Original article

Prognostic value of the N-terminal pro-B-type natriuretic peptide in the elderly with acute myocardial infarction

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Abstract

Background: Recent years have witnessed the increasing role of NT-proBNP as a prognostic tool in acute coronary syndrome (ACS).

Aim: To evaluate prognosis of patients over 65 years of age with acute myocardial infarction (MI), based on NT-proBNP levels measured in the acute phase of MI.

Methods: The study involved 161 patients aged 79±8 hospitalised with acute MI, either with or without ST segment elevation (STEMI/NSTEMI). The NT-proBNP levels in serum were measured and echocardiography with left ventricular ejection fraction (LVEF) was performed in all patients upon admission to hospital. These tests were repeated after six months with the patients additionally subjected to the 6-minute walk test (6MWT).

Results: The average NT-proBNP level in the studied patients at admission to hospital was 7058±9649 pg/ml and increased in proportion to the age of patients. The NT-proBNP level did not differ significantly in STEMI and NSTEMI patients. Fifty-three patients died during the 6-month follow-up period. Their NT-proBNP levels at admission were significantly higher than in patients who were alive at the end of follow-up: 12237±13035 pg/ml compared with 4606±6214 pg/ml (p=0.0001). The NT-proBNP level upon admission to hospital proved to be an independent predictor of death in the six-month period following MI. Six months after MI the average left ventricular ejection fraction in the studied group of patients was 49±10% and the average distance in the 6MWT was 361±151 m. There was a significant negative correlation between these two parameters and the initial NT-proBNP level determined upon admission to hospital.

Conclusions: An increased NT-pro-BNP level, measured in the acute phase of MI, is a significant prognostic factor during six-month follow-up after MI in patients aged over 65.

Key words: NT-proBNP, ejection fraction, 6-minute walk test, myocardial infarction, STEMI, NSTEMI

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B-type natriuretic peptide and the N-terminal fragment of this pro-hormone (NT-proBNP) are released in response to increased intracardiac pressures [1]. The increase of NT-proBNP level is observed in heart failure. Another stimulus of BNP production is myocardial ischaemia; this finding is supported by elevation of NT-proBNP levels in stable coronary artery disease (CAD) patients [2-4]. In patients with acute myocardial infarction (AMI), increased production of NT-proBNP is seen not only in the necrotic region but also in the ischaemic zone, as found in experimental studies [5].

Elderly subjects are characterised by compromised myocardial relaxation leading to increase of both end-diastolic pressure and secretion of NT-proBNP. Increased levels of NT--proBNP in such patients are also influenced by high prevalence of atherosclerotic CAD and resulting myocardial ischaemia as well as impaired renal function and increased blood volume [6]. Various factors contributing to the increase of natriuretic peptide levels in older patients account for considerably higher reference values of serum NT-proBNP levels in the population aged over 75 years as compared to younger ones [7]. Therefore, concentration of NT-proBNP, which may indicate unfavourable prognosis in younger groups of patients, in older patients may turn out to be irrelevant.

The study aimed to evaluate the prognostic value of NT-proBNP levels in patients over 65 years of age hospitalised for acute coronary syndromes (ACS).

Methods

The study involved 161 patients aged 65-100 years (mean 79±8 years), with diagnosis of AMI based on the presence

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of typical clinical symptoms and elevated cardiac troponin T level (>0.1 ng/dl) admitted to the Intensive Cardiologic Care Unit (ICCU). Eighty-seven patients (53%) were admitted to the Unit later than 12 hours from the onset of pain. Demographic and clinical characteristics of the study population are presented in Table I. Patients were managed using an invasive or conservative approach according to the European Society of Cardiology/Polish Cardiac Society guidelines.

The NT-proBNP levels were measured within the first 48 hours of hospitalisation using Roche assay. Based on age the study group was divided into subgroups involving subjects aged 65-75 years, 76-85 years and >85 years and mean NT-proBNP levels were calculated for each group separately.

On the first day of hospitalisation echocardiography was performed, encompassing evaluation of left ventricular ejection fraction (LVEF) with the Simpson method. Cardiac performance on admission was assessed using Killip classification; class III or IV symptoms were indicative of severe heart failure. Prior to discharge 6-minute walk test (6MWT) was performed whenever possible.

Mortality at 6-month follow-up was evaluated. In survivors, follow-up evaluation at 6 months included measurement of NT-proBNP level, echocardiography and exercise capacity estimation based on 6MWT. The relationship between baseline NT-proBNP level and LVEF as well as distance covered during 6MWT were analysed at 6 months.

