Natriuretic peptide testing for heart failure diagnosis, inpatient management and outpatient cardiac care

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The use of natriuretic peptides like B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) has increased during the last decade and so has the medical evidence of their utility.

This article highlights natriuretic peptide synthesis and release. Based on essential clinical trials the article gives medical insights into the use of natriuretic peptides in the emergency setting. The natriuretic peptides help confirm or rule out a diagnosis of heart failure and shorten the visit to the emergency room in addition to reducing the overall cost. However, when interpreting natriuretic peptide results potential confounders also have to be taken into consideration. The confounders include advancing age and therefore age-adjusted cut-points are often used.

Both in the inpatient and the outpatient setting the natriuretic peptides seem to have a potential for optimizing heart failure management. At discharge the natriuretic peptides are prognostic for mortality and/ or readmission and thus give helpful guidance on the appropriate time for discharge. In the outpatient setting the natriuretic-peptide-guided therapy has been shown to give significantly reduced all-cause mortality and heart-failure-related hospitalizations when compared to clinically guided therapy.

This article is based on a literature review, and kindly reviewed by Dr J. Januzzi, US, Prof C. deFilippi, US, and Dr P. Ray, France.

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Introduction

A common reason for patients to visit the emergency room is acute shortness of breath (acute dyspnea). A serious cause of acute shortness of breath can be heart failure.

Accurate diagnosis of heart failure is known to be a significant challenge for healthcare professionals in emergency departments (EDs) [1].

> ### NT-proBNP testing helps us to:
>
> - Increase diagnostic accuracy oh heart failure
> - Reduce patient evaluation times
> - Reduce treatment costs

Complex cases, combined with limitations on time, specialist staff and investigations create uncertainty around admissions and difficulties when communicating with intensive care units (ICUs) and other departments [1]. In a recent US study, 30-day readmission rates for heart failure were high, at 25 % which could be related to these uncertainties [2].

Lengthy patient evaluation and turnaround times coupled with late or incorrect diagnosis and treatment result in higher morbidity and mortality, as well as increasing treatment costs [1,3].

This paper provides a practical overview of the potential for natriuretic peptide (NP) testing to help streamline care pathways and improve outcomes, in both the acute and chronic cardiac care settings.
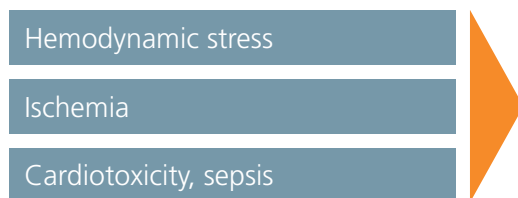
Natriuretic peptide synthesis, release and detection

The brain natriuretic peptide (BNP) gene is activated in cardiomyocytes when myocardial wall stress is increased by an overload of volume or pressure [4]. The resulting precursor peptide (proBNP108) is cleaved into two parts: active BNP, and inactive N-terminal (NT)-proBNP, which are released into the circulation (Figure 1) [5].

ProBNP108, as well as various degradation products of BNP, can also be found in the bloodstream [4]. In cases of heart failure, a large increase in the usually low BNP levels occurs, leading to positive downstream effects, including vasorelaxation and natriuresis [4].

Both BNP and NT-proBNP can be detected in the circulation. Whilst increased levels of these biomarkers are not exclusive to incidences of heart failure, studies have shown that they can be sensitive and specific diagnostic biomarkers for heart failure when used as an adjunct to clinical judgment [6,7]. The 2012 European Society of Cardiology (ESC) and 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines name BNP and NT-proBNP as suitable biomarkers, along with a medical history, physical examination and ECG, for the diagnosis, prognosis and management of patients with acute and non-acute onset heart failure [8,9].

Hemodynamic stress

Ischemia

Cardiotoxicity, sepsis

preproBNP (134 aa) — Ventricular myocycle

signal peptide (26 aa)   proBNP (108 aa)

NT-proBNP (76 aa)   proBNP   BNP (32 aa)
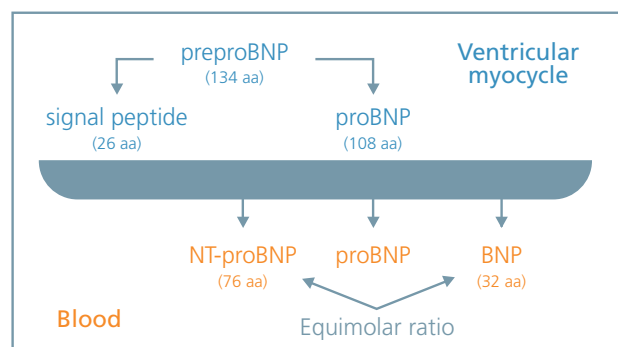
Blood   Equimolar ratio

Figure 1: BNP and NT-proBNP are secreted from cardiomyocytes at the same time.
Adapted from Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi JL. Biology of the Natriuretic Peptides. Am J Cardiol 2008;101[Suppl]: 3A–8A).

