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Review article
Pregledni članak

THE POTENTIAL OF CARDIAC MARKERS TO IMPROVE PATIENT MANAGEMENT

POTENCIJAL SRČANIH MARKERA ZA UNAPREĐENJE LEČENJA PACIJENATA

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Summary: B-type natriuretic peptide (BNP) is a quantitative marker for heart failure. The use of BNP in patients with dyspnea has consistently shown to improve patient management and reduce treatment cost. Additional indications with the potential to improve patient management include treatment monitoring in acute and chronic heart failure, pulmonary embolism, and coronary artery disease.

Keywords: BNP, dyspnea, heart failure, monitoring, cost

Kratak sadržaj: B-tip natriuretskog peptida (BNP) jeste kvantitativni marker za srčane bolesti. Pokazalo se da upotreba BNP-a kod pacijenata sa dispneom unapređuje lečenje i smanjuje troškove tretmana. Dodatne indikacije koje imaju potencijal da unaprede lečenje pacijenata uključuju praćenje toka lečenja u slučajevima akutnih i hroničnih srčanih bolesti, plućne embolije i koronarne arterijske bolesti.

Ključne reči: BNP, dispnea, srčana bolest, praćenje, troškovi

Introduction

B-type natriuretic peptide (BNP) is considered a quantitative marker for heart failure. The most prominent member of the natriuretic peptide family is secreted from the heart mainly due to the increase in intracardiac volume or intracardiac pressure. BNP is a hormone that is released into the blood in relation to disease severity and corresponds to the New York Heart Association (NYHA) functional classification system.

A quantitative marker for heart failure is necessary as the diagnosis of heart failure is difficult. The main symptom, dyspnea is non-specific and has a broad differential diagnosis and initial diagnosis has been shown to be correct in only 50% of patients (1, 2).

Another reason why quantitative biomarkers are vital is that the clinical outcome with the additional data from biomarkers is extremely good. Data published in the »New England Journal of Medicine« has shown that the survival of patients with preserved ejection fraction and reduced ejection fraction was extremely poor when biomarkers were not utilized (3).

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BNP in the Diagnosis of HF

BNP shows high accuracy in the diagnosis of heart failure. The clinical use of BNP in the diagnosis of heart failure was first introduced approximately 15 years ago in New Zealand. Since then, its application has been confirmed by a large multicenter study that shows that BNP levels are very high in patients with dyspnea due to congestive heart failure (4) (*Figure 1*).

The accuracy of the test may also be assessed by performing an ROC analysis as outlined in a recent study (*Figure 2*). Published in Circulation, the study shows that the accuracy of the test performed in the emergency department is 0.86, 0.9 for BNP alone and 0.93 for BNP combined with emergency department judgment (5). The combination increases the diagnostic accuracy for the diagnosis of HF.

BNP in the Prognosis of HF

There is also consistent data that BNP is the most powerful predictor of death in patients with heart fail-

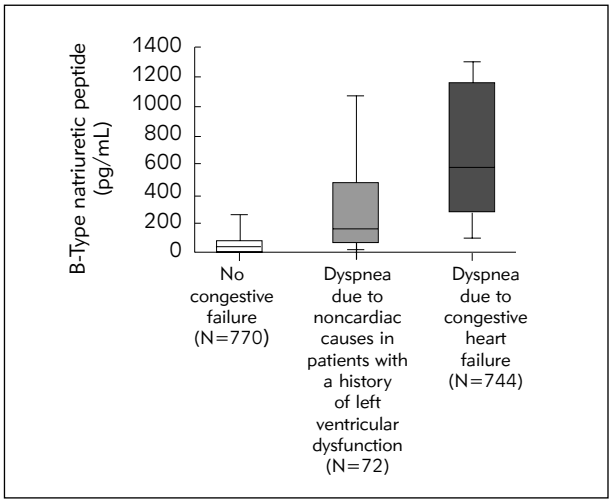

Figure 1 B-Type natriuretic peptide levels in patients with dyspnea (4).

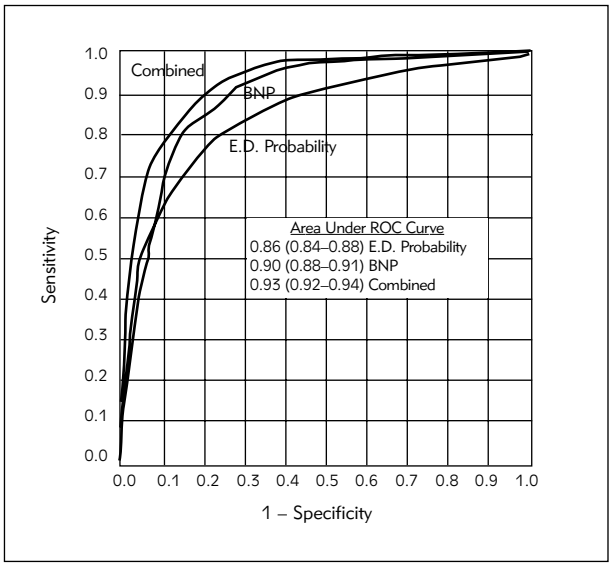

Figure 2 The accuracy of BNP to diagnose heart failure.

ure. A study by Fonarow et al. (6) divided patients into four quartiles according to their BNP levels. The study showed that the percentage of in-hospital mortality was higher with higher BNP levels.

