

ORIGINAL ARTICLE

Brain natriuretic peptide as a predictor of clinical outcome and symptom improvement after a left ventricular assist device implantation

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Summary

Introduction: The predictive value of brain natriuretic peptide in heart failure is well-known, but its importance as an outcome predictor after a left ventricular assist device (LVAD) implantation remains unaddressed. This research aims to examine the significance of brain natriuretic peptide (BNP) as an indicator of treatment outcomes during different post-implantation periods.

Methods: A retrospective cohort study included the analysis of medical records of 87 patients in whom LVAD was implanted at the University Clinical Center of Serbia in the period 2014-2020. The correlation of BNP levels with treatment outcomes after operation was evaluated.

Results: The average preoperative BNP for all patients was 1244 pg/mL. The average ejection fraction (EF) was 15% (median), endsystolic diameter (ESD) was 6.80 cm and enddiastolic diameter (EDD) was 7.70 cm. Eighty-one patients were NYHA class 4, and 6 patients were NYHA 3. Compared to the preoperative BNP level below or above 1000 pg/mL, there was no significant difference in overall survival of patients after operation (Log Rank [Mantel-Cox] test, $p=0.838$). BNP levels postoperatively decreased from 358 pg/mL at 3 months upon surgery to 136 pg/mL 5 years upon surgery (Friedman test, $p<0.001$). BNP levels show strong negative correlation with EF (decrease in BNP level and increase in EF value), and strongly positive correlation with EDD, ESD, and NYHA class (a decrease in BNP and a decrease in EDD, ESD, and NYHA).

Conclusion: Preoperative BNP level may not be an adequate predictor of the outcome after LVAD implantation, but the post-implantation decrease in BNP levels is highly correlated with parameters that indicate an improvement in the clinical status and positive changes in the myocardium and long-term survival.

Keywords: LVAD, BNP, heart failure, reverse remodeling, NYHA

INTRODUCTION

Implantation of a left ventricular assistance device (LVAD) is a widely used method of treatment of end-stage heart failure (HF). It was primarily conceived as a bridge to transplant (BTT) device but was later approved for use as definitive (destination) therapy (DT). (1) The most current publications show survival rates suggesting that the LVAD implantation program can become an alternative to heart transplantation (HTx), otherwise the gold standard in the treatment of HF, considering the inherent limitation of the HTx concept based on the lack of donors and increasingly good results of LVAD implantation (2).

Brain natriuretic peptide (BNP) is secreted primarily by ventricular myocytes as a reactive response to myocardial load and damage. BNP was first isolated in the brain tissue, but it was later proven that the ventricular myocardium is the primary site for the release of this hormone. Increased BNP levels can help clinicians to differentiate HF and monitor the effects of various treatments, stratify the risk after acute ischemic coronary events, and monitor possible cardiotoxicity during chemotherapy, but the final conclusions are supplemented by other clinical signs and examinations (3). Many reports on the prognostic value of BNP in HF have been published but reports on the importance of BNP in the clinical follow-up of LVAD patients are significantly scarcer in terms of content and number (4).

The aim of the paper is to use a retrospective analysis to examine the correlation of brain natriuretic peptide (BNP) level with clinical outcome after LVAD implantation and with anatomical and functional changes in the left ventricular myocardium in the post-implantation period.

MATERIAL AND METHODS

A multidisciplinary cardiology and cardiac surgery team performed a retrospective analysis of the medical records of patients in whom an LVAD device was implanted at the University Clinical Center of Serbia from January 2014 to December 2020. Demographic and clinical data from the pre-implantation period, data from surgery as well as follow-up data (histories, echocardiographic findings, and laboratory results) were collected for the following time points: before implantation, 30, 90 and 180 days post implantation, one year upon implantation, and for every subsequent post-implantation year. Possible unscheduled and additional follow-up visits were analyzed depending on the reason for the visit/hospitalization or adverse events and/or complications.

