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Brain natriuretic peptide a predictive marker in cardiac surgery☆

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Abstract

Background: BNP which stands for B-type natriuretic peptide is a cardiac neurohormone and is secreted in response to myocardial stress and causes natriuresis and vasodilatation. Studies have reported close correlation between a high concentration of BNP in blood and worse short-term and long-term prognosis following myocardial infarction and heart failure. In this study, we have tested its usefulness and predictive value in the outcome post cardiac surgery. **Methods:** Between March 2006 and June 2007, 141 patients, undergoing cardiac surgery, were enrolled in this study. Their BNP concentration was measured prior to the operation and their comorbidities were examined against their BNP levels. Postoperatively their outcome was closely monitored. Main clinical endpoints were atrial fibrillation (AF), inotrope use, renal impairment, early deaths and hospital stay. **Results:** Some preoperative comorbidities, such as renal impairment, peripheral vascular disease (PVD) and low ejection fraction (EF) were associated with higher BNP level. Statistically, EuroSCORE and Parsonnet score showed significant correlation with preoperative BNP concentration ($P<0.0001$). Postoperatively, high-BNP concentration predicted inotropic use, higher than baseline creatinine level, longer ventilation time, longer hospital stay and early mortality ($P<0.05$) but our study did not reveal any predictive value for BNP in identifying those developing AF or infection postoperatively. **Conclusions:** BNP is a valuable biochemical marker, which is easy to measure and can be beneficial in predicting the operative outcome.

Keywords: Coronary artery bypass graft; Valve cardiopulmonary bypass

1. Introduction

BNP stands for B-type natriuretic peptide. It is a neurohormone that was originally isolated from porcine brain in 1988 [1]. In human, it is synthesized in ventricular myocardium, as well as atria in response to increased wall stress [2–4]. BNP modulates plasma volume and myocardial stretch through its diuretic and vasoconstrictive properties, as well as sympathetic inhibition and renin-angiotensin-aldosterone system antagonism [5, 6].

BNP has diagnostic and prognostic values in congestive heart failure and acute myocardial infarction [7–10]. It has been shown previously that BNP concentration increases after the initiation of cardiopulmonary bypass [11–13]. It can also predict the severity of aortic stenosis and is a valuable factor in monitoring the progression of valvular heart disease [14, 15]. The predictive value of BNP in cardiac surgery has only been assessed in a small number of studies, and has shown some promising results. Furthermore, BNP is easy to detect and is becoming available in some centres [16–21].

The main objective of this study was to assess the predictive value of BNP in cardiac surgery. We also analysed the preoperative comorbidities against BNP concentration in plasma sample of patients assigned for cardiac surgery.

2. Methods

This study was conducted prospectively and after obtaining permission from the Research Ethics Committee of our hospital. One hundred and forty-one consecutive patients undergoing any first-time open-heart surgery and agreed to the study were recruited (Table 1). Informed consent was obtained from each individual. The exclusion criteria for the study were: intubated patients and patients who did not agree to the study.

Twenty-four hours prior to the operation, 5 ml of venous blood was obtained from each patient and collected into a Trazylol pre-filled EDTA (ethylenediamine-tetra-acetic acid) bottles, centrifuged at 3000 rpm for 10 min, and subsequently stored at −20 °C until analysis. For analysis, Siemens ADVIA Centaur BNP assay (Siemens, USA) was used. This is a two-site sandwich immunoassay using direct chemiluminescent technology for the measurement of BNP in human plasma. It utilises an acridinium ester labelled monoclonal mouse anti-human BNP $F(ab')_2$ fragment specific to the ring structure of BNP. The second antibody, in the solid phase, is a biotinylated monoclonal mouse anti-human

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Table 1
Patient characteristics

Characteristics	Values
Age, mean years (±S.D.)	66.5±10.5
Male, *n* (%)	98 (69.5)
Urgent, *n* (%)	46 (32.6)
LV function	
Good >50%, *n* (%)	91 (64.5)
Moderate, 30–50%, *n* (%)	42 (30)
Poor <30%, *n* (%)	8 (5.5)
Operation	
AVR±CABG, *n* (%)	30 (21)
MVR±CABG, *n* (%)	11 (8)
AVR+MVR, *n* (%)	3 (2)
CABG, *n* (%)	97 (69)

AVR, aortic valve replacement; CABG, coronary artery bypass graft; MVR, mitral valve replacement; LV, left ventricle.

antibody specific to the C-terminal portion of BNP, which is coupled to a streptavidin magnetic bead.

