

Natriuretic peptides in heart failure: where we are, where we are going

Alberto Palazzuoli · Giovanni Antonelli ·
Ilaria Quatrini · Ranuccio Nuti

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Abstract Tremendous advances have been made in understanding the pathophysiology and treatment of congestive heart failure (CHF). However, diagnosis still remains difficult, even with a comprehensive physical examination. Symptoms such as dyspnea are non-specific and poorly sensitive indicators for early CHF that can be largely undetected. The discovery of natriuretic peptides (BNP) as diagnostic biomarkers has been one of the most critical advances for heart failure diagnosis. Therefore, both B-type and N-terminal pro-B-type have potential role in the diagnosis of heart failure, as well as in prognostic risk assessment. A single determination of BNP at any time during the progression of chronic HF provides a clinically useful tool for risk stratification. The hypothesis that repeated measurements might carry prognostic information beyond a single measure was confirmed in different settings. One of the main interests is given to the values of repeated determinations for monitoring progression of disease, and for the evaluation of the clinical effects of medical therapy. Nevertheless, despite thousands of papers describing their potential utility, current guidelines have not endorsed the highest level of recommendation for their use, in part, because the application in clinical practice is often limited for the absence of well codified cut off. Recently, European guidelines emphasized the role of natriuretic peptides as potential laboratory markers. In the near future, algorithm building will take into consideration clinical and echocardiographic parameters as well as NP measurements, and this may lead to a correct diagnosis and identification of

patients at high risk. The purpose of this review is to discuss the clinical approaches and future applications of natriuretic peptides in heart failure and coronary disease.

Keywords B-Type natriuretic peptide · NT pro-BNP · Heart failure · Coronary artery disease

Introduction

Several studies have suggested the need for new diagnostic capabilities, especially with the increasing prevalence of heart failure in the United States. One of the biggest hopes for utilizing biomarker testing is to determine the level of disease severity as a means to triage medical decisions as well as to monitor their responses. Early diagnosis is very important for a better therapy optimization and to improve the outcomes. However, identification is often difficult because of symptoms aspecificity, and the lack of a gold standard protocol to make the correct diagnosis. After traditional first line evaluations (ECG, thorax radiography and clinical examination), echocardiography is the technique recommended for patients affected by heart failure, thanks to its easy availability and practicability. Although most studies show that brain natriuretic peptide (BNP) is a marker with a high sensitivity and specificity, application in clinical practice is often limited because of the absence of a well codified cut off in the dosage concentration. Confusing factors, including age, race, obesity, and renal dysfunction, may complicate the clinical interpretation of circulating BNP levels in patients with chronic and stable congestive heart failure (CHF), and should be considered when patients are evaluated. However, there is good concordance between presence of heart failure, its severity and elevated natriuretic peptide (NP) levels: high BNP levels are related to high ventricular dysfunction degree

A. Palazzuoli (✉) · G. Antonelli · I. Quatrini · R. Nuti
Cardiology Section, Department of Internal Medicine
and Metabolic Diseases, S Maria alle Scotte Hospital,
University of Siena, Viale Bracci, 53100 Siena, Italy
e-mail: palazzuoli2@unisi.it

and more advanced CHF stages. Serial measurements of BNP in the chronic outpatient setting appear to convey additional prognostic value for relevant adverse outcomes, including death or destabilization of CHF requiring hospitalization, and they are thus recommended in clinical practice.

Past and current heart failure diagnostic criteria

Accurate diagnosis of heart failure can be difficult in the absence of diagnostic tools with high sensitivity and specificity. The diagnosis of CHF in primary care is confirmed by clinical and instrumental evaluation in about 25–50% of cases. The accurate clinical diagnosis of CHF is limited by several causes: poor indicative signs and symptoms, as well as use of diagnostic tools with low sensibility and specificity. Every single sign or symptom has only mild accuracy: for example, fatigue and peripheral edema are, respectively, present in 60 and 40% of cases. Common tests frequently used are poorly sensitive: most often chest radiography is not able to demonstrate venous hypertension or early interstitial edema particularly in patients with chronic heart failure. Similarly the ECG does not have specific CHF signs (specificity 61%, sensibility 93%) Furthermore, low use of echocardiography in the Emergency Department (ED) and lack of diagnostic indices of decompensated CHF with preserved ejection fraction could lead to underestimated or late diagnosis. International guidelines encourage the use of more objective diagnostic tools for etiologic identification and consequential-specific therapeutic approach. Past guidelines recommend aECG, chest X-ray study, laboratory tests, and echocardiogram as a reasonable workup, leaving a marginal role for BNP. The last European guidelines instead, on the basis of numerous scientific papers that demonstrate the high prognostic value of NP, put their measurement at the center of the diagnostic algorithm. In fact, evidence exists supporting their use for diagnosing, staging, making hospitalization or discharge decisions, and identifying patients at risk for adverse clinical events. High levels of BNP despite optimal treatment indicate a poor prognosis [1]. A BNP level below 100 pg/ml suggests a need for revision of the diagnosis, values of BNP between 100 and 400 pg/ml require echocardiographic and other examinations to confirm the heart failure diagnosis; while BNP values above 400 pg/ml are associated with a worse outcome and a high accuracy [2] (Table 1).