BNP levels were determined in the samples using chemiluminescent immunoassay, CLIA method, using Atellica IM, Siemens. The test is a double sandwich immunoassay that uses direct chemiluminescent technology based on constant amounts of two monoclonal antibodies.

The first antibody is a mouse monoclonal antibody to human BNP, labeled with acridinium ester, characteristic of the ring structure of BNP. The second solid phase antibody is a biotinylated mouse monoclonal anti-human antibody characteristic for the C-terminal part of BNP, bound to streptavidin magnetic particles. After the reaction, there is a direct relationship between the amount of BNP in the sample and the relative light units (RLUs) detected by the system. The analytical sensitivity of the test is 2 pg/mL. The reference level (95th percentile) is <100 pg/mL.

The primary endpoints for analysis were patient survival and a decrease in heart failure symptoms, a change in New York Heart Association (NYHA) class, a change in the left ventricular ejection fraction (EF), changes in left ventricular end-systolic (ESD) and end-diastolic diameter (EDD).

Complete statistical analysis was performed with the statistical software package IBM SPSS version 26.0. Attribute variables are presented as the frequency of certain categories, numerical variables are presented as mean values with standard deviation or median with interquartile range (25-75th percentile), depending on the normality of the data distribution, which was tested by the Kolmogorov-Smirnov test. Patient unadjusted survival was calculated using Kaplan-Meier plot (mean value with 95% confidence interval) and the value obtained with the Log Rank (Mantel-Cox) test. Spearman's rank correlation was used to assess the relationship between the observed parameters and BNP levels. All analyses were assessed with the $p < 0.05$ level of statistical significance.

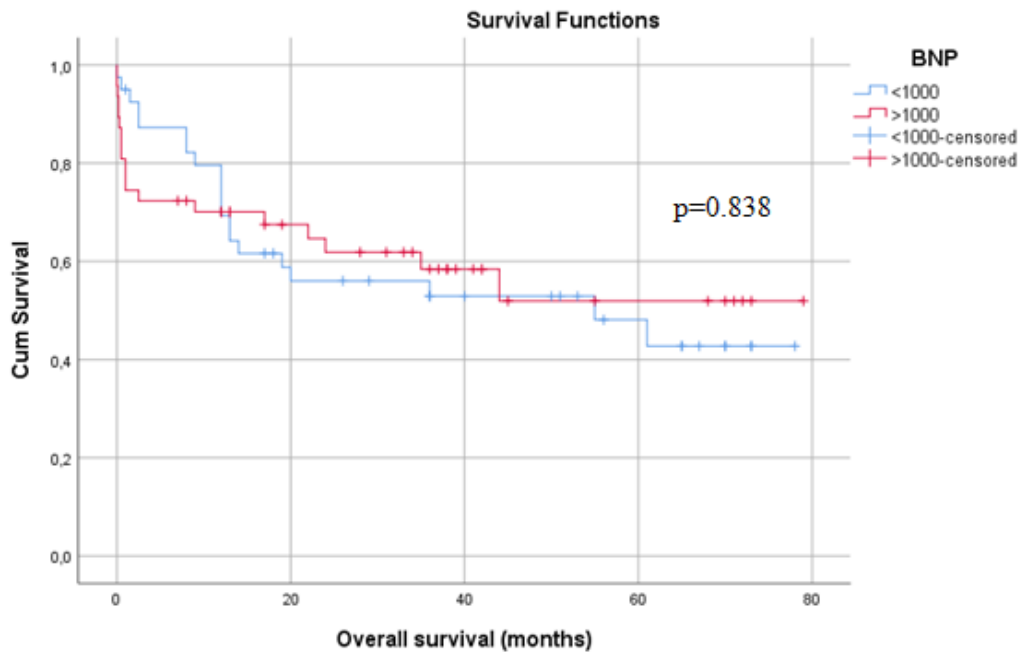
RESULTS

The study included 87 patients implanted with an LVAD pump from 2014 to 2020. **Table 1** shows basic