The result range was reported between 2 and 5000 ng/l. Any results above 5000 ng/l were reported as >5000 ng/l. If necessary the samples were diluted 1:5 using the sample diluents on-board and repeated. Samples with results below this range were reported as '<2 ng/l' by the Centaur. Functional sensitivity was defined as the lowest BNP concentration determined at a coefficient of variation of 20% and was determined as 2.5 ng/l.

Postoperatively all patients had routine postoperative care with close monitoring of the cardiovascular system, renal output and development of arrhythmia. No change in the management of the patients was applied and no treatment was withheld.

Clinical endpoints included: 1) atrial fibrillation; 2) use of inotropic agents or intra-aortic balloon pump on first postoperative day; 3) creatinine level of 20 μmol/l than the baseline on day 3 postoperatively; 4) infection; 5) cardiac events; 6) hospital stay and 7) deaths within 30 days of surgery.

Additionally, correlation between preoperative BNP concentration and patient characteristics, some laboratory results, cardiac pathology, EuroSCORE and Parsonnet score were examined.

3. Statistics

Statistical analysis was performed with Analyse-It software version 2.08 (Analyse-It, Leeds, UK). Data were tested for normal distribution using the Shapiro–Wilk test. Mann–Whitney *U*-test was used to compare the results between groups of numerical data and Spearman rank was used for correlations between continuous variables. For categorical data χ^2 was used. A $P<0.05$ was considered to be statistically significant.

4. Results

BNP was detectable and measured in all 141 patients. As previously reported, BNP had a statistically significant correlation with the age ($P<0.0001$) [22] but no difference of the level between men and women was observed ($P=0.2$). There was also no correlation between BNP and body mass index (BMI). Patients with a higher grade of New York Heart Association (NYHA) had higher concentration of BNP ($P<0.0001$), however, severity of chest pain (Canadian Cardiovascular Society) did not have any association with preoperative BNP concentration. Patients with diabetes, hypertension (HTN), or with a history of myocardial infarction did not have significant higher BNP concentration compared to those without these risk factors ($P>0.05$). Conversely, high-BNP concentrations had a statistically significant association with preoperative AF and preoperative history of peripheral vascular disease (PVD), such as carotid artery stenosis, aortic aneurysm and low ankle brachial

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Table 2
Correlation between preoperative patient characteristics and BNP level

Characteristics	Values	BNP concentration (ng/l) in two groups	Spearman r	*P*-value
Age, years (mean age)	66.5±10.5	NA	0.45	<0.0001
Female/male (*n*)	43/98	155/177	NA	0.2
BMI (mean)	28±5	NA	−0.01	0.867
NYHA≥3/NYHA<3 (*n*)	25/116	549/94	NA	<0.0001
CCS≥3/CCS<3 (*n*)	36/105	191/109	NA	0.42
DM/no DM (*n*)	25/116	188/86	NA	0.63
HTN/no HTN (*n*)	118/23	331/141	NA	0.581
Preoperative AF/SR (*n*)	11/130	253/163	NA	0.008
MI≥2/MI<2 (*n*)	7/134	128/170	NA	0.06
LMS disease/normal LMS (*n*)	38/103	204/157	NA	0.842
PVD/no documented PVD (*n*)	24/117	305/142	NA	0.0009
Preoperative creatinine (mean)	104±7	NA	0.20	0.016
GFR (mean)	64.5±5	NA	−0.30	0.0003
Hb (mean)	13.2±1.4	NA	−0.31	0.0001
Plt count (mean)	252±23	NA	−0.03	0.72
EF<30% (*n*)	8/133	853/129	NA	<0.0001
EuroSCORE (mean)	5±3	NA	0.50	<0.0001
Parsonnet score (mean)	11.8±7.7	NA	0.46	<0.0001

BMI, body mass index; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; DM, diabetes mellitus; HTN, hypertension; AF, atrial fibrillation; SR, sinus rhythm; LMS, left main stem; PVD, peripheral vascular disease; GFR, glomerular filtration rate; Hb, haemoglobin; Plt, platelet; EF, ejection fraction; MI, myocardial infarction.

