Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction

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Background Although echocardiography is an important tool for making the diagnosis of left ventricular (LV) dysfunction, the cost of this procedure limits its use as a routine screening tool for this purpose. Brain natriuretic peptide (BNP) accurately reflects ventricular pressure, and preliminary studies have found it to be highly sensitive and highly specific in diagnosing congestive heart failure in the emergency department. We hypothesized that BNP might therefore be useful as a screening tool before echocardiography in patients with suspected LV dysfunction.

Methods Subjects included patients referred for echocardiography to evaluate the presence or absence of LV dysfunction. Patients with known LV dysfunction were excluded from analysis. BNP was measured by a point-of-care immunoassay (Biosite Diagnostics, San Diego, Calif). The results of BNP levels were blinded from cardiologists making the assessment of LV function. Patients were divided into those with normal ventricular function, abnormal systolic ventricular function, abnormal diastolic function, and evidence of both systolic and diastolic dysfunction.

Results Two hundred patients in whom LV function was unknown were studied. In the 105 patients (53%) whose ventricular function was subsequently determined to be normal by echocardiography, BNP levels averaged 37 ± 6 pg/mL. This was significantly less than in those patients with either ultimate diastolic dysfunction (BNP 391 ± 89 pg/mL (P < .001) or systolic dysfunction (BNP 572 ± 115 pg/mL (P < .001). A receiver-operator characteristic curve showing the sensitivity and specificity of BNP against the echocardiography diagnosis revealed the area under the curve (accuracy) was 0.95. At a BNP level of 75 pg/mL was 98% specific for detecting the presence or absence of LV dysfunction by echocardiography.

Conclusions A simple, rapid test for BNP, which can be performed at the bedside or in the clinic, can reliably predict the presence or absence of LV dysfunction on echocardiogram. The data indicate that BNP may be an excellent screening tool for LV dysfunction and may, in fact, preclude the need for echocardiography in many patients. (Am Heart J 2001; 141:367-74.)
Methods
Study population
The study was approved by the University of California Institutional Review Board and conducted at the San Diego Veteran’s Health care System between June and October 1999. Two hundred consecutive patients referred for echocardiography to evaluate LV function and consented to be studied were included from a total of 262 patients referred for LV function during this time period. The 62 patients with known LV dysfunction were excluded from analysis. Patients referred for echocardiography to assess valve disease, the presence of a vegetation, or to rule out a cardiac cause of stroke were not included in this database. Both outpatients and inpatients were included in this study, and approximately 24% of the sampling population consisted of inpatients.

Echocardiography
Two-dimensional, M-Mode, spectral, and color flow Doppler echocardiograms were obtained with commercially available instruments operating at 2.0 to 3.5 mHz. Two-dimensional imaging examinations were performed in the standard fashion in parasternal long- and short-axis views and apical 4- and 2-chamber views. Pulsed Doppler spectral recordings were obtained from a 4 x 4-mm sample volume placed at the tips of the mitral leaflets and in the pulmonary vein and that was adjusted to yield the maximal amplitude velocity signals. All data were copied to 0.5-inch VHS videotape for subsequent playback, analysis, and measurement.

Two-dimensional echocardiograms were subjected to careful visual analysis to detect regional contractile abnormalities. LV systolic and diastolic volumes and ejection fractions were derived from biplane apical (2- and 4-chamber) views. Pulsed Doppler spectral recordings were obtained from a 4 x 4-mm sample volume placed at the tips of the mitral leaflets and in the pulmonary vein and that was adjusted to yield the maximal amplitude velocity signals. All data were copied to 0.5-inch VHS videotape for subsequent playback, analysis, and measurement.

Echocardiographic classifications
Normal ventricular function. Normal ventricular function was defined by normal LV end-diastolic (3.5-5.7) and endsystolic dimensions (2.5-3.6), no major wall motion abnormalities, an ejection fraction of >50%, and no evidence of impaired or restrictive relaxation abnormalities.

