Should B-Type Natriuretic Peptide Be Measured Routinely to Guide the Diagnosis and Management of Chronic Heart Failure?

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Perhaps more than in any other cardiovascular disorder, the diagnosis and treatment of heart failure rely heavily on the scholarship, skills, and judgment of the practicing physician. Proper management of this syndrome requires clinicians to integrate elements of the history, physical examination, and laboratory evaluations together with knowledge of multiple pharmacological and nonpharmacological treatments in an attempt to produce unpredictable degrees of improvement in patients who have a disabling and inexorably progressive disease. There is no diagnostic test for heart failure, and most therapies for the disorder need to be individually titrated, often with the intent of reproducing the treatment strategies used in clinical trials without any means of demonstrating a prognostic benefit in individual patients. Because of these challenges, the diagnosis of heart failure is frequently missed, and useful treatments for heart failure are commonly underutilized. The situation is complicated by the fact that the vast majority of patients with heart failure are managed by primary care physicians and not by cardiologists.

Given all of these difficulties, it is easy to understand why clinicians would be excited about a potential solution to the challenges posed by the syndrome of heart failure. What if one could perform a simple, inexpensive blood test that could be used not only to make the diagnosis, but also to guide the need for and effectiveness of treatment? In theory, such a test would provide clinicians with an intermediate endpoint similar to the measurement of blood pressure or blood lipids. The treatment of both hypertension and hyperlipidemia has been greatly facilitated by the universal availability of simple tests that allow physicians to not only make the diagnosis of these disorders but to monitor the success of each step in treatment—strengthened by the knowledge that the normalization of blood pressures and/or blood lipids greatly minimizes cardiovascular risk.

The intense hope for a simplifying solution to the management of heart failure explains why some physicians have become passionately interested in the measurement of B-type natriuretic peptide (BNP) as a guide to the management of heart failure. BNP is released by the failing heart in proportion to the increase in cardiac filling pressures, and thus, levels of circulating BNP reflect the severity of the critical hemodynamic abnormality that characterizes most patients with heart failure. Studies have shown that the measurement of BNP can distinguish patients with acutely decompensated heart failure from those who present with other causes of dyspnea. This observation has led many physicians—particularly those who are not cardiologists—to rely on the measurement of BNP in discerning the cause of acute shortness of breath in the emergency room.

Given the utility of the measurement of BNP in the identification of patients with acutely decompensated heart failure, many physicians have assumed that the assay must also be helpful in the diagnosis and management of chronic heart failure. Proponents have suggested that the measurement of BNP might be used to find patients with heart failure in the general community; to assist in the diagnosis of dyspnea in high-risk patients with exercise intolerance; to quantify symptoms and functional limitation; to predict the risk of a major cardiovascular event; to distinguish responders and nonresponders to specific treatments; to guide in the determination of an optimal dose of a therapeutic agent; and to identify patients who require intensification of therapy. If such claims were true, routine monitoring of BNP would substantially simplify and improve the care of patients with chronic heart failure.

Should Brain Natriuretic Peptide Be Used Routinely in the Diagnosis of Heart Failure?

Young healthy people generally have low circulating levels of BNP (<20 pg/mL), but many demographic characteristics and clinical conditions other than heart failure can increase circulating levels of BNP. Elderly individuals and women have BNP levels that are 2 to 3 times higher than those seen in younger individuals or in men, and many disorders (coronary artery disease, chronic pulmonary disease, pulmonary embolism, renal insufficiency) can further increase BNP levels. As a result, although early studies selected a BNP level of 40 to 50 pg/mL as the threshold for making the diagnosis of heart failure, this level was subsequently increased to 100 pg/mL when the assays were approved for clinical use. However, the threshold level of 100 pg/mL was based on studies of patients with acutely decompensated heart
failure rather than chronic heart failure. Furthermore, the goal of measuring BNP is not to distinguish patients with heart failure from young healthy people but to distinguish patients with heart failure from elderly patients who have multiple cardiovascular risk factors and conditions but who do not have heart failure. Many elderly women with hypertension-associated renal impairment but without heart failure have BNP levels >200 pg/mL. The wide range of values of BNP in patients without heart failure explains why BNP measurements have not proved useful as a screening tool for identifying patients with heart failure in the general community.4

