REVIEW PAPER

B-Type Natriuretic Peptide: Application in the Community

Natriuretic peptide assessment has represented a significant advance in the management of heart failure. In a syndrome in which clinical symptoms and signs can be either nonspecific or absent, the presence of a reliable biomarker to aid diagnosis, assess prognosis, and potentially guide treatment and aid in prevention of this syndrome has represented a significant advance. The following review will outline established and potential new roles for natriuretic peptide assessment in the community. Congest Heart Fail. *2008;14(4 suppl 1):12–16. ©2008 Le Jacq*

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Over the years, management of heart failure has been limited by the lack of a reliable reproducible marker of clinical status that is specific or relatively specific to the syndrome. Such an objective marker would be particularly important in heart failure, given the nonspecific nature of symptoms and the frequent lack of abnormal physical signs that can make the initial diagnosis difficult and subsequent follow-up and management more reliant on subjective assessment. In this context, the discovery of the natriuretic peptide system and the development of effective assay methods have been a significant advance.[1] Measurement of this peptide system, either the active moiety B-type natriuretic peptide (BNP) or the inactive breakdown product N-terminal prohormone brain natriuretic peptide (NTproBNP), has now become established as an important biochemical test in many phases of the natural history of the heart failure syndrome, with ongoing investigation into other possible roles. This review will focus on the established uses of natriuretic peptide testing in the outpatient management of heart failure and will also review areas of ongoing research and interest.

Interpretation of Natriuretic Peptide Levels

As with any laboratory test, it is critically important that the user fully understands the value of the test for the particular setting in which it is being requested. Otherwise, misinterpretation of the result is more likely, potentially leading to inappropriate therapeutic decisions. Several important aspects of natriuretic peptide assessment need to be emphasized before embarking on a review of its role in the outpatient management of heart failure.

Biologic Variability of Natriuretic Peptide Values

Several reports have now been published outlining the variability of natriuretic peptide measurements.[2–5] While these studies have differed somewhat in their results, they have all been consistent in showing significant variability in values among patients with stable heart failure. A summary of these data would suggest that the reference change value (RCV) for BNP is approximately 50% and is modestly less for NTproBNP. The RCV relates to the change needed for the clinician to be comfortable that it represents a clinically meaningful alteration and reflects both the analytical variability,[2–5] greater in BNP compared with NTproBNP, and biologic variability. The relatively high RCV does not detract from the utility of natriuretic peptides once it is taken into account when interpreting the BNP or NTproBNP value. Finally, it is possible that the biologic variability is at least in part explained by subtle alterations in hemodynamic status that may not be clinically evident.

Influence of Renal Disease on Natriuretic Peptide Levels

Renal dysfunction is a frequent accompaniment of both decompensated and stable heart failure.[6,7] This coexistence of renal disease and heart failure, and the involvement of renal function in natriuretic peptide metabolism, can make the interpretation of natriuretic peptide levels complex in the presence of renal dysfunction.[8] With declining glomerular filtration rate (GFR), levels of natriuretic peptides increase. This is in part an appropriate physiologic response to the increased intravascular volume characteristic of this population. However, it may also reflect a declining responsiveness to natriuretic peptides as well as decreased filtration and renal clearance by natriuretic peptide receptor

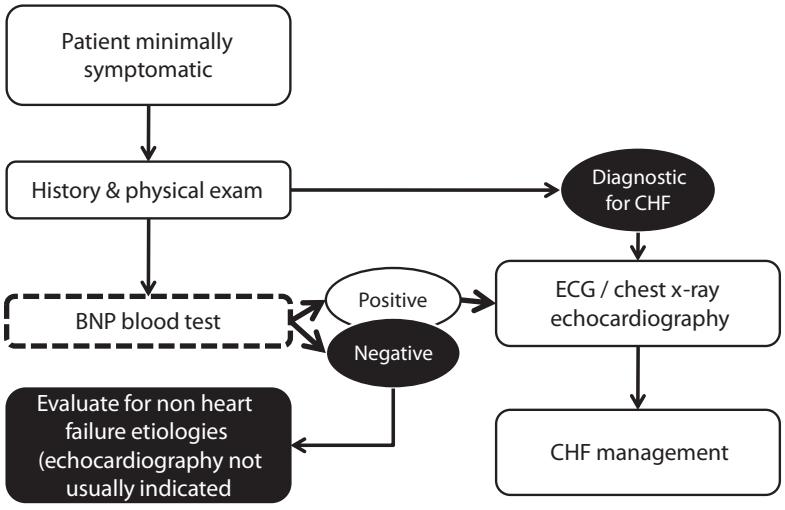

Figure 1. Algorithm for diagnosis of heart failure in primary care. BNP indicates B-type natriuretic peptide; CHF, congestive heart failure; ECG, electrocardiography.

