Natriuretic peptide levels: what's on the horizon?

Alan S Maisel

Veterans Affairs Medical
Center, Cardiology 111-A,
3350 La Jolla Village Drive,
La Jolla, CA 92161, USA
Tel.: +1 858 552 8585
ext. 7344;
Fax: +1 858 522 7490;
amaisel@ucsd.edu

'It is clear that adding [natriuretic peptide] NP levels to clinical judgment improves the accuracy of diagnosis.'

Natriuretic peptide (NP) levels (brain NP [BNP] and N-terminal prohormone [NTpro]BNP) have taken the cardiology world by storm. The uptake of NPs have been quicker and more thorough than troponin I and T- and C-reactive protein. As a result of this excitement, as well as the relatively inexpensive (US\$ 20) and fast turnaround time (20 min), the possibility of misuse looms large. At the outset, it should be said that NP levels should never be used as a stand-alone test; rather, one that is an adjunct to the patient's history and physical and other laboratory or diagnostic procedures. The two peptides, BNP and NTproBNP, are not interchangeable. While both are of value, one cannot suddenly switch assays and expect the same interpretation of the values. Finally, there is a learning curve for using NP levels.

In the emergency department

We know that it is not easy to come up with the correct diagnosis of heart failure (HF) when patients present with shortness of breath. This is because the typical findings of HF, such as rales, elevated jugular venous pressure and edema, are not always present. The chest x-ray also lacks sensitivity. It is clear that adding NP levels to clinical judgment improves the accuracy of diagnosis [1–3]. Especially important are the rule-out values of less than 100 pg/ml for BNP and less than 300 pg/ml for NTproBNP, giving negative predictive values of more than 90%. While NP levels are continuous variables, upper-limit cut-points are placed for convenience of use. Between the lower limit to rule out HF and the upper limit to rule in HF, grey-zone values exist. These are listed in Box 1.

Almost two-thirds of patients in the grey zone have the ultimate diagnosis of HF, although their prognosis is much better. Many of these grey-zone values occur owing to the release of NPs

from the right ventricle. This could be the case in pulmonary hypertension, right ventricular failure or pulmonary embolism. Additionally, the NP level may be related to concomitant diastolic dysfunction or valvular disease. The major caveats in interpreting NP levels in the emergency department (ED) are renal function and obesity. NP clearance is affected by renal function (NTproBNP is observed to be affected more than BNP), so values may be slightly higher than normal cutoffs [4]. By contrast, obese patients have lower levels of NP for the severity of HF than nonobese patients [5].

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Studies have demonstrated that NP use in the ED is cost effective [3,6]. Additionally, it appears that since NP levels are associated with prognosis, they will be effective in the risk stratification of patients. In other words, there are probably cutoffs of NPs below which a patient with HF can be treated and sent home, and another cutoff above which patients would be better off being admitted to the hospital for several days.

In the hospital

Owing to the high readmission rate in hospitalized patients treated for acute decompensation HF, other modalities must be found in order to help solve this problem. NP levels are an evolving, but important, advance in this area. The NP level at the time of admission represents the baseline of euvolemic, that is, 'dry' or 'optivolemic', plus 'wet' NP levels, specifically, the level that is presumed as a result of volume overload. High NP levels in the setting of volume overload almost always represent an elevated ventricular end-diastolic pressure [7]. Thus, NP levels may help guide therapy by approaching the dry, baseline level as euvolemia is obtained. I believe NP levels should be considered as a white blood cell count for HF. As treatment progresses, observing the NP level will ensure that the 'infection' (HF) is improving. In particular, BNP has a half-life of only 20 min so levels fall precipitously with beneficial treatment [7].

Box 1. Grey-zone natriuretic peptide levels (pg/ml).***Brain natriuretic peptide***

- 100–400

N-terminal prohormone

- <50 years old; 300–450
- 50–75 years; 300–900
- >75 years; 300–1800

Therefore, I obtain NP levels at the time of admission, when there is a change in the clinical state (improving or getting worse) and at the time of discharge. This discharge level should be optimum to follow the patient to help prevent early readmission. The lower the NP level at discharge, the greater the likelihood that the patient will stay out of hospital [8]. In the future, it is likely that therapeutic monitoring with NP levels will become standard therapy.

It also appears likely that, in the future, NP levels will be used in other intensive care unit types of patients. In this setting, NP levels do not necessarily correlate to wedge pressure but, instead, correlate to risk of death and morbidity. Ongoing studies are currently looking at the ability of NP levels to assist in weaning from mechanical ventilation.

Outpatient setting

The holy grail for NP testing would be to titrate outpatient HF medications (β -blockers, angiotensin-converting enzyme inhibitors, etc.) in part by NP levels. Thus, NP levels would be used as surrogates for HF management. Other types of surrogates have been used to individualize therapy in hypertension, diabetes, lipid disorders and so on. However, there has been no surrogate for HF that is easy to use, cost effective and altered by effective medications. The NPs may prove to be valuable in this regard. Studies have been, on the whole, somewhat positive in this regard, but these studies are fraught with issues that still need to be resolved [9]. NP levels might be used to titrate HF medications, but they may also be used to help discern who are the likely candidates for cardiac devices (defibrillators and biventricular pacemakers).

It is clear that patients who suffer decompensation from volume overload on the outside have NP levels well above their baseline. I believe that when symptoms of possible decompensation occur (shortness of breath, edema or weight gain), an NP level of less than 50% of baseline indicates that decompensation is likely. An

increase of 25–50% is in the gray zone, where clinical judgment is essential. Finally a BNP increase of less than 25% (or no change) is usually not associated with decompensation [10].

Other areas of interest***Screening for heart disease***

Studies have demonstrated that, in the right population (>1% prevalence of HF), NP screening prior to echocardiography may be helpful. In this setting, age- and gender-specific cutoffs will be important [11].

Screening potential athletes

Most children who drop dead while playing sports have underlying disease that might have been detected by NP screening. These include hypertrophic cardiomyopathy, idiopathic cardiomyopathy and right ventricular dysplasia. The fact that NP testing will soon be available by the finger-stick method makes this appealing to those who believe in screening our children.

Diastolic dysfunction

We are seeing more new-onset HF patients who have preserved left ventricular dysfunction. Almost all of these patients have elevated NP levels. Thus, many believe that NP levels should be used in the definition of HF with preserved systolic function.

Altered forms of natriuretic peptides

It appears that during an episode of decompensation, the wet BNP may not actually be NP, but some altered form. This might include various cleavage products as well as the precursor prohormone.

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This junk BNP is not physiologically active, but assays are underway that will help evaluate dry versus wet BNP, and perhaps contribute to how we monitor and treat acutely decompensated patients.

Acute coronary syndrome

As NP levels represent ventricular stress, levels often rise in the setting of ischemia. Studies have demonstrated an important independent prognostic value of BNP in the setting of acute coronary syndrome (ACS). In the future, it is likely that NPs will be part of a multimarker panel for risk stratification in ACS.

Conclusion

NP testing has come a long way and, in my opinion, it will be the benchmark by which other HF biomarkers will be tested against in the future. Furthermore, NP levels are not stand-alone tests. Used in conjunction with other tools that the physician brings to bear, NP testing has a bright present and an even brighter future.

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Affiliation

- Alan S Maisel, MD, FACC
Veterans Affairs Medical Center,
Cardiology 111-A, 3350 La Jolla Village Drive,
La Jolla, CA 92161, USA
Tél.: +1 858 552 8585
ext. 7344;
Fax: +1 858 522 7490;
amaisel@ucsd.edu