These troublesome observations have led advocates of BNP monitoring to suggest that a diagnosis of heart failure can be confidently made only if BNP levels exceed 400 pg/mL.5 However, any increase in the threshold value of BNP used to make the diagnosis of heart failure necessarily increases the false negative rate. As Tang et al show in the present issue of Circulation, many patients with chronic heart failure have levels of BNP below the threshold criteria that have been proposed for clinical use. In their study, more than 20% of patients with chronic heart failure had BNP levels <100 pg/mL, and recent experience indicates that more than 50% of such patients have BNP levels <400 pg/mL. To complicate matters further, some patients with end-stage heart failure appear to have very low levels of BNP, possibly because the ability of their ventricles to synthesize and release the peptide may have become exhausted. As a result, the concept of a single diagnostic level of BNP has effectively disappeared—at least with regard to the identification of patients with chronic heart failure. Many patients with and without chronic heart failure have BNP values that fall into a nondiagnostic range (40 to 400 pg/mL). Unfortunately, many patients with mild, nonspecific symptoms of dyspnea or fatigue (whose management would be improved by an accurate diagnostic test for heart failure) have such nondiagnostic values for BNP. Labeling such patients as having heart failure—precisely in the patients least likely to tolerate treatments—can lead to the use of unnecessary and potentially harmful treatments.

Even its most ardent advocates agree that the BNP assay does not replace any test currently used to assess patients with chronic heart failure. The BNP assay does negate the need for echocardiography, which is still required for the evaluation of left ventricular function or for the identification of other structural causes of heart failure. The BNP assay does not minimize the need for invasive hemodynamic monitoring, which remains the only way of accurately measuring rapid changes in hemodynamic variables.7 Furthermore, if the range of nondiagnostic values for BNP is wide, it is not clear that BNP measurements can even be used as a screening test to increase the efficient utilization of echocardiography or pulmonary artery catheterization.

Should BNP Measurements Be Used to Guide the Success of Treatment? If single measurements of BNP cannot be used to identify patients with chronic heart failure, changes in BNP might nevertheless be helpful in guiding the management of patients in whom the diagnosis of heart failure is already established. Sequential measurements of BNP in the same patient would not be influenced by demographic factors (age or gender) or concomitant conditions (if the measurements were made over weeks or months). Indeed, changes in BNP levels have been reported to be correlated with changes in functional capacity; i.e., BNP levels decline in patients who improve symptomatically but remain constant or increase in patients whose symptoms fail to respond favorably to treatment.8

However, to interpret changes in BNP levels, it is important to understand what magnitude of change can be considered clinically significant. Unfortunately, we have little information about the stability or reproducibility of BNP measurements over time in patients who have a stable course and are taking stable doses of background medications.5 How many times does a BNP measurement need to be repeated to ensure that the level measured accurately reflects the status of a patient? How much does the level of BNP need to rise or fall to be deemed relevant? Because we do not know the answers to these questions, we simply do not know how to interpret changes in BNP levels.

Even if we assume that BNP measurements were stable and reproducible and that changes in BNP levels were closely correlated with changes in clinical status, it still is not clear how knowledge of changes in BNP would be useful. If physicians wanted to know if a patient with heart failure was improving or deteriorating, would it better to ask about symptoms or the response to treatment, or would it better to measure the level of BNP? The answer should be obvious. Laboratory tests cannot and should not be used as a substitute for a thorough clinical assessment by a competent healthcare provider, especially because the goal of treatment is to improve the symptoms experienced by the patient and not the values on a laboratory test. Some cynics might point to the difficulties that some patients may have in providing an accurate history or the lack of comfort some clinicians may have in interpreting symptoms or the findings on a physical examination. However, no one has shown that any laboratory test for heart failure can substitute for or meaningfully improve upon the information derived from the patient–physician interaction.

To illustrate this point, let us consider two patients who are first seen with class III symptoms of heart failure, are treated with appropriate therapy, and then return for reevaluation after 6 months. During this time, the first patient has improved substantially and no longer has any symptoms, whereas the second has deteriorated and has been rehospitalized twice for worsening heart failure. Would the measurement of BNP help a physician conclude that the first patient had responded favorably to treatment and the second had not? Some physicians might suggest that it would be nice to know that the BNP had decreased by 50% in the first patient but had increased by 20% in the second patient. But what if the BNP levels had not changed in either patient? Would a physician then conclude that the first patient had not improved and the second had not deteriorated? Physicians should never place a higher value on the measurement of BNP than on the documented clinical course of the patient.
Advocates for the BNP assay might recognize these limitations but nevertheless propose that changes in BNP could provide important prognostic information.9 However, physicians have many ways of assessing the prognosis of patients with heart failure, and no study has shown that BNP measurements are superior to these other assessments. Reports showing that BNP levels are “independently” associated with prognosis do not establish either a physiological relationship or clinical utility, particularly because the statistical models used to reach such conclusions can be easily manipulated by the variables selected for inclusion in the analysis. Furthermore, assessments of prognosis rarely change the management of patients. In the case of heart failure, the primary reason to predict the clinical course in an individual patient with heart failure is to identify patients with such advanced disease that they would benefit from heroic interventions (cardiac transplantation or ventricular assistance). Unfortunately, no one has suggested BNP measurements would add useful information to the predictive models already in widespread use for such patients.10

Should Patients Be Monitored to Determine if Treatment Needs to be Intensified?

