Biphasic and Monophasic Pattern of Brain Natriuretic Peptide Release in Acute Myocardial Infarction

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ABSTRACT

This study evaluated brain natriuretic peptide (BNP) release in acute myocardial infarction (AMI), absolute values as well as pattern of its release. There are two different patterns of BNP release in AMI; monophasic pattern – concentration in the first measurement is higher than in the second one, and biphasic pattern – concentration in the first measurement is lower than in the second one. We observed significance of biphasic and monophasic pattern of BNP release related to diagnostic and prognostic value. We included in this prospective observational study total of 75 AMI patients, 52 males and 23 females, average age of 62.3±10.9 years with range of 42 to 79 years. BNP was measured and pattern of its release was evaluated. In AMI group BNP levels were significantly higher than in controls (462.88 pg/mL vs 35.36 pg/mL, p<0.001). We found statistically significant real negative correlation (p<0.05) between BNP concentration and left ventricle ejection fraction (LVEF) with high correlation coefficient (r=–0.684). BNP concentrations were significantly higher among patients in Killip class II and III compared to Killip class I; Killip class I BNP=226.18 pg/mL vs. Killip class II 622.51 pg/mL vs. Killip class III 1530.28 pg/mL, p<0.001. BNP concentrations were significantly higher in patients with; (i) myocardial infarction vs. controls; (BNP 835.80 pg/mL vs. 243.03 pg/mL); (ii) in pts with positive major adverse cardiac events (MACE) vs. negative MACE (BNP 779.08 pg/mL vs. 242.28 pg/mL, p<0.001); (iii) in pts with positive compared to negative left ventricle (LV) remodelling (BNP 840.77 pg/mL vs. 341.41 pg/mL, p<0.001). Group with biphasic pattern of BNP release had significantly higher BNP concentration compared to monophasic pattern group. In biphasic pattern group we found significant presence of lower LVEF, Killip class II and III, LV remodelling and MACE. We found that BNP is strong marker of adverse cardiac events in patients presenting with a myocardial infarction. In our AMI group we found significant elevation of BNP and it is suspected that second peak secretion is not only due to systolic dysfunction and subsequent remodeling of LV but also due to impact of ischaemia. Patients with biphasic pattern probably have worse prognosis due to severe coronary heart disease. Besides its diagnostic role as a simple blood marker of systolic function, BNP is also important prognostic marker who helps making clinical decision about early invasive vs. conservative management.

Key words: brain natriuretic peptide, acute myocardial infarction, biphasic and monophasic pattern of release, diagnostic and prognostic role

Introduction

Brain natriuretic peptide (BNP) is cardiac hormone and acts as a marker of ventricular function. Primary cause of brain natriuretic peptide secretion is stretching, volume overload and high filling pressure of ventricle. Secretion of BNP is part of activated compensatory mechanisms in heart failure syndrome. Many clinical and epidemiological studies showed direct correlation of BNP and lower left ventricle ejection fraction (LVEF)1,2. Study of...
Maisel et al.\textsuperscript{3} was first multicentre prospective study which used BNP in evaluation of dyspnoea making possible differentiation of cardiac and pulmonary dyspnoea.

Recent studies have found that elevation of BNP in AMI is not only a simple consequence of reduced global systolic function (high wall stress) – it seems that ischaemia \textit{per se} induces de novo BNP secretion\textsuperscript{4,5}.

Other studies\textsuperscript{6–8} have confirmed higher level of BNP as a strong and independent prognostic parameter in acute ischaemic events besides traditional i.e. old risk factors\textsuperscript{9–11}. Antman and Braunwald\textsuperscript{11} found that in AMI BNP was released in circulation early so that first peak occurs about 16 hours after beginning of symptoms. In patients with anteroseptal AMI, lower LVEF and symptoms of heart failure there is a second peak in BNP release about 5\textsuperscript{th} to 7\textsuperscript{th} day from the beginning of symptoms\textsuperscript{11}.

BNP in AMI shows two different pattern of release: (i) monophasic pattern – concentration in the first measurement is higher than in the second one), (ii) biphasic pattern – concentration in the first measurement is lower than in the second one.

BNP level is increased in AMI and its rise shows correlation with LV systolic dysfunction. We performed this study to evaluate significance of biphasic and monophasic pattern of BNP release related to diagnostic and prognostic value.