Using natriuretic peptides to increase accuracy of decision-making in the emergency setting

Heart failure is defined by the presence of typical symptoms such as dyspnea, fatigue and/or fluid retention due to cardiac dysfunction. These typical, yet non-specific symptoms can make heart failure difficult to diagnose [8]. Inaccurate emergency diagnosis of elderly patients with acute respiratory failure was shown to be as high as 20 % by the French EPIDASA Study Group [10]. These missed diagnoses were associated with highly significant increases in mortality, and highlighted the need for diagnostic tools with high specificity and sensitivity that can be accessed quickly in a busy ED environment [10].

The potential for NPs to augment clinical judgment and standard diagnostic tools has been identified in US and European studies. In the US Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT), physicians were blinded to BNP levels when making admission decisions, and on analysis, BNP levels were in fact higher in those patients who were discharged [11].

In fact, BNP levels were more than twice as high (2,096 vs. 764 pg/mL) in patients who were deceased at 30 days vs. those who were alive [10]. This pattern was maintained at 90 days, indicating that BNP would indeed have been useful when deciding whether a patient should have been admitted [11].

By helping to confirm or rule out a diagnosis of heart failure, NPs can help inform and expedite treatment decisions. Faster BNP measurement was associated with more expedient initiation of diuretic therapy, with a modest improvement in mortality in an analysis of US Acute Decompensated Heart Failure National Registry (ADHERE) study data [12].

Looking at NP testing as part of the overall care pathway, a randomized controlled trial (RCT) of 452 patients presenting at a Swiss ED – the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study – showed that those assigned to receive rapid, point-of-care BNP testing were discharged faster (8 vs. 11 days, p=0.001) than those assigned to standard assessment [1].

Results also showed that the percentage of patients requiring hospitalization dropped from 85 % to 75 % and those admitted to intensive care dropped from 24 % to 15 % [1]. Although mortality rates were not significantly lower (10 % vs. 12 %, p=0.45), the mean cost of treatment was reduced significantly in the BNP group (USD 5,410 vs. 7,264, p=0.006) [1].

In tests to rule out heart failure, NT-proBNP has been demonstrated to be a cost-effective measure with good diagnostic properties. A Canadian RCT – Improved Management of Patients with Congestive Heart Failure (IMPROVE-CHF) study – investigated the clinical diagnosis with or without NT-proBNP testing. With the addition of NT-proBNP testing shorter ED visits, reduced costs of 15 % overall, as well as fewer rehospitalizations (decrease of 35 %) among patients with acute heart failure was seen over 60 days [3].

Confounders to interpretation of NP levels as a biomarker for heart failure

- Acute coronary syndromes
- Advancing age
- Anemia
- Atrial fibrillation
- Burns
- Cardiac surgery
- Critical illness
- Left ventricular hypertrophy
- Myocarditis
- Prior heart failure
- Pulmonary embolism
- Pulmonary hypertension
- Renal failure
- Sepsis
- Sleep apnea
- Toxic-metabolic insults
- Unrecognized heart failure
- Valvular Heart disease

Adapted from Kazanegra R, Cheng V, Garcia A, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J Card Fail 2001; 7: 21-9.

The N-terminal Pro-BNP investigation of Dyspnea in the Emergency Department (PRIDE) study confirmed NP testing to be particularly useful in cases where there is a high degree of uncertainty about a diagnosis – this group also represent the patients with the poorest prognosis [13,14]. This same study also showed that including NT-proBNP measurement was superior to routine chest radiograph (CXR) interpretation in conjunction with clinical judgment for diagnosis or exclusion of acute heart failure.

However, it should be noted that a 2011 meta-analysis of RCTs reported inconsistent results regarding the impact of systematic NP testing on time to discharge and costs, indicating that care should be taken in the design and implementation of NP testing protocols to gain the maximum benefits [15].