Table 1. Preoperative demographic and clinical characteristics of patients

Gender: Male/Female	79 (90.8) / 8 (9.2)
Age (years)	54.75 ± 12.06
BNP (pg/mL)	1244 (577-2500)
BNP: <1000 / >1000	40 (46.0) / 47 (54.0)
BTT / Definitive therapy	61 (70.1) / 26 (29.9)
NYHA: III / IV	6 (6.9) / 81 (93.1)
INTERMACS class: 1-2 / 3-4 / 5	27 (31.0) / 52 (59.8) / 8 (9.2)
eGFR (mL/min/1.73 m ²)	60 (44-60)
Pump type: Heart Mate II / Heart Mate III / HeartWare	30 (34.5) / 24 (27.6) / 33 (37.9)
Creatinine (μmol/L)	108 (77-142)
Duration of hospital stay (days)	25 (20-31)
Outcome: survival/death	48 (55.2) / 39 (44.8)
EF (%)	15 (12-20)
ESD (cm)	6.80 (6.05-7.45)
EDD (cm)	7.70 (6.70-8.40)

Results are presented as number (%), mean ± standard deviation or median with interquartile range (25-75th percentile).



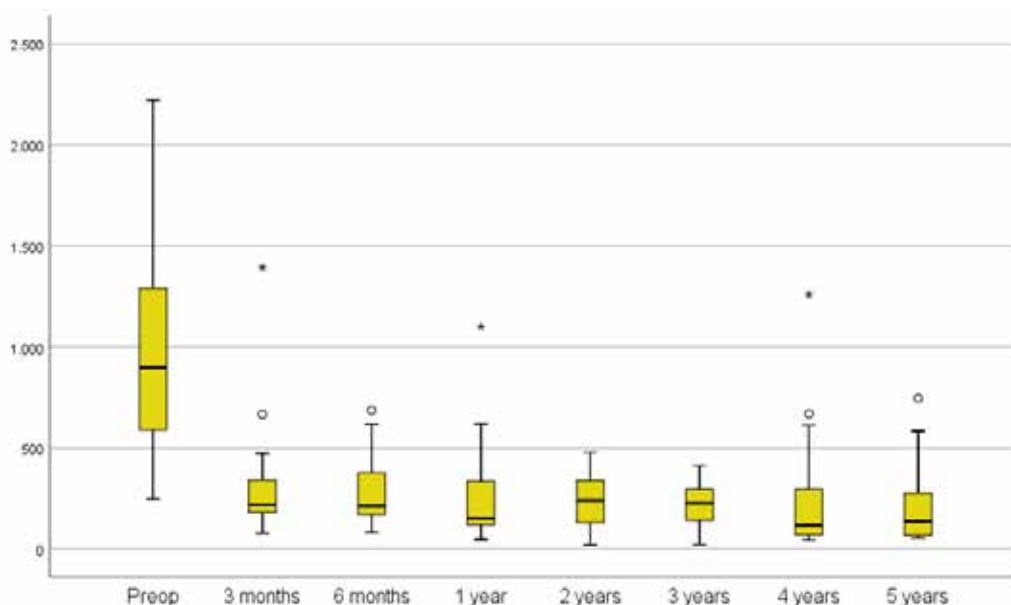
Graph 1. Overall survival relative to BNP level ($p=0.838$)

preoperative characteristics of these patients. Most of them were male, with an average age of about 55 years. All patients were classified as NYHA class III and IV. The average ejection fraction was 15% (median), while ESD was 6.80 cm and EDD 7.70 cm. The average preoperative BNP level for all patients was 1244 pg/mL. Survival rate after 5 years was 43%. For the purpose of statistical analyses, we divided the patients into two groups based on the preoperative BNP level; there were 46% of patients with BNP levels below 1000 pg/mL and 54% of patients with BNP levels above 1000 pg/mL.