Systolic dysfunction. Systolic dysfunction was defined by an ejection fraction less than 50% or either global hypokinesis or discrete wall motion abnormalities.

Diastolic dysfunction. Diastolic dysfunction was defined as impaired relaxation, restrictive pattern, and pseudonormal pattern on the basis of the definitions below.

1. Impaired relaxation: E/A ratio <1 and deceleration time >240 ms in patients <55 years old and E/A ratio <0.8 plus deceleration time >240 ms in patients ≥55 years old. IVRT measurements, which were available in approximately one half of the patients, was >90 ms in 90% or more of patients were abnormal E/A ratio changes or deceleration time >240 ms.

2. Restrictive: E/A ratio >1.5 and deceleration time <150 ms. Confirming evidence included pulmonary vein diastolic > pulmonary vein systolic, pulmonary “A” reversal > forward mitral A wave duration, pulmonary vein diastolic flow reversal, IVRT < 70 ms. Confirming evidence by one or more of the above was seen in >50% of patients.

3. Pseudonormal E/A ratio >1 and deceleration time >240 ms. Confirmation by Valsalva maneuver when possible.

Systolic plus diastolic-restrictive. Systolic plus diastolic-restrictive was defined as ejection fraction less than 50% with global hypokinesis or discrete wall motion abnormalities and deceleration time <150 ms.

Measurement of BNP plasma levels
During initial evaluations, a small sample (5 mL) was collected into tubes containing potassium EDTA (1 mg/mL blood). BNP was measured with the Triage B-Type Natriuretic Peptide test (Biosite Diagnostics, San Diego, Calif). The Triage BNP Test is a fluorescence immunoassay for the quantitative determination of BNP in whole blood and plasma specimens. The concentration of BNP in the specimen is proportional to the fluorescence bound in the detection lane of the device and was quantified by the portable Triage meter. When possible, BNP levels were measured in whole blood and processed within 4 hours. Otherwise, samples were spun down and the plasma frozen until the sample was analyzed (1-2 days). Figure 1 shows a high correlation between the assay used in this study (Biosite Diagnostics) and the Shiono radioimmunoassay (RIA) (Shionogi, Osaka, Japan). The range of detectable levels are 1 to 1300 pg/mL. The average 95% confidence limit of the analytical sensitivity of the test is less than 5 pg/mL (95% confidence interval 0.2-4.8 pg/mL). The average total imprecision is 10.1% at mean values of 28 pg/mL and 16.2% at mean levels of 1080.4 pg/mL. There is no significant cross-reactivity with endothelin-1, α-atrial natriuretic peptide, or aldosterone.

Statistical analysis
Group comparisons of BNP values were made with t tests for independent samples and analyses of variance. In all cases these were computed with raw BNP values and repeated with log-transformed BNP values because the BNP distribution was positively skewed. Both versions yielded the same conclusions.

Sensitivity, specificity, and accuracy were computed for BNP with a selection of possible cut points. The diagnostic utility of BNP alone was compared with the echocardiographic probability of LV dysfunction with receiver-operator characteristic (ROC) curves.
Results

The characteristics of the 200 patients are shown in Table I. Fifty-two percent of patients had unsubstantiated complaints of dyspnea, whereas the remaining were essentially asymptomatic. Nearly all patients had risk factors for heart disease, including 46% with a history of coronary artery disease.

Figure 2 presents BNP values (mean and SE) for patients classified as either “normal LV function” or “abnormal LV function” groups. Patients diagnosed with abnormal LV function (n = 95) had a mean BNP concentration of 489 ± 75 pg/mL, whereas the normal LV function group (n = 105) had a mean BNP concentration of 29.5 ± 62.4 pg/mL. The group difference was significant in raw (P < .001) and log (P < .001) form.