Table 3
Correlation between operative and postoperative variables and preoperative BNP concentration

Variables	Values	BNP concentration (ng/l) in two groups	*P*-value
Urgent/elective (*n*)	46/95	323/99	0.0017
Valve (AVR/MVR)/CABG (*n*)	44/97	273/125	0.0018
Inotropic or IABP use/no support (*n*)	21/120	452/120	0.0015
Postoperative AF/no AF (*n*)	38/103	237/145	0.109
Postoperative (day 4) creatinine (mean)	108 ± 7	NA	0.0008
Postoperative infection (*n*)	27/114	246/152	0.586
Postoperative MI (*n*)	6/135	97/173	0.915
Early death/alive (*n*)	6/135	1018/132	0.019
Hospital stay (mean)	7.4 ± 4.6	NA	0.049

Spearman r for continuous variables, postoperative creatinine and hospital stay has been 0.28 and 0.17, respectively.
AF, atrial fibrillation; IABP, intra-aortic balloon pump; MI, myocardial infarction.

blood pressure index (ABPI) ($P=0.0009$). High-BNP concentrations were also associated with impaired renal function. BNP showed a statistically significant correlation with glomerular filtration rate (GFR) when GFR was <90 ml/min ($P=0.0003$) and preoperative creatinine when this was >120 μmol/l ($P=0.016$). BNP concentration also correlated indirectly with the haemoglobin (Hb) concentration ($P=0.001$) but was not associated with platelet count or other biochemical markers (Table 2).

In view of cardiac morphological problems, BNP concentration was not associated with left main stem (LMS) disease, but high-BNP concentrations were associated with low ventricular ejection fractions (EFs) and impaired left ventricular function ($P<0.0001$). Patients undergoing emergency or urgent operation also had a higher level of BNP preoperatively compared to the elective patients ($P=0.0017$). Furthermore, patients with valvular conditions had higher BNP concentrations compared to patients who underwent CABG only ($P=0.0018$) (Table 3).

To assess the predictive value of BNP, its concentration was compared to the two main risk calculation indices; the EuroSCORE and Parsonnet score. This showed significant correlations between BNP concentration, EuroSCORE and Parsonnet score ($P<0.0001$). High-BNP concentration, also predicted the requirement for inotropic agents postoperatively (Fig. 1), significant increases from baseline creatinine concentration, as well as longer ventilation time and longer hospital stay ($P<0.05$). High preoperative BNP also correlated with mortality within 30 days of the operation ($P=0.019$, Fig. 2). Our study did not predict value for BNP in predicting the development of postoperative AF or infection (Table 3).

5. Discussion

Since the discovery of natriuretic peptides and the endocrine activity of the heart two decades ago, many studies have reported different practical uses for the family of natriuretic peptides. In this study, we have assessed whether BNP measurement as part of the routine blood tests carried out before cardiac surgery could provide information regarding the outcome of the operation or the risk of developing common postoperative complications, such as AF, infection, longer intubation time or longer hospital stay.

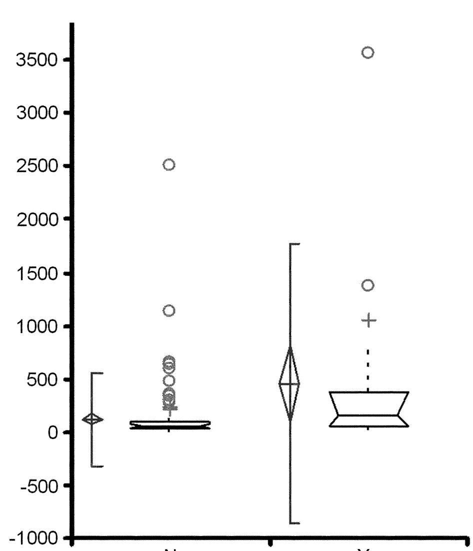

Fig. 1. Correlation between preoperative BNP and postoperative inotropic use.

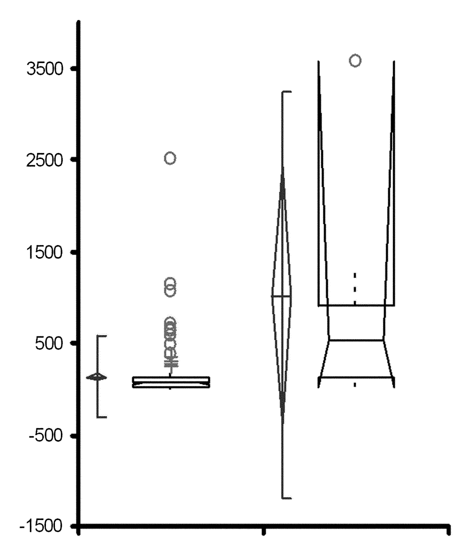

Fig. 2. Correlation between preoperative BNP level and early postoperative mortality.