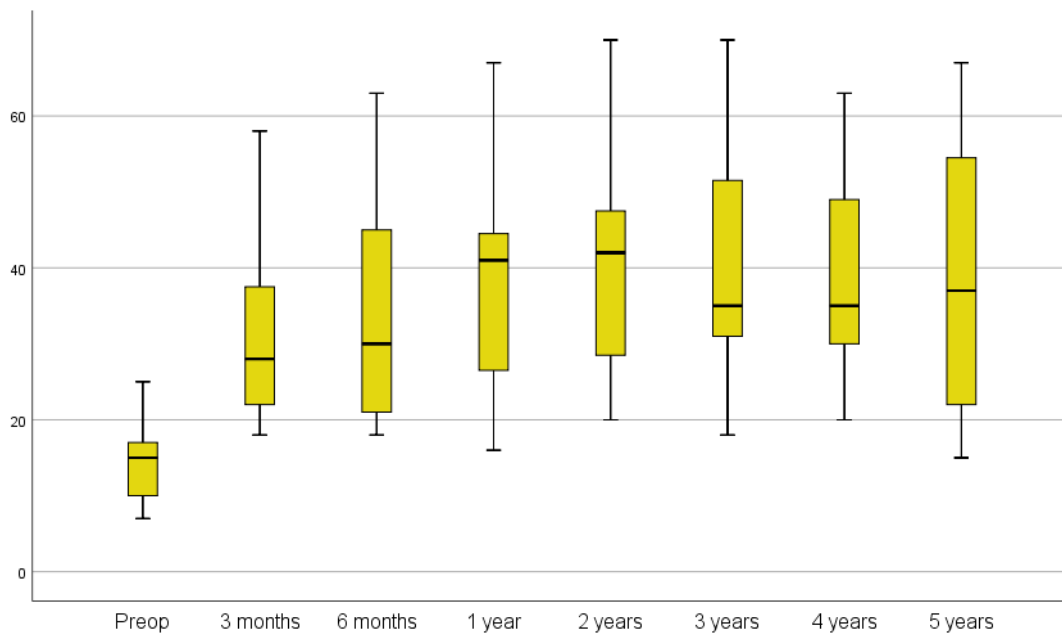
Relative to BNP level (>1000 pg/mL vs. <1000 pg/mL), no significant difference was found in the overall survival after LVAD implantation (Log Rank [Mantel-Cox]

test). **Graph 1** shows that, in the first 20 months, mortality was higher in the group with preoperative BNP level >1000 pg/mL, while after that and until the end of the follow-up period, mortality was higher in the group with preoperative BNP level <1000 pg/mL. The average survival rate was 47.19 months (95% confidence interval: 36.27-58.11) in the group with preoperative BNP level >1000 pg/mL, and 44.44 months (95% confidence interval: 34.09-55.00) in the group with BNP level <1000 pg/mL.

Graph 2 first shows preoperative and postoperative BNP levels during the period of 5 years upon surgery. Preoperative levels had already been shown to be significantly higher with an average of 1244 pg/mL, while postoperative levels improved, showing a decrease from



Graph 2. BNP levels (pg/mL) preoperatively and at 5 years upon surgery



Graph 3. EF values (%) preoperatively and at 5 years upon surgery

358 pg/mL at 3 months after surgery to 136 pg/mL 5 years upon surgery (Friedman test, $p < 0.001$).