Natriuretic peptides in heart failure diagnosis

Despite advances in diagnosis and treatment, heart failure remains a growing medical problem associated with major

Table 1 Causes that altered plasmatic natriuretic peptide levels

Cardiac	Non-cardiac
Heart failure	Acute pulmonary embolism
Systolic dysfunction	Pulmonary hypertension
Diastolic dysfunction	Anemia
Coronary artery disease	Cor pulmonale
Hypertension with LVH	Renal insufficiency
Valvular heart disease	Septic shock
Atrial fibrillation	Hyperthyroidism

hospitalization, hospital mortality, recurrent admissions and a poor prognosis. In the clinical setting, natriuretic peptides are widely utilized as a first-line diagnostic complement to clinical and radiographic data, thereby reflecting the correct diagnosis and the disease's severity [3]. The dosage of BNP, a hormone that is produced mainly by the heart ventricles, is a useful test for CHF diagnosis with high sensitivity and specificity and strong positive predictive values. BNP is synthesized in the heart as a reaction to cardiac wall distension and stretching and neurohormonal activation. BNP leads to natriuresis and vasodilatation activation with concomitant inhibition of the renin angiotensin system and adrenergic activity. After synthesis, the peptide is cleaved first to pro-BNP, then to the biologically active form and the inactive aminoterminal fragment, NT pro-BNP. BNP plasma levels increase results in improved myocardial relaxation, and plays an important regulatory role in response to acute increases in ventricular volume by opposing the vasoconstriction, sodium retention, and antidiuretic effects of the activated renin–angiotensin–aldosterone system. Plasma BNP levels are elevated in patients with acute myocardial infarction and left ventricular dysfunction; this increase persists during the late phases of cardiac remodeling [4]. Elevated peptide levels are directly correlated with prognosis, and they are directly proportional to NYHA class, intra-ventricular pressure, pulmonary pressure, and inversely to cardiac output [5]. Plasma BNP levels are raised in several conditions with wall stress increase: hypertrophic cardiomyopathy, diastolic dysfunction and left ventricular hypertrophy. In all these circumstances, BNP levels appear related to myocardial mass index, interventricular and posterior wall thickness [6]. Several studies confirm the utility of BNP levels in patients presenting with acute dyspnea. In a large study, BNP levels were measured in 321 patients: patients with heart failure have higher hormone levels, as opposed to patients with dyspnea due to respiratory diseases [7]. Dentali et al. [8] emphasize the correlation between BNP and increased pulmonary hypertension, such as in pulmonary embolism. The first multicenter study “Breathing