Figure 3 shows the breakdown of patients with abnormal LV function into purely systolic (n = 53), purely diastolic (n = 42), and the combination of systolic plus diastolic (n = 14) on the basis of echocardiography. Values for all abnormal LV function groups are significantly higher than for the normal LV function group (P < .001). Patients with systolic plus diastolic-restrictive dysfunction had significantly higher BNP values (1077 ± 272 pg/mL) than pure systolic (567 ± 113 pg/mL) or pure diastolic function alone (391 ± 89 pg/mL) (P < .0001). The ejection fraction of the systolic plus diastolic-restrictive group was 34% versus 45% for the pure systolic patients.

Table I. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>200</td>
</tr>
<tr>
<td>Age (y)</td>
<td>65.32 ± 0.9</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>189/11</td>
</tr>
<tr>
<td>All normal</td>
<td>53%</td>
</tr>
<tr>
<td>All abnormal</td>
<td>48%</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>65%</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>34%</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>46%</td>
</tr>
<tr>
<td>History of shortness of breath</td>
<td>52%</td>
</tr>
<tr>
<td>History of edema</td>
<td>28%</td>
</tr>
</tbody>
</table>

Characteristics of all 200 patients recruited into the study. History included presence or absence of diabetes, hypertension, or coronary artery disease and symptoms included presence or absence of shortness of breath or edema when referred for echocardiogram.
An ROC curve showing the sensitivity and specificity of BNP against the echocardiography diagnosis for LV function in all 200 patients is shown in Figure 4. The area under the curve (accuracy) was 0.959 (0.932-0.987).

Table II represents the sensitivity, specificity, positive and negative predictive values, and accuracy of various BNP levels. The various cut points were obtained from ROC curve analysis.

Table II. BNP levels: normal versus abnormal

<table>
<thead>
<tr>
<th>BNP levels (pg/mL)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
</table>

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of various BNP levels. The various cut points were obtained from ROC curve analysis.

Figure 4

ROC of Normal Versus Abnormal

ROC curve comparing the sensitivity and specificity of BNP and echocardiography diagnosis of LV dysfunction. Selected BNP values are indicated in picograms per milliliter.

An ROC curve showing the sensitivity and specificity of BNP against the echocardiography diagnosis for LV function in all 200 patients is shown in Figure 4. The area under the curve (accuracy) was 0.959 (0.932-0.987).

Table II represents the sensitivity, specificity, positive and negative predictive values, and accuracy of various BNP levels in determining LV function with use of echocardiography as the gold standard. The different cut points were picked from the ROC curve. As can be seen, a BNP level cutoff value at 38.5 pg/mL was 95% sensitive for the detection of LV dysfunction and 66% specific. Levels at or below 38.5 pg/mL had a negative predictive value of 93%. A BNP cut point of 75 pg/mL exhibited the best specificity (98%), best positive predictive value (98%), and the highest accuracy (93%).

Table III shows characteristics of patients belonging to the two groups (normal and abnormal LV function). As can be seen, histories of hypertension, diabetes, and coronary disease are frequently seen in both groups of patients. Yet BNP levels >100 pg/mL were seen in only 1% of patients with normal ventricular function compared with 80% of patients with abnormal ventricular function (P < .001).

Figure 5 shows a depiction of all cardiac referrals for assessment of LV function. Twenty-four percent of patients in the referral group had known LV dysfunction. The mean BNP in this group was 798 ± 106 pg/mL. Sixty percent of patients referred had unknown LV function. Breakdowns of BNP levels in these groups are discussed above.

Table III. Normal LV function versus abnormal LV function

<table>
<thead>
<tr>
<th>Normal LV function (n = 105)</th>
<th>Abnormal LV function (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;55 y</td>
<td>71%</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>56%</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>28%</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>33%</td>
</tr>
<tr>
<td>History of shortness of breath</td>
<td>42%</td>
</tr>
<tr>
<td>History of edema</td>
<td>24%</td>
</tr>
<tr>
<td>BNP levels [pg/mL]</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>1%</td>
</tr>
<tr>
<td>&gt;100</td>
<td>1%</td>
</tr>
<tr>
<td>&gt;120</td>
<td>1%</td>
</tr>
</tbody>
</table>

Clinical presentation and BNP levels among the two groups of patients—normal and abnormal LV function, by echocardiography. Abnormal group included either systolic dysfunction, diastolic dysfunction, or both systolic and diastolic dysfunction.