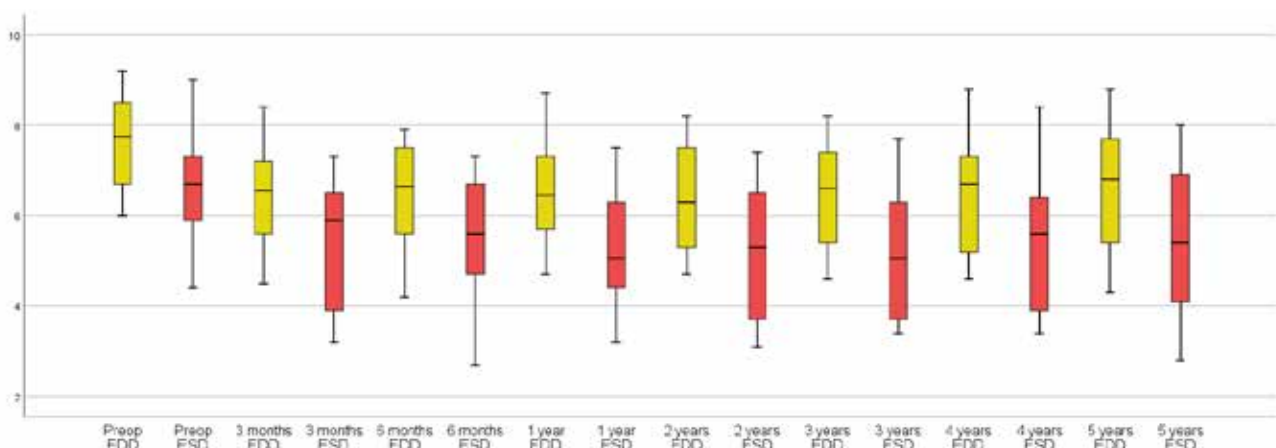
Graph 3 shows preoperative and postoperative EF values during the period of 5 years after surgery. Preoperative value had already been shown to be significantly lower at an average of 15%, while postoperative value improved, showing an increase from 30% at 3 months upon surgery to 37% 5 years upon surgery (Friedman test, $p < 0.001$).

Graph 4 shows preoperative and postoperative EDD and ESD values preoperatively and postoperatively during the period of 5 years after surgery. Preoperative ESD value had already been shown to be significantly higher at an average of 6.80 cm, while postoperative value improved, showing a decrease from 5.80 cm at 3 months after surgery to 4.90 cm at 5 years after surgery (Friedman test, $p < 0.001$). Preoperative EDD value was significantly higher at an average of 7.70 cm, while postoperative value improved, showing a decrease from 6.55 cm at 3 months

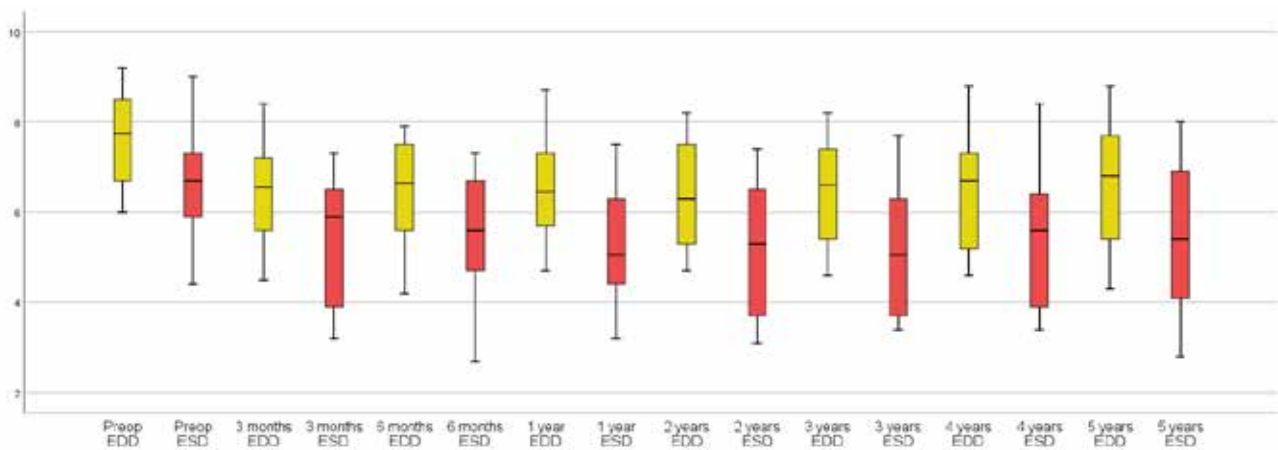
after surgery to 6.80 cm at 5 years upon surgery (Friedman test, $p < 0.001$).