C and endopeptidases.[8] The influence of renal function on BNP levels was well demonstrated in the Breathing Not Properly study, in which dyspnea unrelated to heart failure was associated with relatively high BNP values depending on the estimated GFR.[9] It should be noted that these observations were obtained from an emergency department population. Furthermore, they do not negate the use of BNP in heart failure and renal dysfunction but do underline the need to adjust the diagnostic cutoff upward by a factor of 2 for BNP in patients with significant renal dysfunction.[9] The influence of renal function on NTproBNP is more significant, given its greater dependence on renal clearance, but the usefulness of this assay in renal dysfunction persists as demonstrated by data from the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study.[10,11]

Influence of Obesity of Natriuretic Peptide Levels. Patients with particularly high body mass index values (>35 kg/m^2) may demonstrate lower than anticipated values of natriuretic peptides.[12,13] The explanation for this is unclear but may reflect increased clearance by natriuretic peptide receptor C concentrations on adipocytes.[14] The importance of this observation is the need for a lower cutoff for diagnostic purposes in the obese patient (50 pg/mL for BNP) and an awareness to double BNP levels in this population when assessing values in the outpatient setting.

Influence of Pulmonary Disease in Natriuretic Peptide Levels. Any form of pulmonary disease that puts strain on the right heart can cause an elevation in natriuretic peptide levels. While these elevations are usually modest, it has been demonstrated that major right ventricular strain, as occurs in right heart failure and possibly in acute pulmonary embolism, can result in more dramatic elevations, which could lead to misdiagnosis of left ventricle failure.[15]

Established Use of BNP Assessment in Outpatient Care

New Diagnosis. This is a critical point in the natural history of heart failure. Accurate, speedy diagnosis is essential for ensuring complete investigation of the presentation, prescription of effective therapies, and the commencement of patient education in a manner to obtain maximum benefit. However, it has been well demonstrated that diagnosis of heart failure in the community is difficult, with approximately only one-third of initial diagnoses accurate.[16] This reflects the nonspecific nature of symptoms, the frequent lack of physical signs, and the fact that in many cases the diagnosis is left to the general practitioner, who sees relatively few cases of heart failure. It is in this setting that an important and accurate "rule-out" or "diagnosis-confirming" blood test is required. Natriuretic peptide assessment has been shown to be very useful in a rule-out capacity, with few false-negatives, when a cutoff of 100 pg/mL is used for BNP.[16] Moreover, the onset of heart failure symptoms is often gradual and may not be appreciated or acknowledged by patients with mild heart failure. Aspromonte and colleagues[17] demonstrated that BNP measurement can effectively rule out heart failure in minimally symptomatic patients referred in a structured manner by general practitioners. By receiver operating characteristic analysis, BNP level showed good diagnostic power to detect heart failure (area under the curve, 0.94–0.98). In this setting, a BNP cutoff of 50 pg/mL increases diagnostic accuracy, with high discriminating power to detect a true decompensated state, even in the presence of other high-risk heart disorders and multidrug treatment.[17] Therefore, if applied correctly in this setting, possible diagnoses of heart failure can be excluded and further investigation can be started in individuals with an elevated BNP value. Not only would this approach result in more accurate diagnoses of new-onset heart failure but it is likely that it would also prove cost-effective, potentially reducing referral for more costly echocardiography (Figure 1).

Prognosis at Hospital Discharge. Patients surviving hospitalization for management of heart failure are at significant risk for early readmission. The ability to risk-stratify patients at discharge to identify those at risk for recurrent morbidity would be of benefit in allowing those individuals to be followed more closely. Conversely, those with a relatively low BNP concentration at discharge would be less

at risk and therefore may require less intensive follow-up. Several data sets have now demonstrated that BNP value at discharge is a reliable independent predictor of recurrent admission and morbidity.[18,19] Values <300 pg/mL are generally associated with a relatively benign course, while higher levels portend a poorer outlook. What remains unclear from these data is what is driving the elevated BNP in patients deemed to be clinically euvolemic at discharge. It remains possible that fluid overload persists in these patients despite the reassuring clinical status. Alternatively, persistent elevations of BNP in euvolemic patients may also reflect increased wall stress, subclinical ischemia, or excess fibrosis. This issue needs further clarification to allow focused therapy in these settings to reduce postdischarge risk.

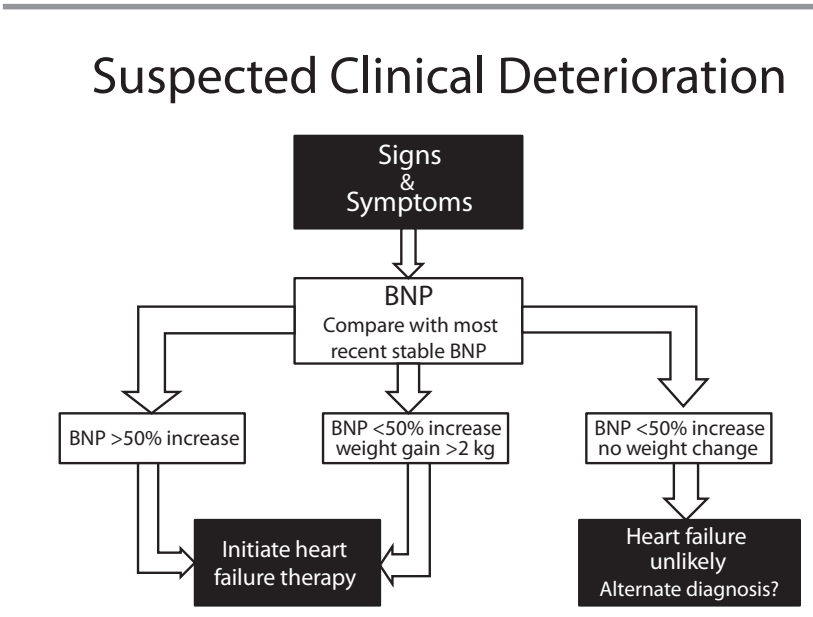

Figure 2. Algorithm for management of suspected clinical deterioration. BNP indicates B-type natriuretic peptide; HF, heart failure.