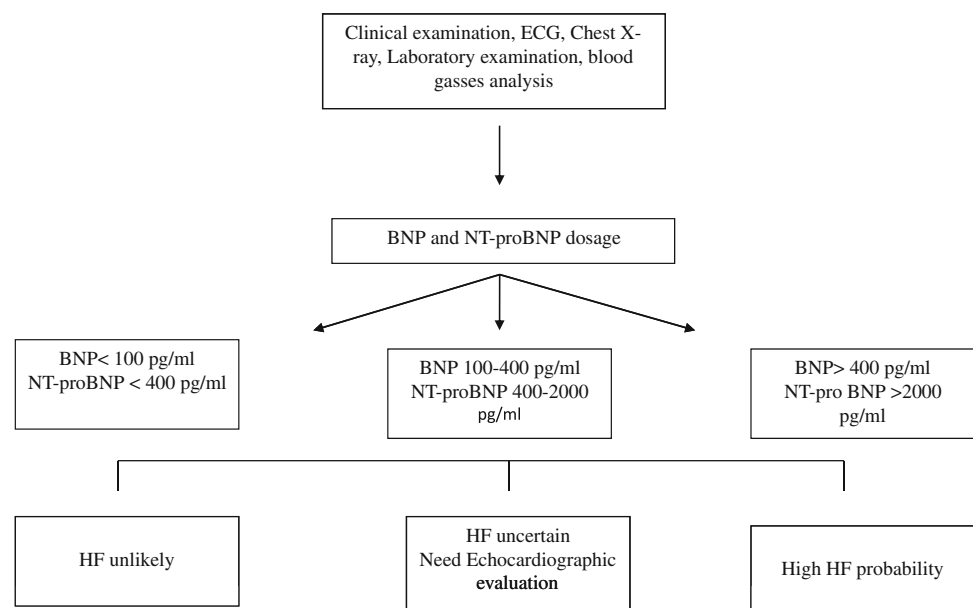
not Properly Study”, enrolled 1,586 patients in the ED: they all had acute dyspnea, and had BNP measurement. The gold standard for CHF was adjudicated by two independent cardiologists unaware of the laboratory results, who reviewed all the clinical data and standardized scores. BNP values correlated with NYHA functional class: a linear correlation was seen among patients in NYHA I (197 pg/ml) compared to patients in NYHA IV (978 pg/ml) [9]. Several parameters like high venous pressure recruitment, increase of left ventricular dimension and interstitial edema at chest radiogram were also evaluated. They did not reveal a similar predictive power accuracy as useful as BNP in the correct diagnosis identification. BNP is a good marker not only for diagnosis, but also for the CHF severity with linear value increasing in relation to the stage. The levels of BNP are also correlated with some echocardiographic parameters of both ventricular systolic and diastolic dysfunction [10–14]. Whereas the prognostic value of BNP in patients with impaired left ventricular systolic function is well documented, there are fewer data for the population of patients with chronic HF and preserved systolic function. In a prospective study that included 161 patients, the probability of death within 12 months after hospital admission was predicted by plasma levels of pro-BNP in patients with systolic dysfunction as well as in patients with preserved systolic function [15] (Fig. 1).

Natriuretic peptides in ACS

Acute coronary syndromes (ACS) without ST elevation is an heterogeneous group of events, ranging from stable

angina pectoris to myocardial infarction in which there is an important increase in troponin and isoenzyme MB creatine kinase. Risk stratification is characterized by clinical history and examination, electrocardiographic characteristics, markers of myocardial damage, but it remains relatively unspecified [16]. Diagnostic and prognostic value of NT pro-BNP and BNP appears similar to CHF, but it is different for ACS. BNP or BNP-related marker is used for the diagnosis of patients suffering from acute coronary syndrome, the level of BNP, or a marker related to BNP, unstable angina, non-ST-elevation non-Q wave myocardial infarction, ST-elevation, non-Q wave MI [17, 18]. However, a progressive increase in BNP levels in relation to the extent of coronary disease has been demonstrated. For example, patients with descending anterior coronary disease show the highest level of BNP. In patients with unstable angina, non-ST elevated myocardial infarction (UA/NSTEMI), elevated BNP levels have been demonstrated to be strongly associated with an increased risk of adverse outcome. Because of its release in response to increased ventricular chamber pressure or wall tension, in UA/NSTEMI patients with manifest heart failure or a decreased LV ejection fraction, elevated BNP reflects a great degree of myocardial dysfunction, associated with a greater risk of death and recurrent CHF. In particular, the strong association of BNP levels and mortality even among patients without myocardial necrosis indicates that BNP and NT pro-BNP may reflect the extent of severity of the ischemia, even in the absence of an irreversible injury. Ezekowitz et al. in the COMMA study measured the NT pro-BNP at baseline, 24 and 72 h after presentation with acute STEMI. They show that BNP is an independent predictor of poor outcome and

Fig. 1 BNP algorithm for diagnosis of acute heart failure (modified by ESC guidelines 2008)



adds clinically useful prognostic information. In post-MI, BNP measurement is able to predict adverse ventricular remodeling and enlargement together with future cardiac events [19].