Before surgery, most patients were NYHA class IV (**Graph 5**) and the rest were NYHA class IIIb. However, at 3 months after surgery, the relationship changed with most of them being NYHA class II, while at 5 years after surgery most of them were NYHA class I, suggesting that the long-term survival of these patients is highly correlated with the degree of HF symptom reduction.

By analyzing the association of BNP levels with several most significant parameters that were monitored before and after surgery (**Table 2**), we observed a significant negative association between preoperative BNP levels and EF. BNP levels at 6 months are associated with NYHA class only, while BNP at one year is strongly negatively associated with EF (a decrease in BNP level and an increase in EF value), and strongly positively associated with EDD, ESD and NYHA class (a decrease in BNP level and a decrease in EDD, ESD and NYHA category



Graph 4. EDD and ESD values (cm) preoperatively and at 5 years upon surgery



Graph 5. Number of patients by NYHA class, preoperatively and at 5 years upon surgery

Table 2. Association of BNP with EF, EDD, ESD, and NYHA class

BNP	EF	EDD	ESD	NYHA
Preoperatively	$r=-0.278$ $p=0.009^*$	$r=0.173$ $p=0.109$	$r=0.144$ $p=0.189$	$r=0.079$ $p=0.464$
After 3 months	$r=-0.171$ $p=0.160$	$r=0.228$ $p=0.059$	$r=0.162$ $p=0.184$	$r=0.219$ $p=0.071$
After 6 months	$r=-0.142$ $p=0.250$	$r=0.212$ $p=0.083$	$r=0.218$ $p=0.074$	$r=0.353$ $p=0.003^*$
After 1 year	$r=-0.320$ $p=0.012^*$	$r=0.445$ $p<0.001^*$	$r=0.427$ $p=0.001^*$	$r=0.471$ $p<0.001^*$
After 2 years	$r=-0.396$ $p=0.009^*$	$r=0.181$ $p=0.245$	$r=0.255$ $p=0.099$	$r=0.501$ $p=0.001^*$
After 3 years	$r=-0.370$ $p=0.029^*$	$r=0.349$ $p=0.040^*$	$r=0.355$ $p=0.040^*$	$r=0.602$ $p<0.001^*$
After 4 years	$r=-0.344$ $p=0.127$	$r=0.317$ $p=0.162$	$r=0.340$ $p=0.132$	$r=0.070$ $p=0.764$
After 5 years	$r=-0.660$ $p=0.007^*$	$r=0.424$ $p=0.115$	$r=0.474$ $p=0.075$	$r=0.371$ $p=0.173$

Sperman's rank correlation; * - $p<0.05$

values). BNP levels after 2 years showed the association with NYHA class and EF similarly to those after year 1, and again after 3 years in the same way with all monitored variables. After 5 years, BNP levels remained strongly negatively associated to EF only.

DISCUSSION

Our research showed that all patients who are candidates for LVAD implantation have increased BNP levels several times above the reference levels, which is consistent with end-stage heart failure. Considering that the reference level of BNP is less than 100 pg/mL, and that all patients had a preoperative level far higher than normal (even several tens of times higher), it did not prove to be a parameter that can provide a prognosis of survival immediately after implantation, even at levels >1000 pg/mL which, according to some publications, is the value that categorizes NYHA class IV end-stage heart failure. Over a longer post-implantation period, the BNP level showed a significant decline compared to pre-implantation levels and stood in correlation with patient long-term survival. Also, a decrease in BNP level is correlated with observed echocardiographic changes, an increase of EF, and a decrease of ESD and EDD, as well as with an improvement in NYHA class. This suggests a reverse process remodeling of the myocardium after LVAD implantation, i.e., recovery of myocardial function at the level of heart

ventricles and BNP serum levels as predictors of such positive physiological-anatomical myocardial changes.