General Prognosis. Throughout the natural history of ventricular dysfunction and heart failure, natriuretic peptide levels accurately reflect outcome.[20–22] Of particular note is that an isolated reading has been shown to be superior to well-established predictors of outcome including peak VO_2, ventricular function, the heart failure survival score, and levels of plasma norepinephrine.[23,24] In addition, changes in natriuretic peptide levels are also predictive of outcome in both patients with stable heart failure as well as those with advanced heart failure.[25,26]

Assessment of Clinical Deterioration. Episodes of clinical deterioration are a frequent occurrence in the heart failure syndrome. Early diagnosis and intervention are critical to prevent the episode from developing to a stage in which hospitalization may be required. The early diagnosis of clinical deterioration may be difficult because of the nonspecific nature of symptoms and the frequent lack of physical signs consistent with fluid overload or declining cardiac output. Patients are educated to measure and record weight daily and to contact a clinician when body weight changes by approximately 2 kg over a short period, typically 2 or 3 days. Change from baseline natriuretic peptide level would also seem to be of potential use in establishing this diagnosis. In a recent study from our unit, we assessed the sensitivity and specificity of changes in BNP and body weight from baseline euvolemic values in patients with clinically proven clinical deterioration.[27] We found that neither were particularly sensitive in helping establish this diagnosis, but changes of >2 kg in body weight or >50% in BNP value were very specific for clinical deterioration. The lack of sensitivity of BNP value probably reflects many factors, including the already-discussed biologic variability of natriuretic peptides. Nonetheless, the specificity of change does underline its value in this clinical setting, which can be best summarized as follows: little change does not exclude deterioration, but significant change strongly supports the diagnosis (Figure 2).

Roles Under Investigation

Guide to Therapy. There has been intense interest in the use of natriuretic peptide measurement in the titration of therapy in heart failure. Presently, therapy is directed by guidelines based on clinical trials, with little information on how to individualize therapy. Knowing that the lower the level of natriuretic peptide, the better the outlook, the concept has evolved that therapy should be escalated or titrated based on natriuretic peptide levels. This concept was first tested by Troughton and colleagues[28] in a relatively small single-center study in which the authors showed that titrating therapy based on BNP levels was more effective than clinical judgement alone. A larger multicenter study recently published from Jourdain and colleagues[29] provided further supportive data for this approach. In this study, patients with reduced left ventricular systolic function who were optimally treated with disease-modifying therapies (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-receptor blockers) were randomly assigned to continued routine management by physicians expert in heart failure care or to BNP-guided therapy, with a goal to drive the BNP value to <100 pg/mL. Patients were reviewed every month and followed to assess for study end points of heart failure–related death or hospitalization. Patients in the BNP-guided

group had more medication changes in all categories except digoxin and at the end of the study period were receiving significantly higher doses of angiotensin-converting enzyme inhibitors and β-blockers. Of interest, >30% of patients treated according to BNP levels had levels of BNP reduced to <100 pg/mL. During a median follow-up of 15 months, patients in the BNP-guided arm reached the primary end point less frequently than those treated with the routine clinical approach (24% vs 52%).

In summary. the results of these studies strongly suggest that BNP-guided therapy may be of value, and ongoing studies such as NTproBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) will provide further information on this important area.[27,30] However, further work is required with regard to the drivers of elevated BNP in otherwise stable patients to provide information on what therapeutic strategies should be employed in persons with a persistently elevated BNP level. It is likely that different stimuli for natriuretic peptides may be at play, including persistent elevation in filling pressures, increased wall stress from a remodeled ventricle, or a response to pathologic myocardial fibrosis. Finally, it is interesting to speculate that BNP-guided therapy may allow for prescription of less therapy in certain circumstances in which clinical response to initial strategies has been clinically and biochemically very reassuring.

Screening for Development of Heart Failure and Risk Assessment for General Cardiovascular Disease. Screening populations for those individuals at risk for heart failure is now receiving increasing attention as a means of effectively curbing the growing numbers of patients with this syndrome. The value of natriuretic peptide testing in this setting has been discussed in detail in a separate paper in this review.

Conclusions

Natriuretic peptide assessment has become an important aid to the physician in the outpatient management of heart failure. Published data strongly support its role in the new diagnosis of heart failure, prognosis, management of clinical deterioration, and determination of risk following hospital discharge. Ongoing research will help further define its role in heart failure prevention and the titration of therapy.

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