**Methods**

In AMI group were involved 75 patients, their blood samples for analysis of BNP were taken during first 48h i.e. 1\textsuperscript{st} to 2\textsuperscript{nd} day (first measurement) and from 5\textsuperscript{th} to 8\textsuperscript{th} day of hospitalisation (second measurement). LVEF was calculated before discharge by echocardiography and signs of ventricular remodelling were also registered. Major adverse cardiac events; repeated chest pain, reinfarction, heart failure, ventricular arrhythmias and sudden cardiac death were registered. Structure of control group (n=61) was similar by age and gender to AMI group but without arterial hypertension and coronary heart disease and with normal echocardiography.

Data are expressed as a $\bar{X}\pm SEM$ or median and interval. For parametric variables not belonging to the same population Student t-test was used while for nonparametric variables we used $\chi^2$-test. Mann-Whitney U-test is a test for assessing whether two of observations come from the same distribution. Pearson correlation test was used to assess association between measured parameters. P-values less than <0.05 was considered as statistically significant.

**Results**

**Baseline characteristics**

Brain natriuretic peptide was observed in 75 patients with acute myocardial infarction, 52 males and 23 females, average age of 62.3±10.9 years with range of 42 to 79 years. The baseline characteristics of the study patients are provided in Table 1.

**BNP levels and left ventricle ejection fraction**

BNP concentration rises proportionally as LVEF lowers in AMI group. Patients with significant decrease of systolic function had the highest BNP levels, while pa-
Patients with normal systolic function had the lowest BNP levels. Patients with LVEF <30% – BNP 1129.03 pg/mL, patients with LVEF 31–40% – BNP 690.17 pg/mL, patients with LVEF 41–50% – BNP 274.39 pg/mL, and patients with LVEF >51% – BNP 189.56 pg/mL, significance of p<0.001.

Test of correlation showed statistically significant real negative correlation (p<0.05) between BNP concentration and decrease of LVEF with high correlation coefficient (r=–0.684) (Figure 1).

**BNP in heart failure**

BNP concentrations were significantly higher among patients in Killip class II and Killip class III compared to those of Killip class I. We found gradual increase in BNP levels from Killip class I to Killip class III as follows; BNP 226.18 pg/mL, 622.50 pg/mL, 1530.27 pg/mL, significance of p<0.001.

**BNP and MACE**

We evaluated BNP levels in patient with MACE and found that patients with complications in intrahospital period had significantly higher BNP levels, MACE positive vs. MACE negative; BNP 779.07 pg/mL vs. 242.28 pg/mL, significance of p<0.001.

**Pattern of BNP release**

Group with biphasic pattern of BNP release has significantly higher BNP concentration in first measurement (BNP 1 – first measurement in the 1st to 2nd day of admission) and second measurements (BNP 2 – second measurement in the 5th to 8th day of admission) compared to group with monophasic pattern (Table 2).

In biphasic pattern group compared to monophasic group left ventricle ejection fraction was significantly lower compared to monophasic pattern group; LVEFbiphasic=36.26% vs. LVEFmonophasic=48.07%, significance of p<0.001.

In biphasic pattern group compared to monophasic group we found significantly more patients with anteroseptolateral AMI compared to other allocations of AMI; monophasic pattern (1 pt) vs. biphasic pattern (14 pts), significance p<0.001.

In biphasic pattern group compared to monophasic group were significantly more patients with Killip class II and Killip class III, while in Killip class I there were significantly more patients with monophasic BNP pattern (Table 4).

In biphasic pattern group were significantly more patients with MACE positive vs. MACE negative; biphasic pattern (25 pts) vs. monophasic pattern (8 pts), significance of p<0.001 (Table 5).

**TABLE 2**

<table>
<thead>
<tr>
<th>Pattern of BNP release</th>
<th>BNP 1 (pg/mL)</th>
<th>BNP 2 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monophasic</td>
<td>278.44</td>
<td>706.23</td>
</tr>
<tr>
<td>Biphasic</td>
<td>221.23</td>
<td>583.97</td>
</tr>
</tbody>
</table>

**TABLE 6**

<table>
<thead>
<tr>
<th>LV remodel. posit.</th>
<th>LV remodel. neg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monophasic</td>
<td>2</td>
</tr>
<tr>
<td>(n=44)</td>
<td>(4.54%)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>17</td>
</tr>
<tr>
<td>(n=31)</td>
<td>(54.84%)</td>
</tr>
</tbody>
</table>
In biphasic pattern group were significantly more patients with LV remodelling; biphasic pattern (17 pts) vs. monophasic pattern (2 pts), significance of \( p<0.001 \) (Table 6).