Natriuretic peptide system includes three elements. A-type, the atrial natriuretic peptide mostly synthesized in the atria in response to stress of this part of the heart. C-type is produced in the brain, pituitary gland, kidneys, and endothelial cells, but generally at low serum concentrations. Ventricles initially secrete prohormone called pro BNP, which is then transformed by enzymatic processing into NT-proBNP, which consists of 76 amino acids and BNP with its 32 amino acids. These two proteins are isolated from serum in clinical practice, but the concentration of NT-pro BNP is 3 to 6 times higher than the concentration of BNP due to its longer half-life (5,6). The basic cardioprotective mechanism of this peptide is the reduction of volume load by reducing the concentration of salt and water in the body and by vasodilation. Basically, BNP is an antagonist to renin-angiotensin-aldosterone cardiovascular hormonal cascade that is released in response to a decrease in atrial pressure (7).

In addition to pathological conditions that cause myocardial strain, serum BNP levels are also increased in diabetes, acute coronary damage, and kidney disease. It is important to note that the BNP level is lower in people with obesity. Also, BNP level increases depending on the patient age, sex (women tend to generally have higher levels than men), and there are daily variations in the level in many patients. Therefore, the assessment of the clinical cause of BNP level disorders and its predictive value

should be assessed taking into consideration the individual characteristics of the patient (8). A level of 100 pg/mL is usually taken as the cut-off value that discerns cardiac from non-cardiac causes of dyspnea (9). BNP levels progressively increase as the patient's NYHA category increases, so the levels above 1000 are usually present in heart failure with NYHA IV category and are characteristic of patients with pronounced symptoms of end-stage heart failure (10,11).

As discussed above, the number of studies specifically dealing with BNP as a predictor of outcome after LVAD implantation is small. Sato et al. showed the significance of a decrease in BNP levels after LVAD implantation concluding that such a trend was associated with long-term patient survival. A significant number of previous publications point out that the greatest recovery of cardiac function occurs in the period up to 60 days upon surgery, and especially after the first post-implantation month. The mentioned period represents the interval in which the reverse myocardial remodeling reaches its maximum. The results of our study are generally in agreement with this conclusion (12).

Yost et al. in their publication state that 14 days is the optimal time point for determining the level of BNP decrease and subsequent interpretation of such decrease as an outcome predictor (13).

Papathanasiou et al. in their research reported a decrease in BNP levels after LVAD implantation, but with levels that are still high. They emphasize the importance of using other biomarkers and considering non-cardiological parameters to obtain relevant conclusions related to the predictive role of BNP (14).

In addition to the proven increase in the survival rate and an improvement in quality of life compared to non-surgical methods of treatment of end-stage heart failure, LVAD patients are exposed to the risk of various post-implantation complications. These include, but are not limited to infections, hemorrhages in various organs, the right ventricle weakness, pump thrombosis, and cerebrovascular insult (15). In their research, Hegarova et al. tested a hypothesis that elevated levels and changes in BNP concentration in LVAD patients correlated with the occurrence of adverse events. The increase in BNP levels due to post-implantation adverse events is thought to be primarily due to increased ventricular filling pressure and stress on ventricular myocytes. This study suggested special, individual BNP levels that can potentially warn and correlate with certain adverse events and complications, but these conclusions were not confirmed by larger studies (16).

Methods of LVAD implantation were described in many publications and are part of regular cardiac surgical practice. The input cannula is placed in the top part of the left ventricle, the output graft is connected to the aorta, and the energy for work is obtained through an external

(extracorporeal) source that is connected to the device via a drive line (drawn through the skin of the abdomen). After implantation, LVAD device takes over the action of the left ventricle and increases the systemic circulation flow. Subsequently, this leads to a significant increase in the inflow to the right ventricle (this is the reason why the right ventricle must have sufficient contractile reserve), which responds to this with increased work and pulmonary circulation flow. At the same time, faster and more efficient emptying of the left ventricle reduces the load in the pulmonary circulation. Such a hemodynamic cascade, along with an additional improvement of kidney function in most patients, leads to a major unloading of the myocardium at the level of both ventricles and, subsequently, to a decrease in BNP synthesis.