Advocates for the BNP assay might recognize the assay’s inability to identify and monitor the course of heart failure, but they might nevertheless propose that serial measurements of BNP could provide physicians with a useful target that would guide the titration of drug treatments. The finding of a persistently high elevation of BNP could inform a healthcare provider that a patient with heart failure was at high risk and might motivate physicians to intensify their use of diuretics, angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists until the levels of BNP (and thus risk) were reduced, thereby improving the prognosis of patients. Such a strategy has appeal, even though advocates would readily admit that they do not know what elevations of BNP levels should be treated and by how much these levels should be reduced.

One small study has suggested that BNP-guided therapy (adjusted to reduce BNP levels to <200 pg/mL) was associated with substantially better outcomes than conventional approaches to treatment.11 Unfortunately, this study is exceedingly difficult to interpret. The two treatment groups were not well balanced at the start of the study (the BNP-guided group was more intensely diuresed). Furthermore, the groups with and without BNP guidance did not differ with regard to symptoms, exercise tolerance, or hospitalizations. The investigators did report fewer outpatient visits for titration of medication in the BNP-guided group, but this could be explained by the fact that titration visits triggered by the measurement of BNP were excluded from the primary analysis of outcome. Most importantly, the underlying hypothesis of the trial was that outcomes would be improved in the group with BNP guidance because this group would receive more intensive therapy as a result of the physician’s knowledge of BNP levels, but the two groups did not differ meaningfully in the degree of intensification of treatment during the course of follow-up. Consequently, this trial fails to support the premise that BNP-guided therapy can improve the clinical status or reduce the risk of a major clinical event in patients with chronic heart failure.

The fact is that we do not need BNP measurements to remind us to prescribe and titrate the drugs used to prolong life in patients with chronic heart failure. All guidelines make clear that physicians should initiate and titrate the doses of angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists to the doses shown to prolong life in clinical trials, unless such doses are contraindicated or cannot be tolerated. If a patient is not receiving or is taking less than optimal doses of any of these neurohormonal antagonists, the drugs should be prescribed and the doses should be increased to target whether or not sequential measurements indicate that BNP levels remain high or are suppressed. Advocates for the BNP assay might argue that physicians are not aware of or do not follow guidelines; that life-saving drugs are currently underutilized and underdosed; and that sequential measurements of BNP would provide a powerful reminder to comply with current recommendations. Such advocacy, however, is tantamount to saying that the BNP assay should serve as an intellectual crutch to remind physicians to practice optimal medicine. Do physicians really need such a crutch? If they do, what crutch is available for the majority of patients with chronic heart failure who do not have markedly increased levels of BNP but are nevertheless receiving suboptimal therapy? If we decide to embrace a strategy that implicitly recognizes our inability to practice optimal medicine, at least such a strategy should provide a solution for the majority of affected patients.

Despite this philosophical quagmire, several trials are currently underway to determine if BNP-guided therapy can reduce the risk of a major cardiovascular event. Are these trials likely to show that BNP levels contribute meaningfully to our management of heart failure? In the final analysis, the benefits of BNP guidance cannot be greater than the benefits of the drugs for which the assay would provide guidance for use. Therefore, because the intensity of dosing of a single agent is not likely to have a major effect on risk,12 the success of BNP guidance cannot rely on its ability to optimize the dosing of a single neurohormonal antagonist. Instead, the success of these trials depends on the hope that risk can be meaningfully reduced by (1) optimizing multiple neurohormonal strategies in concert, (2) optimizing the dose of diuretics, or (3) a combination of both. Indeed, if BNP measurements were useful only because they could provide an optimal titration point for diuretics, they could have an important impact on the care of patients with chronic heart failure.

Summary

Additional study is needed to define the role of routine BNP measurements in the diagnosis and management of chronic heart failure. However, evidence to date suggests that levels of BNP (if measured) should not be viewed as a diagnostic test for chronic heart failure. The results of the assay should be interpreted cautiously; specific threshold values should not be used; and the test cannot replace or supersede the judgment of the clinician. Sequential measurements in patients with established heart failure have not been shown to be
useful in assisting in the follow-up of patients or in the
initiation or titration of appropriate medications. Given these
limitations and uncertainties, we might wonder why the
measurement of BNP has become so popular in some circles.
Are physicians monitoring BNP because they really believe
the assay provides unique and valuable information? Or do
physicians think that heart failure has become so difficult to
manage that they no longer trust their own skills and clinical
judgment?

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