Statistical methods

Results are presented as mean ± SD or number and percentage. Differences between groups were evaluated with Student's t-test and non-parametric Wilcox test. Relationships between variables were analysed using a correlation test and analysis of regression as well as multivariate analysis using the Cox model. Patients' survival was presented using Kaplan-Meier curves for each quartile of NT-proBNP levels.

The analysis was carried out with JMP statistical software (SAS Institute). A p value <0.05 was considered significant.

Results

Mean NT-proBNP level on admission in the whole study population was 7058±9649 pg/ml and correlated with the age of patients (Figure 1). No significant differences of NT-proBNP concentrations between patients with ST segment elevation MI (STEMI) and non-ST segment elevation MI (NSTEMI) were found (7735±10142 vs. 6565±9301, NS).

Evidence of severe heart failure (Killip class III or IV) on admission was found in 66 patients. Patients presenting with heart failure had significantly higher NT-proBNP levels than those without (11 619±11 707 pg/ml vs. 3991±6410 pg/ml, p <0.0001).

Table I. Demographic and clinical data of the study population

Parameter	Percentage
Diabetes mellitus	26.1
Hypertension	67.1
Significant heart failure on admission	41
Significant mitral regurgitation on admission	31.1
History of coronary artery disease	62.7
Previous myocardial infarction	28.6
Female gender	49

Mean LVEF in the study population was 42.6±12.7%. It was normal (>50%) in 41 patients, and reduced (<50%) in 120 patients. Levels of NT-proBNP were significantly lower in patients with normal LVEF in comparison with subjects with reduced LVEF (3848±7264 pg/ml vs. 8198±10 168 pg/ml, p=0.0002).

During a 6-month follow-up 53 patients died (32%), including 25 (13%) in-hospital deaths. Mean baseline NT-proBNP in this group was 12 237±13 035 pg/ml. Patients who survived 6-month follow-up had significantly lower mean baseline NT-proBNP level (4606±6214 pg/ml, p <0.0001) (Figure 2). Fatal cases were significantly older than subjects who survived 6 months (82±9 years vs. 76±7 years, p <0.0001).

The Kaplan-Meier survival curves for subgroups of patients with NT-proBNP levels below and above the 3rd quartile revealed statistically significant differences (Figure 3).

To identify factors of unfavourable prognosis multivariate analysis was carried out, including serum NT-proBNP levels, LVEF and patients' age. It showed that NT-proBNP level and age of patients were independent predictors of 6-month mortality (Table II).

Mean LVEF during hospitalisation was 42.6±12.7% and increased to 49±10% at 6 months (p <0.0001). Mean distance covered during 6MWT test on discharge was

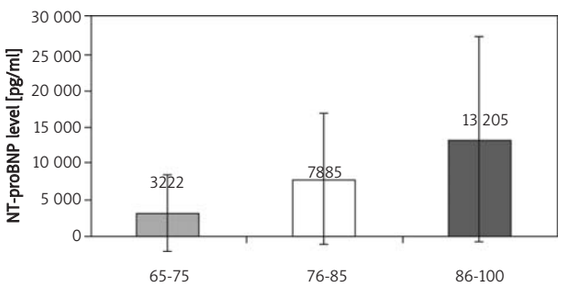

Figure 1. Comparison of mean NT-proBNP levels in age-groups. Differences between the age-groups: p <0.0001

Table II. Cox multivariate model of survival

Variable	Hazard Ratio	95% CI	p
NT-proBNP (two groups: below and above 3rd quartile)	0.3	0.13-0.68	0.0042
Age (two groups: below and above 3rd quartile)	0.26	0.11-0.58	0.0011
LVEF (two groups: below and above 3rd quartile)	1.93	0.68-6.43	0.2442

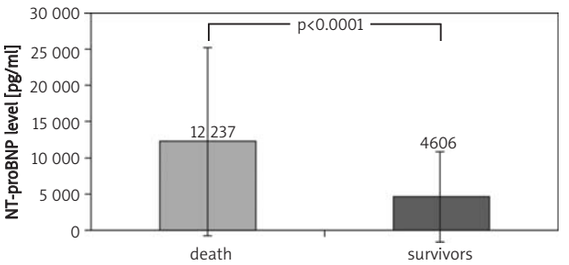

Figure 2. Comparison of mean NT-proBNP levels in patients who died during or survived 6-month follow-up

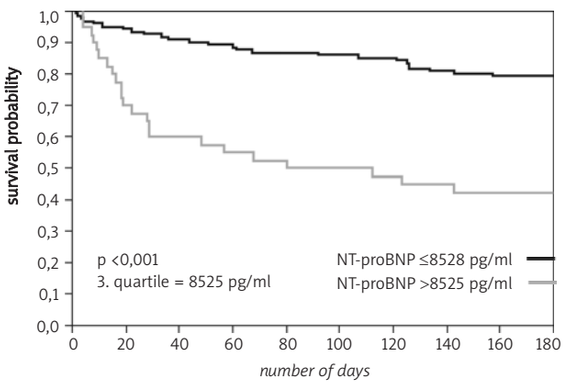

Figure 3. Comparison of survival curves during 6-month follow-up in patients with baseline NT-proBNP levels above and below the 3rd quartile