Natriuretic peptide and outcome

In CHF patients, BNP measurement appears very important for risk stratification; in fact, high levels are associated with recurrent hospitalization and risk of sudden death [20]. Several studies that have used natriuretic peptides predischARGE suggest as well that the BNP level appears to be the strongest predictor for identifying subsequent death or hospital admission at 6 months [21–23]. In patients with coronary disease and preserved ventricular function, BNP gives strong prognostic data over traditional risk factors [24]. The best evidence of the prognostic value of BNP in chronic CHF comes from statistically robust controlled clinical trials that include a large number of clinically well-characterized patients from different sites. The first data on pro-BNP from such a trial came from the Australia–New Zealand Heart Failure Group [25]. In approximately 300 patients with well-characterized chronic CHF of ischemic etiology (left ventricular ejection fraction, LVEF, <0.45) randomized to receive carvedilol or placebo, levels of NT pro-BNP above the median were associated with increased risks for new decompensated CHF events [relative risk (RR) 4.7, 95% confidence interval (CI) 2.2–10.3] and all-cause mortality (RR 4.7, 95% CI 2.0–10.9) during 18 months of follow-up, independent of age, NYHA functional class, LVEF, previous myocardial infarction, or previous HF admission. The Valsartan heart failure (Val-HeFT) trial, 5,010 patients (85% with blood samples collected at study entry) with mild-to-moderate chronic CHF receiving recommended medical therapy, was randomized to an angiotensin II type 1 receptor blocker or placebo [26]. An increment of 500 ng/l above the baseline concentration of NT pro-BNP carries an increased adjusted risk of 3.8% for mortality and 3.0% for hospitalization for CHF. On multivariate analysis, pro-BNP ranks as the best prognostic factor in these patients again, independent of and more powerful than traditional risk factors, such as NYHA class, age, left ventricular dilation, or renal dysfunction [27]. A single determination of NT pro-BNP at any time during the progression of chronic CHF provides a clinically useful tool for risk stratification. The Val-HeFT study shows BNP to be prognostically superior to several other recognized neurohormonal markers of risk in HF, including norepinephrine, renin activity, aldosterone, and endothelin 1, and echocardiographic variables. As with acute CHF, the hypothesis that repeated measurements carry prognostic information beyond a single measure has been confirmed in

different settings. The value of repeated determinations of NT pro-BNP levels appear very important for monitoring progression of disease, and may help in evaluating the clinical effects of medical therapy. The importance of natriuretic peptides for risk stratification in patients with acute coronary syndrome, encompasses both BNP and NT pro-BNP; both peptides show independent and incremental prognostic value above traditional diagnostic tools and conventional risk markers, such as the ECG and biochemical risk indicators, such as troponin. A recent report shows that elevated levels of BNP predict a two- to threefold increased risk of death by 10 months.

Future perspectives and application in clinical practice

There are increasingly convincing data that correlate the measurement of NP with heart failure diagnosis and prognosis. Higher values of BNP are associated with a worse outcome and a greater degree of left ventricular dysfunction. For these reasons, BNP should be considered a powerful tool that can help the physician in diagnosis, prognosis, and treatment of decompensated patients from admission to hospital discharge. BNP is a useful tool to assess risk stratification and predict myocardial ischemia in ACS. In patients with non-ST elevation myocardial infarction (NSTEMI), the magnitude of the risk relationship associated with natriuretic peptides seems to be higher than associated with other markers. In these clinical conditions they represent markers for left ventricular dysfunction and enlargement as well as for coronary disease extension. However, we must consider the presence of confounding factors that can alter the plasma NP values. In these cases, others biochemical markers, echocardiography and other tools can identify with better accuracy patients with heart failure or acute coronary disease. Furthermore, several interesting small molecules (such as galectin-3, copeptin, metalloproteinases, and many others) have already provided some evidence of risk stratification in patients with acute heart failure or post-myocardial infarction [28, 29].

Conclusions

Natriuretic peptide levels are strictly correlated with CHF severity. They are found to correlate with the severity of left ventricular systolic dysfunction, right ventricular dysfunction and pressures, and left ventricular filling alteration. As well as in CHF in ACS with or without ST elevation, NP was appearable to predict severity of coronary disease and ischemic area extension. For the above reasons, and the ability to give additional prognostic information with respect to traditional biomarkers (i.e.

troponin and C-reactive protein), natriuretic peptides are candidates for utilization in the setting of principal risk scores.

Conflict of interest None.

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