Initial GFR	52	62.29±16.11
Actual GFR	137	56.14±16.34
ΔGFR	52	-7.71±12.9
Stable phase NT-proBNP	137	1553.00 pg/mL (median)
Decompensated NT-proBNP	32	2944.50 pg/mL (median)
ΔNT-proBNP (%)	32	1524.50 pg/mL (92.05) (median)

GFR: Glomerular filtration rate, NT-proBNP: N-terminal pro-B type natriuretic peptide, SD: Standard deviation, n: Number
 Δ: Change
 Hence NT-proBNP is distributed non-normally, median values are used

Table 3. Correlation of renal functions and NT-proBNP with some clinical parameters

		Creatine	ΔCreatine	GFR	ΔGFR	NT-proBNP	ΔNT-proBNP
Age	r	0.053	-0.192	-0.622**	-0.092	0.212*	0.274
CHA ₂ DS ₂	r	0.062	-0.299*	-0.232**	-0.090	0.156	0.291
CHA ₂ DS ₂ VASc	r	0.058	-0.333*	-0.308**	-0.079	0.237**	0.192
Systolic BP	r	0.001	0.337*	0.018	-0.126	0.004	0.474**
Heart rate	r	-0.048	-0.201	0.056	0.042	0.178*	0.065
LVEF	r	0.015	0.219	0.031	-0.121	-0.266**	-0.092
LAD	r	-0.125	0.246	0.148	-0.061	0.193*	0.192
SPAP	r	-0.023	0.183	-0.076	0.004	0.330**	0.468**
Hemoglobin	r	-0.063	-0.007	0.308**	-0.016	-0.206*	-0.125

BP: Blood pressure, LVEF: Left ventricle ejection fraction, LAD: Left atrial diameter, SPAP: Systolic pulmonary artery pressure, NT-proBNP: N-terminal pro-B type natriuretic peptide, SD: Standard deviation

*=p<0.05, **=p<0.01, r= Spearman's Rho Correlation (0.01-0.29 low, 0.30-0.69 medium, 0.70-0.99 high relation, -negative relation)

negative strong correlation with CHA_2DS_2 and CHA_2DS_2 VASc scores make close follow-up of renal functions essential in high-score patients to avoid overdosing. The positive correlation of GFR and hemoglobin indicates the clinical importance of anemia, which is not uncommon in HF patients. The presence of anemia in this group of patients should also raise attention for careful follow up renal function to avoid misdosing.

AF and HF augment each other in multi-different ways. To interpret the NP in this group of patients is especially difficult hence both diseases are related to increased levels of NP⁽⁶⁾. NPs are very important in the diagnosis of acute HF. Different cut-off values are proposed for different NPs and even different societies suggest different cut-off values for the same NP. Until a recent time, European guideline recommended NT-proBNP >125 pg/mL for the diagnosis of acute HF hence American recommendation was between 300 and 1800 pg/mL based on particular age groups and clinical presentations^(3,7-10). Very recently, HF study group of European Society of Cardiology published a position paper on NP's and updated recommendations for upper limits of NT-proBNP to diagnose acute HF. The new European position paper put forward the data of PRIDE study and updated its recommendations similar to the American recommendations according to age-specific upper limits^(8,9,11). The last European guideline recommends NT-proBNP >450 pg/mL if the patient is younger than 50 years, >900 pg/mL if between 50 and 75 years and >1800 pg/mL if older than 75 years to diagnose acute HF⁽¹¹⁾. With the growing number of AF patients, the interpretation of NP has become a hotspot nowadays, searching for the inclusion cut-off's in this group. Very recently, Santema and colleagues published an original article using the data of BIostat-CHF trial. They compared biomarker profiles such as NT-proBNP of patients with HF comparing AF versus sinus rhythm and reduced versus preserved LVEF⁽¹²⁾. While studying patients with reduced LVEF according to the last European definition as LVEF <40%, patients with mildly reduced (40-49%) LVEF are excluded from the analysis,

which represents an important group especially in AF. To overcome this dilemma, we included all the HF patients even reduced and mildly reduced by the definition, and named the group as "impaired" LVEF, which can be used to define patients excepting the ones with preserved ejection fraction HF. Santema et al.⁽¹²⁾ showed a median of NT-proBNP as 3093 pg/mL in AF with reduced LVEF (a mean \pm SD of $36\pm 14\%$) during decompensation, which is very similar to our findings. Although elevated levels of NT-proBNP is expected in AF, there is no consensus about the upper normal limit and the interpretation is far more difficult in the presence of HF with impaired LVEF without knowing how much increase is related to AF and how much to reduced ejection fraction. The most important contribution of the present study is the value of NT-proBNP level in stable phase of HF with impaired LVEF in the presence of AF while there is no consensus on upper limits. Besides the present study underlines the importance of stable phase NT-proBNP in follow-up such high risk patients. Also, the present study suggests that decompensation is related to a median 92.05% increase in NT-proBNP in this special population.

Study Limitatons

There are some important limitations in our study. Retrospective single center design is an important limitation. Also, a control group in sinus rhythm with similar LVEF and HF could unveil the effect of AF on NT-proBNP levels far better. Because of archive screening design, some adverse events like bleeding or embolic event may be overlooked. Despite these limitations, our study presents useful information for clinical practice, hence our data represents real-world closed cohort data for a long follow-up duration, which was more than 3 years in 36.8% of patients.

Conclusion

Our study suggests the importance of NT-proBNP levels in patients with stable phase of HF with impaired ejection fraction and AF, who represent a high-risk group in clinical practice. As renal function test, GFR should be

monitored closely, but not serum creatine, especially in patients with anemia and high CHA_2DS_2 and CHA_2DS_2 VASc scores to avoid erroneously over-dosing, which may cause adverse events.

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Ethics

Ethics Committee Approval: The ethic approval of the present the study was obtained on 14. 11.2018 from the University of Health Sciences Turkey, İzmir Tepecik Health Practice and Research Center, with the decision number: 2018/13-13.

Informed Consent: Retrospective study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.İ.T., Design: E.İ.T., E.Ç.K.Ç., Data Collection or Processing: E.İ.T., E.Ç.K.Ç., Analysis or Interpretation: E.İ.T., E.Ç.K.Ç., Literature Search: E.İ.T., Writing: E.İ.T., E.Ç.K.Ç.

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