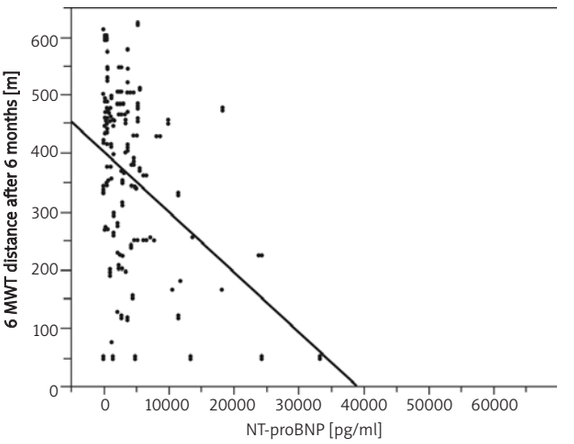

Figure 4. Relationship between baseline NT-proBNP level and distance covered during 6-minute walk test performed at 6 months after myocardial infarction

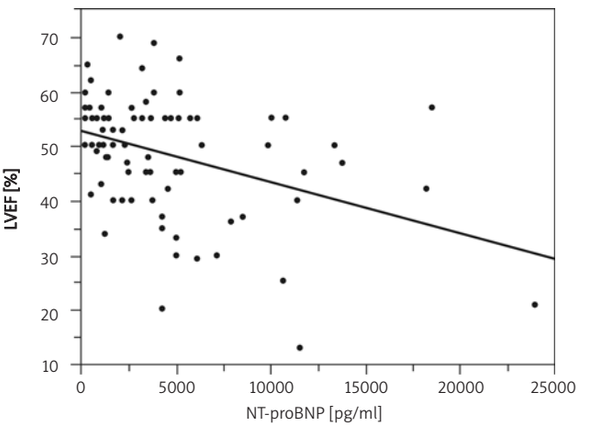

Figure 5. Relationship between baseline NT-proBNP level and LVEF at 6 months after MI

286.35 ±154.3 m and at 6 months increased to 361±151 m (p <0.0001).

Mean NT-proBNP level at 6 months was significantly lower than at baseline, amounting to 1980±3274 ng/ml in the study group; no differences were observed between NSTEMI and STEMI subjects.

Baseline NT-proBNP level showed a significant negative correlation with LVEF at 6 months (r=–0.387, p=–0.0001, n=102) and mean distance covered during 6MWT (r=–0.378, p=0.0001, n=108) (Figures 4 and 5).

Discussion

High concentration of NT-proBNP is a significant predictor of death in patients with ischaemic heart disease. Prognostic value of increased NT-proBNP levels is particularly well documented in patients with ACS [8, 9]. According to Omland et al. NT-proBNP level measured in the subacute phase of MI was predictive of 4-year mortality also in patients without heart failure [10]. De Winter et al. reported that in patients treated with coronary angioplasty NT-proBNP was an

independent risk factor of death or MI in one-year follow-up [11]. Moreover, the dynamics of NT-proBNP level changes represents prognostic value. Patients in whom no significant decrease in NT-proBNP level increased at baseline was observed within 72 hours from admission were characterised by unfavourable short-term prognosis, which is relevant when planning therapy and hospitalisation duration [12]. A high NT-proBNP level on admission was associated with significantly worsened short-term prognosis in STEMI patients treated with primary coronary interventions and higher rate of no-reflow phenomenon after coronary angioplasty [13].

There are limited data available on the prognostic value of NT-proBNP in the population of elderly patients, i.e. >65 years, presenting with ACS. It has been shown that high BNP level was associated with increased cardiovascular risk during the follow-up in elderly patients hospitalised for their first episode of heart failure [14].

In our study population NT-proBNP level was shown to be an independent predictor of death over 6-month follow-up. The NT-proBNP levels in the analysed group were several times higher than reported in the above-mentioned papers. Similarly, a significant relationship with age, coexisting heart failure and decreased LVEF [15, 16] was found. At 6 months post MI, NT-proBNP levels, although significantly decreased, were still elevated and by far exceeded reference values.