Practical implementation of natriuretic peptide testing in the emergency department

NPs must be considered as part of a wider diagnostic pathway, as an adjunct to clinical assessment. When establishing testing in the ED setting, it is important to reach a consensus about how best to integrate NPs within the individual hospital, and to understand how to interpret NP findings.

Given the key importance of rapid NP results [12], NP levels are best measured at the point of care, but the central lab should play a key role in developing and overseeing testing protocols. The choice of NP to use can be made to suit local needs, since BNP and NT-proBNP appear to be similar in diagnostic accuracy [16-18] and both are recommend for use by the ESC and ACCF/AHA [8,9].

Interpretation of NP results requires knowledge of potential confounders – factors other than heart failure that could cause increased NP levels [7,19].

Due to this variation of NP levels, particularly relating to age, it is easier to rule out heart failure using NPs than to confirm heart failure. 300 pg/mL was an age-

independent cut-off for NT-proBNP for ruling out heart failure in the International Collaborative of NT-proBNP Study (ICON), with a 98 % negative predictive value [7]. However, false negatives can still occur, potentially due to: right heart failure, mild heart failure, chronic, more compensated heart failure, nonsystolic heart failure, and obesity. Due to the fact that NT-proBNP values increase with age, adding age stratification greatly improved positive predictive value in ICON – i.e. confirming the presence of heart failure (Table I) [7].

Category	Optimal cut-point	Sensitivity (%)
Confirmatory cut-points		
<50 years	450 pg/mL	97
50-75 years	900 pg/mL	90
>75 years	1800 pg/mL	85
Rule in, overall		90
Exclusionary cut-point		
All patients	300 pg/mL	99

Table I: Optimal NT-proBNP cut-points for the diagnosis or exclusion of acute heart failure among dyspneic patients.
Adapted from Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NTproBNP Study. Eur Heart J 2006; 27: 330-7.

In gray areas, other disease patterns such as pulmonary embolism or pneumonia must also be considered in the differential diagnosis as these conditions can also result in an increase in the marker (Table I) [7]. Recommendations from Januzzi et al. for the overall integration of NP measures into acute dyspnea diagnostic pathways are shown in Figure 2 [6].

The role of natriuretic peptides within inpatient and outpatient cardiac care

Once a patient has been admitted, NPs can play a role in monitoring treatment success and discharge planning. BNP levels were observed to decrease in correlation with falling pulmonary capillary edge pressure in a study of patients being treated for decompensated heart failure, which suggested a role in monitoring response to therapy [20].

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┌─────────────────────────────────────────────────────────┐
│           Patient presents with acute dyspnea           │
└─────────────────────────────────────────────────────────┘
                          │
                          ▼
┌─────────────────────────────────────────────────────────┐
│  History, physical examination, chest X-ray,            │
│  electrocardiogram, measure NT.proBNP                   │
└─────────────────────────────────────────────────────────┘
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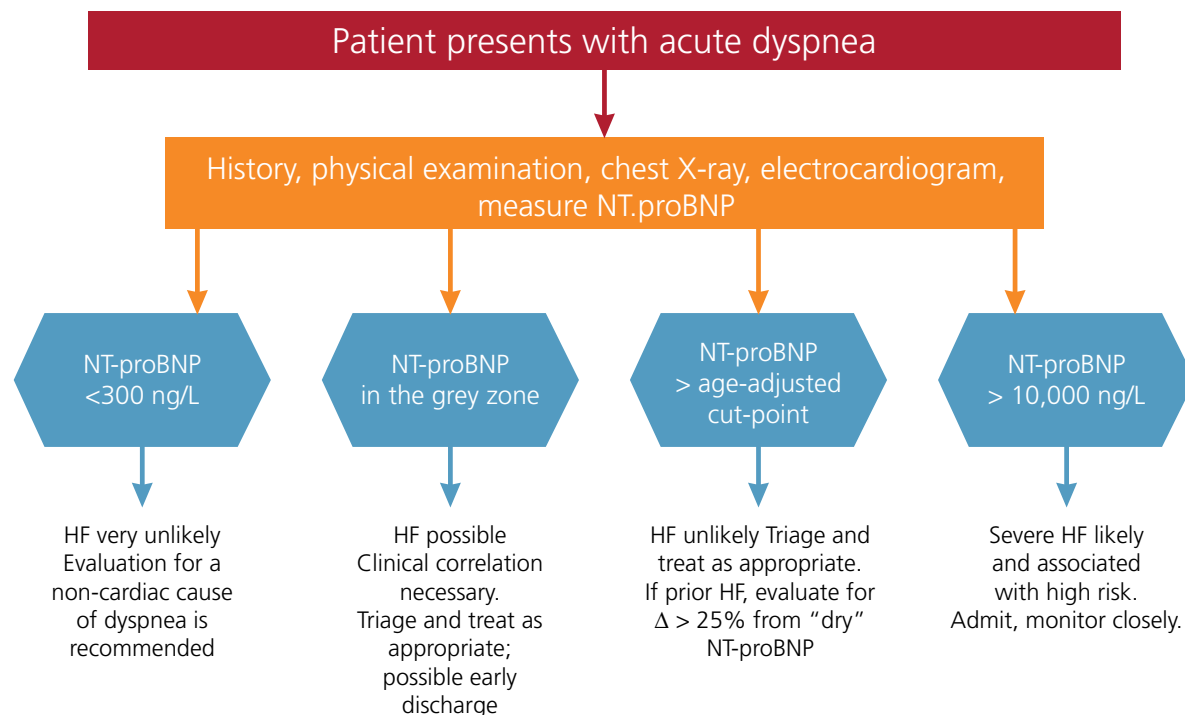| NT-proBNP <300 ng/L | NT-proBNP in the grey zone | NT-proBNP > age-adjusted cut-point | NT-proBNP > 10,000 ng/L |
| HF very unlikely Evaluation for a non-cardiac cause of dyspnea is recommended | HF possible Clinical correlation necessary. Triage and treat as appropriate; possible early discharge | HF unlikely Triage and treat as appropriate. If prior HF, evaluate for Δ > 25% from "dry" NT-proBNP | Severe HF likely and associated with high risk. Admit, monitor closely. |