Wazani et al. reviewed the association between preoperative plasma BNP concentration and postoperative development of AF. Reviewing 187 patients retrospectively, they concluded that raised BNP was a strong predictor of developing AF postoperatively [20]. However, our results failed to find a similar correlation between preoperative BNP and postoperative AF incidence. A recent study by Jogia et al. showed that patients with preoperative AF have significantly higher NT-pro BNP compared to patients in sinus rhythm (SR). In our study, this correlation was statistically insignificant. Jogia's study failed to prove the predictive value of BNP in occurrence of postoperative AF or mortality. Despite their findings of association between preoperative BNP and slow postoperative recovery, the authors were still unclear about the role of BNP in predicting the outcome after cardiac surgery [19].

Chello et al. measured plasma ANP and BNP in a small group of patients with poor left ventricular function undergoing CABG. They showed that BNP is a significant predictor of left ventricular recovery after cardiac surgery. However, they did not include a control group with preserved left ventricular function [17]. Hutfless et al. achieved similar results in almost 100 male patients undergoing heart surgery. They concluded that high concentrations of BNP pre- and postoperatively were associated with longer hospital stay and higher mortality rates within one year post-cardiac surgery. They also advocated following BNP-guided therapy for a better outcome after cardiac surgery [18]. In a study by Provenchère et al., BNP was measured for the assessment of outcome up to one year post-cardiac surgery. This study showed an elevation in plasma BNP that correlated with a 12-fold increase in potential risk of developing postoperative heart failure, however, in their multivariate analysis, only left ventricular EF was shown to be significantly associated with one-year survival [21]. In another study by Weber et al., BNP was assessed as an indicator of severity of aortic stenosis, the progression of the disease and as an indication for the optimal timing for aortic valve replacement [14]. Furthermore, in neonates undergoing atrial switch operation for transposition of great arteries, BNP was measured preoperatively and was found to have a high-predictive value for postoperative complications and outcome [16].

Our study is not the first to assess the predictive value of BNP in cardiac surgery, but it did include a number of variables which are associated with certain complications post-cardiac surgery, such as inotropic requirement, renal impairment and increased ventilation time which had not been investigated before. The statistically strong correlation between the preoperative BNP concentration and risk stratification calculators, such as EuroSCORE and Parsonnet score, demonstrates the value of preoperative testing of BNP in cardiac surgery. BNP measurement is not expensive and can give us an idea of ventricular function if ventriculogram or echocardiogram is not readily available. Furthermore, correlation between low-Hb and high-BNP concentration has not been reported previously and may suggest optimisation of Hb prior to the surgery, however, this requires further investigations.

There are several methods and scoring systems used by cardiac surgeons to predict the outcome. Each method has been developed from large databases of cardiac surgical patients, however, the performance of each system has been investigated in several publications due to differences observed in various patient populations. These studies have suggested that each method may be better suited for some analyses but not for others as expected from formal risk quantitation; some underestimate or over estimate mortality risk. Therefore, using a simple blood test is more objective and can potentially apply to all patients, however, many cases are required to enable us to calculate the risk of postoperative morbidity and mortality with different values of plasma BNP preoperatively.

BNP measurement is not expensive and can give us an idea of ventricular function if ventriculogram or echocardiogram is not readily available. Furthermore, correlation between low-Hb and high-BNP level has not been reported previously and may suggest optimisation of Hb prior to the surgery, this, however, requires further investigations.

This study has its own limitations; higher number of patients is required to prove the significance of preoperative BNP measurement. Furthermore, our study is also lacking the results of the long-term follow-up of our patients. This study concentrated only on preoperative BNP concentration and postoperative complications. We did not measure postoperative BNP, which increases after cardiopulmonary bypass, to analyse its increase against developing complications.

More importantly, in this study we are unable to offer a cut-off value BNP level that would be able to predict postoperative complications due to the low incidence of complications post-cardiac surgery and requires the study to be carried out on a large number of cases and in several centres. This will be possible with routine measurement of BNP in cardiac surgery.