Discussion

Early detection of LV dysfunction enables administration of treatment that can improve survival and increase well-being.2,6 But ventricular dysfunction may be difficult to diagnose because patients may be asymptomatic, and abnormal findings on physical examination are often absent.3,4 Echocardiography, the most commonly used method to diagnose LV dysfunction, is one of the fastest growing procedures in cardiology.25 However,
both the limited availability of echocardiography in community settings and its expense may not make it the best screening test for patients with low probability of LV dysfunction.

Although studies using logistic regression models with features of the history, physical examination, chest x-ray film, and ECG have been used to predict the probability of an abnormal echocardiogram,7,26 a simple, rapid blood test that is both sensitive and specific for LV dysfunction would be of significant clinical benefit. The test should reliably rule out LV dysfunction with an adequate positive predictive value.

The fact that increased levels of neurohumoral factors such as norepinephrine, renin, and endothelin-1 have been found to be significant prognostic predictors in congestive heart failure (CHF) suggests an important role of these vasoconstrictors in the pathogenesis of CHF.27-34 However, the use of these neurohumoral factors to diagnose LV dysfunction is impractical, in large part because of difficult assay characteristics, general instability of the compounds, and wide-ranging, often overlapping values.35,36

BNP is a 32 amino acid polypeptide containing a 17 amino acid ring structure common to all natriuretic peptides.37 The source of plasma BNP is cardiac ventricles, which suggests that it may be a more specific indicator of ventricular disorders than other natriuretic peptides.5,8,32 The nucleic acid sequence of the BNP gene contains the destabilizing sequence “tatttat,” which suggests that turnover of BNP messenger RNA is high and that BNP is synthesized in bursts.8 This release appears to be directly proportional to ventricular volume expansion and pressure overload.8,11,32 BNP is an independent predictor of high LV pressure10 and correlates to NYHA classification.11

### BNP as a screen for LV dysfunction

BNP appears to be a useful addition in the evaluation of possible CHF.13-15,18 In a community-based study where 1653 subjects underwent cardiac screening, the negative predictive value of BNP of 18 pg/mL was 97% for LV systolic dysfunction.14 In a study of 122 consecutive patients with suspected new heart failure referred by general practitioners to a rapid-access heart failure clinic for diagnostic confirmation, a BNP level of 76 pg/mL, chosen for its negative predictive value of 98% for heart failure and similar to the cutoff value in the current study, had a sensitivity of 97%, a specificity of 84%, and a positive predictive value of 70%.13 Finally, Davis et al15 measured the natriuretic hormones atrial natriuretic peptide and BNP in 52 patients with acute dyspnea and found that admission plasma BNP concentrations more accurately reflected the final diagnosis than did ejection fraction or concentration of plasma atrial natriuretic peptide.

### Point-of-care testing of BNP

This is the first study that examines the utility of a rapid, point-of-care test for BNP to predict LV dysfunction as determined by echocardiography. This immuno-
assay is automatic, uses 5 mL of whole blood, and is small enough to use at the bedside or the echocardiography clinic. Our findings suggest that BNP may be a useful screen for patients with LV dysfunction and yields an ROC curve of 0.959 compared to echocardiography. This accuracy is similar to that of the prostate-specific antigen for prostate cancer detection, which had an area under the curve (AUC) of 0.94 and is superior to those of Papanicolaou smears and mammography (AUC 0.70 and 0.85, respectively). We found that BNP levels were elevated in both systolic and diastolic dysfunction, with the highest values being reported in patients with systolic dysfunction plus a decreased mitral valve deceleration time. Interestingly, this group of patients has also been shown to have the worst prognosis of all echocardiogram classifications of LV dysfunction.12,17

The European Society of Cardiology recently published its recommendations regarding the diagnosis of isolated diastolic heart failure, which included the presence of symptoms, presence of normal or mildly reduced systolic function, and evidence of abnormal LV relaxation and filling, diastolic distensibility, and diastolic stiffness. Our results are similar to those of Redfield et al, who studied 657 subjects with normal systolic function and found that BNP levels were higher in those with isolated diastolic dysfunction. Although BNP levels cannot differentiate between systolic and diastolic dysfunction, elevated BNP levels likely represent true diastolic dysfunction when systolic function is normal by echocardiography.