The clinical impact of using the diagnostic and prognostic information provided by BNP was investigated in the BASEL study, a randomized controlled trial that examined the use of BNP in the evaluation and management of acute dyspnea in the Emergency Department (7). Four-hundred and fifty-two patients were enrolled in the trial and randomized to standard clinical evaluation or the same evaluation with the inclusion of rapid assay for BNP. The BNP group showed a significant reduction in »time to adequate therapy« from 90 mins to 63 mins when compared to the standard clinical evaluation group (*Figure 3*).

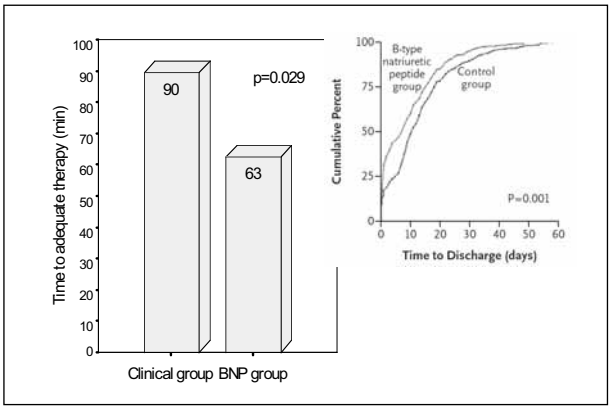

Figure 3 Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea.

Looking at 'time to discharge', there is a shift of the cumulative curve to the left indicating a reduction in time to discharge. Hence, if we treat patients earlier, we are able to discharge them sooner from hospital.

The data was also confirmed by a Canadian multicenter study published in Circulation which showed a reduction in duration of the Emergency Department, a reduction in rehospitalization and a reduction in direct medical costs in the BNP group when compared to the clinical group (8). There is a consistent message here that the additional use of BNP improves medical and economic outcomes, even though these results were restricted to 30 days.

BNP is not only cost effective but there are cost savings in the long-term. Another study was performed to evaluate the outcome beyond 30 days. The study, performed by Breidhardt et al., showed that there was an initial savings with the additional use of BNP and the savings still existed after 360 days (9).

It is important to see that BNP is a quantitative variable and should always be used in conjunction with other clinical information. A patient presenting with dyspnea and BNP levels below 100 pg/mL strongly argues against heart failure. On the other hand, a BNP above 400 pg/mL has a very high positive predictive value. We can be quite certain that the patient has heart failure and initiate appropriate treatment like nitrates, diuretics and ACE inhibitors as soon as possible.

The vast majority of patients (75%) will present with either low levels or high levels. Twenty-five percent of patients will present with BNP levels between 100 pg/mL and 140 pg/mL. These patients need further clinical evaluation for a correct diagnosis. BNP levels also need to be adjusted in obese patients and those with severe kidney disease, but do not have to be adjusted for gender or age.

The typical time course for BNP in the Logeart study shows a drop from admission, Day 1, Day 2 and

up to discharge. BNP can be measured at any of these days but the BNP measurement just prior to discharge has the highest diagnostic accuracy for the prediction of death or readmission (10).

Figure 4 illustrates the point further and uses the combined end points of death and readmission. If the pre-discharge BNP > 700 pg/mL, there is a 90% risk of death or readmission within 180 days. If the BNP is below 350 pg/mL, there is a low risk of death or readmission. If the BNP prior to discharge is between 350–700 pg/mL, there is already a 50% risk of either dying or readmission within the next 180 days. These data strongly suggest to check the BNP prior to discharge, and one should really worry about the patients if they still have BNP levels above 700 pg/mL even though they may show improvement in their symptoms.

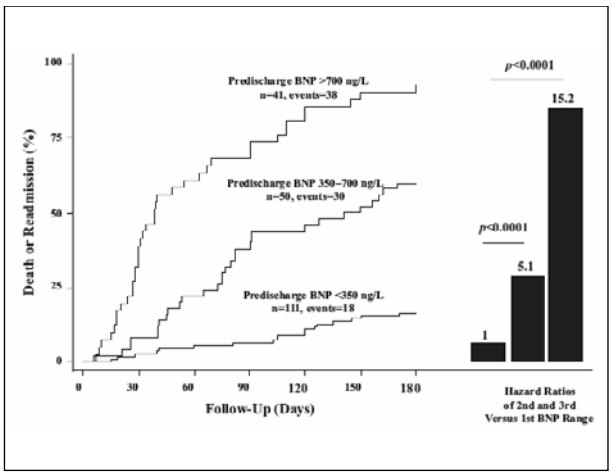

Figure 4 Discharge BNPs predict death/readmission.

The same data has been validated in outpatients. In the Valsarten Heart Failure Trial (Val-HeFT), stable patients with chronic heart failure had survival rates dependent on their BNP levels (11). The higher the BNP, the higher the mortality and the lower the survival rate. This value is derived from a single measurement.