Figure 2: Recommendations for integrating NP measures into diagnosis for patients presenting with acute dyspnea.

Adapted from Januzzi JL, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. Am J Cardiol 2008; 101(Suppl): 29A-38A.

In the Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) study, patients who achieved less than a 30 % decrease in NT-proBNP from Day 0 to Day 2 of treatment with serelaxin had an increased 180-day-all-cause-mortality vs. patients who achieved a greater decrease [20]. However, NPs might not be appropriate for monitoring success of all heart failure therapies. A study of nesiritide infusion showed that most patients who did achieve a clinical response did not show a significant decrease in BNP/NTproBNP levels [22].

Several studies have confirmed that NP levels at discharge (more than at admission) are prognostic for mortality and/or readmission, giving helpful guidance on the appropriate time for discharge according to the risk of future complications [23-30].

In the outpatient setting, BNP and NT-proBNP are promising tests to optimize chronic heart failure management, aiming to reduce readmissions and death. Two meta-analyses of RCTs testing therapy guided by NP levels (i.e. up-titrating therapy to achieve a certain level of or reduction in NP levels) have shown that this strategy led to significantly reduced all-cause mortality and heart failure-related hospitalizations vs. clinically guided therapy [31,32].

This strategy is now being tested in a large, US NIH-funded RCT called Guiding Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT). GUIDE-IT is examining a strategy of titrating medical therapy based on minimizing NP levels in comparison with usual care, in high risk heart failure patients with left ventricular systolic dysfunction [33]. The primary endpoint is a composite of heart failure hospitalizations or cardiovascular mortality [33]. The planned recruitment is 1,100 patients, and the final data collection for the primary endpoint is expected in September 2017 [33].

Conclusions

NT-proBNP and BNP are biomarkers for heart failure in patients with dyspnea that have the potential to improve diagnostic accuracy in EDs, speed up and

enhance management and admission decisions, and ultimately, improve outcomes and reduce costs when successfully integrated into care pathways [1,3,4,6,7]. Diagnostic thresholds have been developed that make this integration straightforward.

NPs should always be used as an adjunct to clinical assessment, rather than a replacement. Central labs and other stakeholders should play a key role in developing and overseeing point-of-care testing protocols [6-8].

NPs can help indicate the optimum time for patient discharge, and act as a prognostic tool to inform the future risk of heart failure events upon patient discharge, as well as the success of some heart failure treatments [8,9,13,14].

The potential for NPs to guide up-titration of heart failure therapy is supported by an increasing body of evidence, and is currently being assessed in GUIDE-IT [33].

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