In conclusion, we strongly believe that BNP is a valuable, inexpensive, reliable, simple and strong predictor of the outcome post-cardiac surgery and should be measured alongside the routine blood tests preoperatively.

References

[1] Sudoh T, Kangawa K, Minamino N, Matsuo H. A new natriuretic peptide in porcine brain. Nature 1988;332:78–81.

[2] Doyama K, Fukumoto M, Takemura G, Tanaka M, Oda T, Hasegawa K, Inada T, Ohtani S, Fujiwara T, Itoh H, Nakao K, Sasayama S, Fujiwara H. Expression and distribution of brain natriuretic peptide in human right atria. J Am Coll Cardiol 1998;32:1832–1838.

[3] Ogawa Y, Nakao K, Mukoyama M, Shirakami G, Itoh H, Hosoda K, Saito Y, Arai H, Suga S, Jougasaki M. Rat brain natriuretic peptide: tissue distribution and molecular form. Endocrinology 1990;126:2225–2227.

[4] Mukoyama M, Naka K, Hosoda K, Suga S, Saito Y, Ogawa Y, Shirakami G, Jougasaki M, Obata K, Yasue H. Brain natriuretic peptide as a novel cardiac hormone in humans: evidence for an exquisite dual natriuretic peptide system, ANP and BNP. J Clin Invest 1991;87:1402–1412.

[5] Luchner A, Stevens TL, Borgeson DD. Differential atrial and ventricular expression of myocardial BNP during evolution of heart failure. Am J Physiol 1998;274:H1684–H1689.

[6] Struthers AD. Ten years of natriuretic peptide search: a new dawn for their diagnostic and therapeutic use? Br Med J 1994;308:1615–1619.

[7] Suzuki S, Yoshimura M, Nakayama M, Mizuno Y, Harada E, Ito T, Nakamura S, Abe K, Yamamuro M, Sakamoto T, Saito Y, Nakao K, Yasue H, Ogawa H. Plasma level of B-type natriuretic peptide a prognostic marker after acute myocardial infarction: a long-term follow-up analysis. Circulation 2004;110:1387–1391.

[8] Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. J Am Med Assoc 2005;293:1609–1616.
[9] Hartmann F, Packer M, Coats AJ, Fowler MB, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Anker SD, Amann-Zalan I, Hoersch S, Katus HA. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: a substudy of the carvedilol prospective randomized cumulative survival (COPERNICUS) trial. Circulation 2004;110:1780–1786.
[10] Ationu A, Singer D, Smith A, Elliott M, Burch M, Carter N. Studies of cardiopulmonary bypass in children: implications for the regulation of brain natriuretic peptide. Cardiovasc Res 1993;27:1538–1541.
[11] Guerin V, Ben Ayed S, Varnous S, Golmard JL, Leprince P, Beaudeux JL, Gandjbakhch I, Bernard M. Release of brain natriuretic-related peptides (BNP, NT-proBNP) and cardiac troponins (cTnT, cTnI) in on-pump and off-pump coronary artery bypass surgery. Surg Today 2006;36:783–789.
[12] Morimoto K, Mori T, Ishiguro S, Matsuda N, Hara Y, Kuroda H. Perioperative changes in plasma brain natriuretic peptide concentrations in patients undergoing cardiac surgery. Surg Today 1998;28:23–29.
[13] Avidan MS, Meehan N, Pnte J, El-Gamel A, Sherwood R. Changes in brain natriuretic peptide concentrations following open cardiac surgery with cardioplegic cardiac arrest. Clin Chim Acta 2001;303:127–132.
[14] Weber M, Arnold R, Rau M, Brandt R, Berkovitsch A, Mitrovic V, Hamm C. Relation of N-terminal pro-B-type natriuretic peptide to severity of valvular aortic stenosis. Am J Cardiol 2004;94:740–745.
[15] Ray S. Natriuretic peptides in heart valve disease. Heart 2006;92:1194–1197.
[16] Cannesson M, Bionda C, Gostoli B, Raisky O, di Filippo S, Bompard D, Védrinne C, Rousson R, Ninet J, Neidecker J, Lehot JJ. Time course and prognostic value of plasma B-type natriuretic peptide concentration in neonates undergoing the arterial switch operation. Anesth Analg 2007;104:1059–1065.
[17] Chello M, Mastroroberto P, Perticone F, Cirillo F, Bevacqua E, Olivito S, Covino E. Plasma levels of atrial and brain natriuretic peptides as indicators of recovery of left ventricular systolic function after coronary artery bypass. Eur J Cardiothorac Surg 2001;20:140–146.
[18] Hutfless R, Kazanegra R, Madani M, Bhalla MA, Tulua-Tata A, Chen A, Clopton P, James C, Chiu A, Maisel AS. Utility of B-type natriuretic peptide in predicting postoperative complications and outcome in patients undergoing heart surgery. J Am Coll Cardiol 2004;43:1873–1879.
[19] Jogia M, Kalkoff M, Sleigh JW, Bertinelli A, La Pine M, Richards AM, Devlin G. NT-pro BNP secretion and clinical endpoints in cardiac surgery intensive care patients. Anaesth Intensive Care 2007;35:363–369.
[20] Wazni O, Martin D, Marrouche N, Latif AA, Ziada K, Shaaraoui M, Almahameed S, Schweikert RA, Saliba WI, Gillinov AM, Tang WH, Mills RM, Francis GS, Young JB, Natale A. Plasma B-type natriuretic peptide levels predict postoperative atrial fibrillation in patients undergoing cardiac surgery. Circulation 2004;110:124–127.
[21] Provenchère S, Berroeta C, Reynaud C, Baron G, Poirier I, Desmonts JM, Iung B, Dehoux M, Philip I, Bénessiano J. Plasma brain natriuretic peptide and cardiac troponin I concentrations after adult cardiac surgery: association with postoperative cardiac dysfunction and 1-year mortality. Crit Care Med 2006;34:995–1000.
[22] Nageh T, Chin D, Cooke J, Meehan N, Monaghan M, Sherwood R. Interpretation of plasma brain natriuretic peptide concentrations may require adjustment for patient's age. Ann Clin Biochem 2002;39:151–153.