**Discussion**

In patients with acute myocardial infarction BNP levels are significantly higher compared to controls. Recent studies explained that BNP in AMI was released not only due to systolic dysfunction, it seems that ischaemia *per se* induces its release.\(^5\)\(^,\)\(^6\)\(^,\)\(^12\)\(^,\)\(^13\)

We found inverse proportional correlation between BNP level and LVEF, correlation test demonstrated statistically significant real negative correlation with high coefficient of correlation \( r=-0.684 \). This makes BNP as unique biochemical marker of systolic dysfunction of left ventricle what is consistent with study of Groenning et al.\(^2\) and Mega et al.\(^8\).

BNP concentrations were significantly higher among patients in Killip class II compared to Killip class I, while BNP concentration in patients with Killip class III were significantly higher compared to Killip class II (Killip I 226.18 pg/mL vs. Killip II 622.51 pg/mL vs. Killip III 1530.28 pg/mL, \( p<0.001 \)), and it is clear that BNP increases in a graded manner. Our results are similar to results in recent studies.\(^6\)\(^,\)\(^14\)\(^,\)\(^16\)

Measuring BNP concentration we can estimate stage of heart failure or diagnose it even when patient is asymptomatic or when typical signs of heart failure are absent.\(^3\)\(^,\)\(^15\)

Brain natriuretic peptide levels were higher among patients with MACE (major adverse cardiac events: angina, reinfarction, heart failure, ventricular arrhythmias, sudden cardiac death) (779.08 pg/mL vs. 242.28 pg/mL, \( p<0.001 \)). Our results are consistent with works of Richards et al.\(^14\) who found BNP not only as a prognostic marker of LVEF but also predictor of new ischaemic events as well as future hospitalisation due to heart failure and mortality even in Killip class I group of patients.

BNP levels were significantly higher among patients with LV remodelling (840.77 pg/mL vs. 341.41 pg/mL, \( p<0.001 \)), promoting BNP as an early biochemical predictor of LV remodelling.

In patients who died during hospitalisation BNP levels were significantly higher compared to survivors (1694.33 vs. 478.47 pg/mL, \( p<0.01 \)). According to de Lemos et al.\(^7\) higher BNP levels in prediction of mortality are not only consequence of systolic dysfunction but also reflect severity of ischaemia.

In AMI it is important to do risk stratification and especially to identify »high« risk patients for future MACE events. Study of Jernberg\(^15\) proves a benefit of early invasive management in patients with highest tercils of BNP level.

According to BNP levels now it is possible to profile »low« and »high« risk patient and make a decision about conservative or invasive management.\(^15\)

Group with biphasic pattern of BNP release has significantly higher BNP concentration in first and second measurements vs. monophasic pattern. In biphasic pattern group were significantly more patients with lower LVEF, anteroseptalateral AMI, Killip class II and Killip class III, LV remodelling and MACE.

First peak in BNP secretion is due to myocardial necrosis and its release from necrotic myocytes. It is suspected that second peak is due to expansion of infarction, systolic dysfunction and subsequent remodelling of LV. Ischaemia in second peak-patients with biphasic pattern leads to worse prognosis due to more severe coronary heart disease.\(^15\)

Goetze\(^16\) define BNP as »an intermedium between coronary artery disease and heart failure giving information of critical importance in identification of »low risk« and »high risk« patients«.

**Conclusion**

In conclusion, we found that BNP is strong marker of adverse cardiac events in patients presenting with a myocardial infarction. BNP levels are elevated in AMI and its rise is proportional to decrease of LVEF. BNP rise is proportional to severity of heart failure but it is also predictor of left ventricular remodelling, MACE and mortality. BNP in AMI is important prognostic marker for future post infarction left ventricle function, morbidity and mortality.