The results of this study can be extended to other venues where rapid screening for left ventricular dysfunction is important. We recently evaluated point-of-care testing of 250 patients seen in the emergency department for acute dyspnea. At the cut point for BNP of 80 pg/mL, the negative predictive value was 98%. BNP levels added significantly to variables found in the history, physical examination, and the laboratory. Patients whose dyspnea was subsequently found to be the result of pulmonary disease had BNP levels 10-fold less than those of patients with CHF. Twenty-nine of 30 cases of acute dyspnea misdiagnosed by emergency department physicians would have been correctly identified had BNP levels been available.

**Role of BNP in asymptomatic or minimally symptomatic LV dysfunction**

It is estimated that 3% of the population above the age of 45 years may have ventricular dysfunction and that 50% of them may be asymptomatic. The National Institutes of Health sponsored Studies of Left Ventricular Dysfunction (SOLVD) in patients with asymptomatic LV dysfunction, demonstrated humoral activation characterized by increases in the natriuretic peptides without activation of the circulating renin-angiotensin system. In the current study we found that nearly half the patients were asymptomatic, yet BNP levels were elevated in the majority of patients.

Our data amplify the suggestion of Mair et al, who concluded that there is sufficient evidence to encourage physicians to gain experience with BNP as a supplement in the diagnosis of patients suspected of having heart failure. The current study demonstrates the usefulness of BNP for selecting patients for further cardiac evaluation. It is clear that BNP should not replace imaging techniques in the diagnosis of CHF because these methods provide complementary information. An increase in BNP is serious enough to warrant follow-up echocardiography. Because BNP also provides information on neurohormonal activation in CHF, which is independent and of additive prognostic value to hemodynamic variables, BNP might also be helpful for the cardiologist to monitor therapy and disease course in patients with CHF and for estimating prognosis in these patients.

**Limitations**

This was an observational study done at a single Veteran’s hospital, so one must be careful about generalizing the results to the entire population. Both the AUC from an ROC, as well as the negative predictive values are dependent on the patient population studied. Our population represents generally older, predominantly male, veterans.

Echocardiographic recordings form the basis of the diagnosis of systolic and diastolic dysfunction in the current study. Numerous previous reports have validated the ability of cardiac ultrasonography to detect abnormalities of contractile function and to quantitate LV volumes and ejection fraction. All patients in this study so designated had clear-cut evidence of LV systolic dysfunction. Although diastolic dysfunction implies an abnormal relationship between LV volume and pressure, echocardiography is capable of assessing only parameters related to volume. Therefore transmural and pulmonary venous flow velocities provide only indirect measurements of diastolic performance. Nevertheless, these parameters have been shown to provide reliable markers of impaired diastolic function and are applied for this purpose in clinical practice.

Finally, in this study BNP is being used to identify “any” impairment of ventricular function rather than “significant” impairment. Thus symptoms in such patients are not necessarily of cardiac origin and could challenge the value of labeling those patients as “abnormal” with BNP.

**Conclusion**

An easy, rapid test for BNP, which can be performed at the bedside or clinic, with a whole blood sample,
can reliably predict the presence or absence of LV dysfunction on echocardiography. We believe that BNP may be an excellent screening tool for LV dysfunction, especially in the community where the greatest burden of disease exists and where there is limited access to echocardiography. In this setting it is likely that BNP analysis would greatly assist in appropriateness of patient referral and in the optimization of drug therapy.

References


35. Edvinsson L, Ekman R, Hedner P, et al. CHF: involvement of perivas-