Clinical utilization of natriuretic peptide determination in acute congestive heart failure

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ABSTRACT

Natriuretic hormones are a family of vasoactive peptides with many powerful physiological properties and have emerged as highly effective biomarkers in cardiovascular disease. In particular, the B-type natriuretic peptide (BNP) and the N-terminal fragment of proBNP (NT-proBNP) are natriuretic peptides secreted by the cardiac ventricles as a response to plasma volume expansion, pressure overload and resulting ventricular wall distension. Their determination has revolutionized the approach to diagnosis and management of acute heart failure over the past decade, having shown additive diagnostic value to clinical judgment in the evaluation of patients with acute dyspnea. Moreover, the prognostic value of BNP and NT-proBNP has been established in several studies, providing a useful addition to clinical assessment for risk stratification of patients with acute heart failure. This review summarizes the current evidence concerning the clinical utilization of natriuretic peptides in acute congestive heart failure.

INTRODUCTION

In many industrialized Countries, congestive heart failure (HF), a progressive disease with a mortality exceeding most cancers, represents one of the most expensive disorders for the health system (1). In United States, hospital discharges for HF rose from 877,000 in 1996 to 1,106,000 in 2006 (2).

Most patients with HF may eventually present to the emergency department (ED). Because HF occurs predominantly in older subjects, the clinical presentation can often be complicated by multiple comorbidities that contribute to the symptoms. The most common symptom of HF is dyspnea, a complaint that is neither specific nor sensitive for HF diagnosis, and physical examination could be not sensitive enough to make a correct diagnosis (3, 4). At the moment, the "gold standard" for HF diagnosis is echocardiography, which is quite expensive and not easily available (5). Moreover, treatment for HF could be hazardous for patients who have other condition with a similar clinical presentation, such as pulmonary disease (6). Thus, the challenge for the emergency physician is to rapidly and accurately triage patients presenting with dyspnea due to HF from those affected by other common etiologies with similar symptoms.

In patients with HF, increased cardiac wall stretch resulting from volume and pressure overload leads to increased concentrations of circulating cardiac natriuretic peptides, i.e. atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and the amino-terminal fragments of their prohormones (NT-proANP and NT-proBNP, respectively) (7, 8). The determination of natriuretic peptides has revolutionized the approach to diagnosis and management of HF over the past decade, having shown additive diagnostic value to clinical judgment in the evaluation of patients with acute dyspnea and highly promising ability to guide therapeutic decision in chronic HF management (9).

ANP and BNP are released primarily from the heart, but circulate as hormones to act in various tissues in the body and induce vasodilation, natriuresis, and diuresis (10). Unlike ANP, which is stored in granules and thus released with even minor triggers such as exercise, BNP has minimal storage in granules; rather, it is synthesized and secreted in bursts (11). In the setting of volume expansion and pressure overload, the resulting wall stress upregulates in ventricular myocytes BNP gene encoding for a preproBNP molecule of 134 amino acid residues. Subsequently, preproBNP is cleaved first to proBNP1-108 and further proteolytic processing cleaves from proBNP1-108 a mature 32 amino acid peptide, designated BNP1–32, that produces vasodilation and increased urinary salt clearance, and the inactive NT-proBNP 1–76 fragment that also circulates in plasma without known physiological activity. Both BNP and NT-proBNP can be used in the evaluation of HF patients (12). Although their concentrations are well correlated, their values are, however, not interchangeable, because they have different half-lives, different metabolic pathways and, most importantly, method-dependent results.

NATRIURETIC PEPTIDES IN PATIENTS PRESENTING TO EMERGENCY SETTING WITH ACUTE DYSPNEA

Several studies have analyzed the clinical accuracy of BNP and NT-proBNP in diagnosing HF in emergency setting. The Breathing Not Properly multinational study

was a large prospective study conducted in seven centers to evaluate the diagnostic efficiency of BNP using a point-of-care testing (POCT) fluorescence immunoassay kit (13, 14). Maisel et al. found that the area under the ROC curve (AUC), when BNP was used for distinguishing HF from other causes of dyspnea, was 0.91 and a cutoff of 100 ng/L was optimal for diagnosis of HF, with a specificity of 76% and a negative predictive value (NPV) of 89%. Noteworthy, in a multiple logistic regression analysis, a BNP value ≥100 ng/L was the strongest predictor of congestive HF (odds ratio 29.6; 95% confidence interval: 17.8-49.4).

The ProBNP investigation of dyspnea in the emergency department (PRIDE) study evaluated the role of NT-proBNP testing compared with standard clinical assessment for the diagnosis of acute HF in patients who present with dyspnea in the ED (15). The PRIDE study population was enrolled from consenting patients ≥21 years of age, who presented to the ED with a complaint dyspnea. The median NT-proBNP concentration of patients (n=209) who had acute HF was 4054 ng/L vs. 131 ng/L in patients (n=390) who did not have (P <0.001) (15). ROC analyses demonstrated NT-proBNP to be highly sensitive and specific for the diagnosis of acute HF, as indicated by an overall age-independent AUC of 0.94. At the cut-point of 900 ng/L, sensitivity was 90%, specificity 85%, and the positive predictive value (PPV) was 76%.