Using the same data sets from the Val-HeFT study, and if we repeat testing, the relative change of BNP has additional prognostic information. Percent change in BNP predicts death independently from baseline BNP levels.

BNP in the Management of Heart Failure

The concept of using BNP for the monitoring of heart failure is that low BNP levels are associated with low mortality and low morbidity. If we achieve a drop in BNP levels, the risk of death further declines. It makes perfect sense to aim for a maximum reduction in BNP. This should be achieved without hypoperfusion. Serum creatinine should also be used as a renal biomarker to assess safety, just as BNP is used as a biomarker to assess efficacy.

The effect of medication on BNP levels has been investigated for most of the drugs such as diuretics, spironolactone, ACE inhibitors and angiotensin receptor blockers. These drugs have proven benefits not only in improving survival or reducing symptoms, but also show a reduction in BNP levels. β-blockers are the exception as if these are administered too fast, the symptoms deteriorate and BNP levels may also increase. BNP levels may therefore be important to appropriately titrate β-blockers.

Studies with BNP for Monitoring Therapy

The additional use of BNP improves the combined endpoint of death due to heart failure or heart failure readmission. There are a number of randomized controlled studies that use BNP for monitoring therapy in patients with chronic heart failure. The first study from Christchurch was performed in a small group of patients with systolic dysfunction (12).

The study showed that additional use of BNP improved outcome – there was a significantly higher survival rate. The study was criticized for being small, for including young patients and for not being treated appropriately, but nevertheless gave very important information related to outcomes. Other studies now have replicated the results, including the STARS-BNP multicenter study (13). They confirm that the additional use of BNP improves the combined endpoint of death due to heart failure or heart failure readmission.

In the management of heart failure, the use of BNP makes perfect sense from the pathophysiological point of view and four out of five randomized controlled trials have shown a positive outcome.

There are no unique target levels with BNP and we may not achieve the same target in elderly patients as in younger ones. It should be used in conjunction with other options to improve heart failure management. These include regular weight assessment, blood pressure control, and potential use of heart failure nurses, telemedicine and heart failure clinics. β-blocker uptitration could be considered, but should be used in conjunction with the assessment of renal function to avoid morbidity induced by too aggressive treatment.

BNP in Acute Coronary Syndrome and Pulmonary Embolism

The TACTICS-TIMI study shows BNP to be the most powerful predictor of death in patients with acute coronary syndrome. BNP concentrations of at least 80 pg/mL had higher rates of death, myocardial infarction and CHF at both 30 days and 10 months when compared to those with BNP values below 80 pg/mL (*Figure 5*) (14).

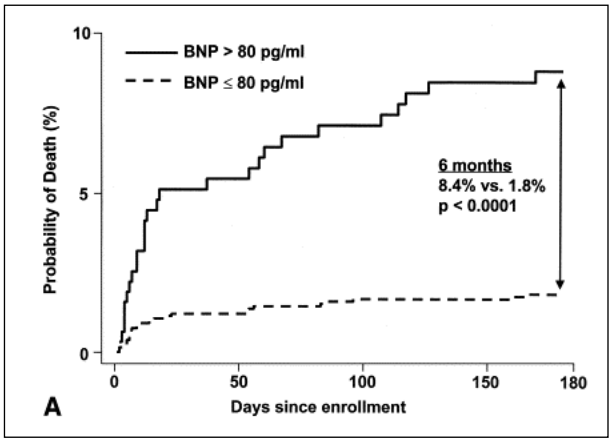

Figure 5 Prognosis in ACS – the TACTICS-TIMI 16 study (14).

Very recent data has shown that the higher the BNP, the more extensive the right ventricular dysfunction in patients with non-massive pulmonary embolism. BNP has a very high accuracy if we need to define severe or moderate right ventricular dysfunction.

BNP in Screening for Left Ventricular Dysfunction

BNP is useful for the biochemical detection of left ventricular dysfunction. It is known that ACE inhibitors reduce morbidity in patients that are asymptomatic, hence it is useful to identify patients who have asymptomatic left ventricular dysfunction. A study by McDonagh et al. (15) has shown that BNP has a high accuracy in this indication. BNP levels were shown to be significantly elevated in patients who have left ventricular ejection fraction (defined as an ejection fraction below 40) compared to patients with no left ventricular dysfunction (15). The accuracy is also higher than that of other biomarkers.

BNP Utilization with Pneumonia

Recent studies by our group and others have shown that the rate of improvement or cure is significantly predicted by BNP (16). The study risk stratified patients with community-acquired pneumonia by calculated, optimal BNP cut-offs. The study showed that if BNP was below 100 pg/mL, there was a high rate of improvement within the following three months. The risk of either death from pneumonia or having a recurrence was shown to be extremely high if BNP was elevated. These results highlight that cardiac stress determines mortality and outcome in non-cardiac conditions such as pneumonia.

BNP is therefore very helpful in the various indications as discussed, namely the diagnosis, prognosis and the management of heart failure. There are other indications on the horizon and there is a lot of research in this area.

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