The improvement of myocardial function that has been damaged by certain cardiac pathology after surgical or non-surgical treatment, with the correction of previously occurring pathoanatomical changes, is defined in literature as "reverse myocardial remodeling" (17,18). There is a significant number of reports that point to the unequivocal conclusion that the LVAD implantation leads to such positive changes that also affect the outcome of treatment. Reverse LV remodeling after LVAD implantation has been associated with a decrease in plasma BNP levels. Reduced synthesis of BNP has been documented even in samples of myocardial cells (19).

CONCLUSION

LVAD implantation significantly alleviates symptoms of heart failure with accompanying positive changes at the anatomical and physiological level of the myocardium. Preoperative BNP level is not an adequate predictor of survival after LVAD implantation. Postoperative BNP levels, i.e., a drop in BNP levels after implantation is correlated with long-term patient survival accompanied by an increase in EF, a decrease in EDD and ESD, as well as changes in the NYHA category.

LIMITATIONS

The conclusions were based on the study performed at a single cardiac surgery center. The analysis was performed on 87 patients, which represents a relatively small number of subjects. This research has limitations typical of other retrospective, non-randomized studies.

Ethical Statement: Conducting such a retrospective study is in accordance with the provisions of Helsinki Declaration and was approved by the Ethics Committee of the University Clinical Center of Serbia.

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MOŽDANI NATRIURETSKI PEPTID KAO PREDIKTOR KLINIČKOG ISHODA I POBOLJŠANJA SIMPTOMA NAKON UGRADNJE UREĐAJA ZA TRAJNU MEHANIČKU CIRKULATORNU POTPORU

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Sažetak

Uvod: Moždani natriuretski peptid (BNP) potvrdio je svoju prediktivnu vrednost u stanju srčane insuficijencije, ali njegov značaj kao prediktora ishoda nakon ugradnje uređaja za trajnu mehaničku cirkulatornu potporu (LVAD) nije obrađivan u dovoljnoj meri da bi se izveli nedvosmisleni zaključci. Cilj istraživanja je da ispita značaj BNP-a kao parametra koji može ukazivati na ishode lečenja u različitim postimplantacionim vremenskim periodima.

Metode: Učinjena je retrospektivna kohortna studija analizom medicinske dokumentacije 87 bolesnika kojima je LVAD uređaj ugrađen u Univerzitetском Kliničkom Centru Srbije od 2014. godine do 2020. godine. Analizirana je korelacija nivoa moždanog natriuretskog peptida sa ishodima nakon operativnog lečenja.

Rezultati: Preoperativni BNP je u proseku bio za sve pacijente 1244 pg/ml. Ejekciona frakcija (EF) je u proseku bila 15% (medijana), endsistolni dijametar (ESD) 6,80cm,

a enddijastolni dijametar (EDD) 7,70cm. 81 bolesnik pripadao je NYHA klasi 4, a 6 bolesnika NYHA klasi 3. U odnosu na to da li je vrednost BNP preoperativno bila manja ili veća od 1000 pg/ml nije nađena značajna razlika u ukupnom preživljavanju pacijenata nakon ugradnje LVAD pumpe (Log Rank (Mantel-Cox) test, $p=0,838$). Vrednost BNP –a postoperativno se smanjivala od 358 pg/ml 3 meseca nakon operacije do 136 pg/ml 5 godina nakon operacije (Friedman test, $p<0,001$). Vrednosti BNP negativno je izrazito povezan sa EF (pad vrednosti BNP-a, a rast vrednosti EF), a pozitivno izrazito povezan sa EDD, ESD i NYHA klasom (pad vrednosti BNP-a i pad vrednosti EDD,ESD i kategorije NYHA).

Zaključak: Preoperativni BNP nije adekvatan prediktor ishoda nakon LVAD ugradnje, ali postimplantacioni pad vrednosti BNP-a visoko korelira sa parametrima koji ukazuju na poboljšanje kliničkog statusa i pozitivnim promenama na miokardu i dugoročnim preživljavanjem.

Ključne reči: LVAD, BNP, srčana slabost, reverzni remodeling, NYHA

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