In our group no differences were found regarding NT-proBNP levels between STEMI and NSTEMI patients. Others reported that NT-proBNP levels measured within the first 3 hours from the onset of symptoms were significantly higher in NSTEMI than in STEMI patients; after this period the concentrations became similar. It seems that time from the onset of symptoms to blood sampling has a significant impact on the differences in NT-proBNP levels between STEMI and NSTEMI subjects. More dynamic increase of serum NT-proBNP may result from larger ischaemic to necrotic zone ratio in the early phase of non-ST elevation MI. Later in the course, coexisting necrosis and ischemia cause superimposition of NT-proBNP curves [17, 18]. It should be noted that there are no differences in NT-proBNP levels between the groups at 6 months.

The quality of life, independence and exercise capacity play an important prognostic role in the elderly population [19, 20]. In our study, 6MWT – a validated tool to measure exercise capacity in heart failure patients, was used. This test may be safely performed even early post infarction, including in older patients [21, 22]. In our study group the test was carried out in patients presenting with sufficient fitness prior to discharge and at 6 months. The NT-proBNP levels during infarction were shown to be significantly correlated with distance covered at 6 months. High baseline NT-proBNP levels were also correlated with persistent LV systolic dysfunction of 6 months.

Elderly patients are at higher risk of adverse events in the acute phase and after ACS. Higher prevalence of disseminated coronary and peripheral artery atherosclerotic lesions as well as number of co-morbidities [23-26] contribute to much higher risk. Because of atypical symptoms and the common 'psychological barrier', older patients with ACS often call for help after a delay, making implementation of adequate therapy impossible; this was clearly shown in our study, where more than 50% of patients were admitted to the hospital over 12 hours after the onset of pain. In addition, side effects of medical agents and complications are more frequent in this group of patients.

Although patients aged >65 years make up a growing group of subjects hospitalised at intensive cardiologic care units, data on the optimal therapeutic methods in management of acute coronary syndromes in such patients are limited [19, 20]. High serum NT-proBNP level indicating increased risk of death and disability may promote more aggressive treatment in this group of patients, followed by age-matched rehabilitation, medical treatment and regular checkups.

Conclusions

Increased NT-proBNP level in the acute phase of MI is a strong predictor of clinical outcomes at 6-month follow-up in patients aged 65 years and over.

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Stężenie NT-proBNP czynnikiem prognostycznym po zawale serca u chorych w podeszłym wieku

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Streszczenie

Wstęp: W ostatnich latach wzrasta rola NT-proBNP jako czynnika prognostycznego w przebiegu ostrych zespołów wieńcowych.

Cel: Ocena rokowania chorych po 65. roku życia z zawałem serca (MI) na podstawie stężenia NT-proBNP w surowicy.

Metodyka: Badaniem objęto 161 chorych w wieku 79±8 lat, hospitalizowanych z powodu MI z uniesieniem (STEMI) bądź bez uniesienia odcinka ST (NSTEMI). Przy przyjęciu do szpitala u chorych oznaczano poziom NT-proBNP w surowicy oraz wykonywano badanie echokardiograficzne z oznaczeniem frakcji wyrzutowej lewej komory (LVEF). Po 6 mies. przeprowadzano badanie kontrolne, które, oprócz wyżej wymienionych, obejmowało 6-minutowy test marszu (6MWT).

Wyniki: Średnie stężenie NT-proBNP przy przyjęciu do szpitala w badanej grupie wynosiło 7058±9649 pg/ml i rosło proporcjonalnie do wieku chorych. Stężenie NT-proBNP nie różniło się istotnie u chorych ze STEMI w porównaniu z chorymi z NSTEMI. W trakcie 6-miesięcznego okresu obserwacji zmarło 53 chorych. Poziom NT-proBNP u tych chorych w chwili przyjęcia na oddział kardiologii był znamiennie wyższy niż u chorych, którzy przeżyli 6-miesięczny okres obserwacji (12237±13035 *vs* 4606±6214 pg/ml, p=0,0001). Stężenie NT-proBNP przy przyjęciu do szpitala było w analizie wieloczynnikowej niezależnym czynnikiem ryzyka zgonu w okresie 6 mies. od przebytego MI. Po 6 mies. średnia LVEF w grupie badanych chorych wynosiła 49±10%, a średni dystans marszu w 6MWT wyniósł 361±151 m. Wartości LVEF i dystansu w 6MWT w 6 mies. po MI wykazywały istotną ujemną korelację z wyjściowym stężeniem NT-proBNP.

Wniosek: Wzrost wartości NT-proBNP w ostrym okresie choroby jest istotnym czynnikiem prognostycznym przebiegu klinicznego MI w obserwacji 6-miesięcznej u chorych po 65. roku życia.

Słowa kluczowe: NT-proBNP, frakcja wyrzutowa, test korytarzowy, zawał serca, STEMI, NSTEMI

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