eComment: Re: Brain natriuretic peptide a predictive marker in cardiac surgery

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The results of the study were thoroughly analyzed in the reviewed article. The level of BNP concentration in 141 patients undergoing cardiac surgery was measured prior to operation and their comorbidities were examined against their BNP [1]. These results fully reflect all objectives of the study which were the evaluation of the BNP predictor in postoperative patients and the detection of connection between the level of this marker and the postoperative prognosis. In particular, the authors revealed that high level of BNP before intervention was found in patients with renal impairment, peripheral vascular disease and low ejection fraction. In patients with high inotropic use and longer ventilation time BNP level was statistically higher than in patients with routine postoperative period. However, there was no predicting value of BNP marker in patients with atrial fibrillation and infection in early postoperative period.

In recent years, the study of neurohormonal activation and the role of BNP as a diagnostic and prognostic marker has taken a remarkable start [2]. BNP is a neurohormone which is synthesized in ventricular myocardium in response to increased wall stress. Pro-BNP marker (a terminal part of prohormone BNP) has a high diagnostic accuracy and predicting value due to longer stay in blood in comparison with BNP [3].

BNP marker is widely and regularly used at the Bakulev Center for Cardiovascular surgery. This marker can be useful in the diagnostic and long-term prognosis of different cardiac pathologies. It helps to estimate the heart failure grade, to define high-risk patients and conditions which lead to high operative mortality. BNP and pro-BNP markers now are defined as a good diagnostic tool in asymptomatic patients. BNP measurement assists in evaluating the efficacy of the medical treatment in outpatients in the short- and long-term follow-up period.

BNP level also allows to define patients with symptoms which require further research in order to choose the right algorithm of treatment [4].

References

[1] Attaran S, Sherwood R, Desai J, Langworthy R, Mhandu P, John L, El-Gamel A. Interact CardioVasc Thorac Surg 2009;9:662–666.
[2] Bettencourt P. NT-proBNP and BNP: biomarkers for heart failure management. Eur J Heart Fail 2004;6:359–363.
[3] Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. Eur J Heart Fail 2004;6:261–267.
[4] Suzuki S, Yoshimura M, Nakayama M, Mizuno Y, Harada E, Ito T, Nakamura S, Abe K, Yamamuro M, Sakamoto T, Saito Y, Nakao K, Yasue H, Ogawa H. Plasma level of B-type natriuretic peptide as a prognostic marker after acute myocardial infarction: a long-term follow-up analysis. Circulation 2004;110:1387–1391.