Biphasic pattern of BNP release is associated with higher BNP levels, lower LVEF, Killip class II and Killip class III, higher incidence of MACE and ventricular remodelling. First peak in BNP secretion is due to myocardial necrosis and its release from necrotic myocytes. Patients with biphasic pattern probably have worse prognosis due to more severe coronary heart disease.

**REFERENCES**

DVOFAZNI I JEDNOFAZNI UZORAK LUČENJA MOŽDANOG NATRIURETSKOG PEPTIDA U AKUTNOM INFARKTU MIOKARDA

S A Ž E T A K

Studija je istraživala lučenje moždanog natriuretskog peptida (brain natriuretic peptide – BNP) kod pacijenata sa akutnim infarktom miokarda (acute myocardial infarction – AMI), i to njegove apsolutne vrijednosti, kao i uzorke lučenja. Postoje dva različita uzorka lučenja BNP u akutnom infarktu miokarda; jednofazni – koncentracija u prvom mjerenju je veća nego u drugom, i dvofazni – koncentracija u prvom mjerenju je niža u odnosu na drugo mjerenje. Promatrali smo značajnost jednofaznog i dvofaznog uzorka lučenja BNP u odnosu na njegovu dijagnostičku i prognozičku vrijednost. U prospektivnu observacionu studiju uključili smo ukupno 75 pacijenata sa AMI, 52 muškarca i 23 žene, srednje starosne dobi od 62,3±10,9, u rasponu od 42 do 79 godina. Promatrana je vrijednost BNP kao i uzorak lučenja. U AMI grupi vrijednost BNP bila je statistički značajno veća u odnosu na kontrolnu skupinu pacijenata (462,88 pg/mL vs. 35,36 pg/mL, p<0,001). Utvrdili smo statistički značajnu negativnu korelaciju (p<0,05) vrijednosti BNP prema istisnoj frakciji lijeve klijetke (left ventricular ejection fraction – LVEF) sa visokim koeficijentom korelacije (r=–0,684). Vrijednosti BNP bile su značajno više kod pacijenata sa srčanom slabosti Killip klase II i III, poredeno sa Killip klasom I; Killip klasa I BNP=226.18 pg/mL vs. Killip klasa II 622.51 pg/mL vs. Killip klasa III 1530.28 pg/mL, p<0,001. Vrijednosti BNP bile su značajno više kod pacijenata sa; (i) infarktom miokarda prema kontrolnoj skupini (BNP 835,80 pg/mL vs. 243,03 pg/mL), (ii) kod pacijenata sa prisutnim značajnim nepovoljnim srčanim događajima (major adverse cardiac events – MACE) prema pacijentima bez MACE (BNP 779,08 pg/mL vs. 242,28 pg/mL, p<0,001); (iii) kod pacijenata sa prisutnim preoblikovanjem lijeve klijetke (left ventricular remodelling) u odnosu na pacijente bez preoblikovanja lijeve klijetke (BNP 840,77 pg/mL vs. 341,41 pg/mL, p<0,001). Grupa pacijenata sa dvofaznim uzorkom lučenja BNP imala je značajno veću vrijednost BNP u odnosu na grupu pacijenata sa jednofaznim uzorkom BNP lučenja. Kod dvofaznog lučenja našli smo statistički značajnu prisutnost snižene istisne frakcije lijeve klijetke (LVEF), zatim srčane slabosti Killip klase II i III, zatim prisutnosti BNP, i značajnih nepovoljnih srčanih događaja (MACE). U našem istraživanju utvrdili smo da je BNP statistički značajan pokazatelj nepovoljnih srčanih događaja kod pacijenata sa akutnim infarktom miokarda. U AMI grupi pacijenata značajno su bile povećane vrijednosti BNP i smatra se da drugi vrh lučenja nije već značajna ljudska disfunkcija kao i posljedično preoblikovanja lijeve klijetke, nego i za prisutnu ischemiju. Pacijenti sa dvofaznim uzorkom lučenja vjerovatno imaju lošiju prognozu što se u vezi sa teškim srčanom koroštom bolesti. Pored dijagnostičke uloge određivanja BNP, kao jednostavnog pokazatelja srčane disfunkcije, BNP je također važan prognozički pokazatelj koji pomaže kod donošenja odluke o odabiru između ranog invazivnog ili standardnog konzervativnog liječenja.