Because natriuretic peptide concentrations increase significantly with age (16), it is widely accepted that a diagnosis of acute HF based on a single NT-proBNP cutoff could be difficult: in the PRIDE study, patients were stratified in two age groups of <50 years and >50 years; in this case, cut-points of 450 and 900 ng/L, respectively, were optimal for ruling in, with AUC of 0.98 and 0.93, respectively (Table 1). Moreover, authors showed that NT-proBNP testing can be used to rule-out the diagnosis of HF using a single age-independent cut-point of 300 ng/L. The analysis showed, however, that the cutoff of 450 ng/L, while maintaining the same NPV (99%) of the 300 ng/L value, had better specificity (76% vs. 68%). Recently, Dolci et al. in a retrospective study including 498 patients with acute dyspnea, have confirmed that an NT-proBNP cut-point of 450 ng/L is better than the 300 ng/L one, displaying similar NPV but higher specificity (17).

After the PRIDE study, results of others trials concerning the clinical use of NT-proBNP in acute HF have been published (18, 19). Particularly, Moe et al. (20) showed that in patients presenting to ED with dyspnea, the use of NT-proBNP test in diagnosis of HF reduced costs for ED visits, hospitalization and outpatient services. Moreover, adding NT-proBNP testing to clinical judgment improved performance, with an AUC increasing to 0.90. Interestingly, although these significant results, authors found that NT-proBNP testing was not more accurate than clinical judgment.

Several evidences support that BNP and NT-proBNP concentrations are lower in obese people, both with and without HF (21, 22). Although the reason for this interaction remains undetermined, the increased concentration of the natriuretic peptide receptor-C on adipocytes has led to postulate that increased clearance might be the reason for lower natriuretic peptide concentrations (23, 24). As there seems to be a linear decrease in natriuretic peptide concentrations with increasing body mass index (BMI), the higher the BMI is the lower the cutoff is that provides the highest accuracy (25, 26). Particularly, a low BNP cutoff (<50 ng/L) should be used to rule-out HF in obese patients (BMI >35 kg/m^2).

As quantitative biomarkers, natriuretic peptides are best interpreted as a continuous variable: the higher the value, the greater the likelihood that dyspnea is due to HF. While the use of cut-points can be criticized, for clinical usefulness specific cutoffs can provide benchmarks correlating with relevant statistical thresholds. When BNP is low (<100 ng/L), it is unlikely that HF is contributing to the clinical presentation (27). On the other hand, a high BNP (>400 ng/L) suggests that HF is a contributor to the patient's symptoms with specificity exceeding 90% (27). The cutoff for rule-out (BNP <100 ng/L) can exclude HF from the differential diagnosis. However, to rule-in HF is more complex, because BNP may be persistently elevated in chronic conditions and may not be representative of an acute haemodynamic change. Other conditions resulting in myocardial stretch (acute pulmonary embolus, acute coronary syndrome, primary pulmonary hypertension, etc.) and renal failure should also be considered in natriuretic peptide evaluation. This does leave a "grey zone" of BNP values between100 and 400 ng/L, where

Table 1
Optimal NT-proBNP cut-points for diagnosing acute congestive heart failure according to the PRIDE study (modified from ref. 15)

	Optimal cut-point	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Rule-in cut-point					
All patients	900 mg/L	90%	85%	76%	94%
<50 yrs old	450 mg/L	93%	95%	67%	99%
≥50 yrs old	900 mg/L	91%	80%	77%	92%
Rule-out cut-point					
All patients	450 mg/L	98%	76%	68%	99%

clinical acumen and ancillary testing are required to make a correct diagnosis (28). When using NT-proBNP, a cut-point of 300 ng/L is proposed to rule-out acute HF, while higher age-dependent cut-points are suggested to rule-in (29). Patients with NT-proBNP concentrations >450 ng/L (<50 years), >900 ng/L (50-75 years), and >1800 ng/L (>75 years) all have a high likelihood of final HF diagnosis. In a recent meta-analysis conducted on nine selected retrospective and prospective studies, Worster et al. evaluated the diagnostic accuracy of both BNP and NT-proBNP (30). Authors concluded that BNP and NT-proBNP have very similar diagnostic performance characteristics and can be used to rule-out HF as a cause of dyspnea in the acute clinical setting. However, there is no easily identifiable optimum cut-point value for each peptide (30).

As a quantitative marker of HF, the use of natriuretic peptides is not only helpful for diagnosis, but also for risk stratification and may, therefore, assist in triage decisions. Natriuretic peptide concentrations at admission in ED identify the risk of death or readmission within 30 days (31, 32). At this regard, Fonarow et al. found that patients with BNP value at presentation in the fourth quartile (>1730 ng/L) had an in-hospital mortality rate that was more than 3-times that of patients in the first quartile (<430 ng/L) (32). In the PRIDE study NT-proBNP concentrations >1000 ng/L in the ED were associated with severe HF and an adverse prognosis (15).

CONCLUSIONS

Natriuretic peptides are markers of hemodynamic stress of the heart, such as observed in HF, indicating the neurohumoral activation of the myocardium. BNP and NT-proBNP are predominantly secreted from the ventricle in response to myocardial wall stress; therefore, they are sensitive and specific biomarkers of cardiac function. Their blood concentrations correlate with severity of cardiac dysfunction and are helpful for the differential diagnosis of symptoms that might be due to HF. When used in conjunction with other clinical information, rapid measurement of natriuretic peptides in the ED improves the care of patients presenting with acute dyspnea and reduces the time to discharge as well as total cost of treatment. BNP and NT-proBNP assays give different values and clinicians should become familiar with just one, at least initially. Plasma biomarker concentrations should be interpreted in the context of the clinical setting and in conjunction with a test of renal function. Serial measurement may possibly determine whether a patient's prognosis has changed in response to therapy, but it is not yet clear whether and how this should be used to guide treatment.

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