Comparative Accuracy of B-Type Natriuretic Peptide and Tissue Doppler Echocardiography in the Diagnosis of Congestive Heart Failure

Hisham Dokainish, MD, William A. Zoghbi, MD, Nasser M. Lakkis, MD, Miguel A. Quinones, MD, and Sherif F. Nagueh, MD

B-type natriuretic peptide (BNP) and early diastolic transmitral velocity/tissue Doppler mitral annular velocity (E/Ea) both estimate left ventricular filling pressure, but have not been compared in the diagnosis of congestive heart failure (CHF). One hundred twenty-two hospital inpatients with suspected CHF underwent simultaneous clinical examination, BNP measurement, and comprehensive echo-Doppler examination. The accuracy of BNP and echocardiography was compared with the Framingham criteria diagnosis of CHF. Seventy patients (57%) had clinical CHF, whereas 52 (43%) did not. In all patients, the optimal BNP cutoff was >250 pg/ml (sensitivity 86%, specificity 77%), E/Ea >15 had 83% sensitivity and 82% specificity, whereas comprehensive echo-Doppler had 95% sensitivity and 88% specificity for CHF. In patients with normal ejection fraction, the optimal BNP cutoff was >150 pg/ml (sensitivity 79%, specificity 85%). E/Ea >15 had 79% sensitivity and 93% specificity, whereas comprehensive echo-Doppler had 85% sensitivity and 96% specificity for CHF. In patients with reduced ejection fraction, the optimal BNP cutoff was >300 pg/ml (sensitivity 88%, specificity 60%). E/Ea >15 had 92% sensitivity and 72% specificity, whereas comprehensive echo-Doppler had 96% sensitivity and 80% specificity ($p = 0.08$ compared with BNP) for CHF. Overall, BNP and E/Ea have similar diagnostic accuracy for CHF in this patient population. In patients with reduced ejection fraction, comprehensive echo-Doppler trended toward higher specificity than BNP for clinical CHF.

METHODS

The study protocol was approved by the Baylor Institutional Review Board.

Patient population: Consecutive inpatients at our institution, referred to the cardiology consult service for suspected CHF, were eligible. All subjects underwent history and physical examination by the same attending cardiologist who had access to the patients’ charts, and laboratory and radiographic tests. The cardiologist then applied Framingham criteria\(^8\) to determine the presence or absence of clinical CHF. Immediately after this determination, consenting patients underwent a comprehensive 2-dimensional and Doppler echocardiographic study with BNP measurement. The clinical evaluation, BNP measurement, and echocardiography were performed within 20 minutes of each other in all patients.
Patients were excluded if they had non-sinus rhythm, severe mitral regurgitation, mitral stenosis, a prosthetic mitral valve, or severe mitral annular calcification, which reduce the accuracy of Doppler in estimating left ventricular filling pressures. Patients with unstable angina or myocardial infarction were excluded because BNP can be elevated in these conditions.

**BNP determination:** Two milliliters of venous blood were drawn from consenting patients and placed in a vacutainer tube containing potassium ethylenediaminetetraacetic acid. The blood was placed within 30 minutes on a Triage B-Type Natriuretic Peptide test slide (Biosite Diagnostics, San Diego, California) and analyzed in the Biosite MeterPlus machine, a point-of-care test based on fluorescence immunoassay. The test has a range of 5 to 1,300 pg/ml.

**Echocardiography and Doppler:** Two-dimensional measurements were obtained according to recommendations of the American Society of Echocardiography\(^9\) and included ejection fraction by the previously validated multidiameter method,\(^10\) and maximal left atrial volume by the method of discs.\(^11\) An ejection fraction of \(\geq 50\%\) was defined as normal, whereas \(<50\%\) was considered reduced.\(^12,13\) Pulsed Doppler echocardiography was performed to record transmitial and pulmonary venous flow in the apical 4-chamber view.\(^14\) Tissue Doppler velocities were then acquired at the septal and lateral annular sites as previously described.\(^6\)

Studies were analyzed by an echocardiologist blinded to all clinical and BNP data. Mitral inflow measurements included peak early (E) and peak late (A) velocities, E/A ratio, deceleration time of E velocity, and duration of A.\(^14\) For pulmonary venous flow, measurements included peak velocities, systolic filling fraction, and duration of the atrial reversal (Ar) wave.\(^14\) The early diastolic (Ea) velocity by tissue Doppler at the septal and lateral annular sites was measured and E/Ea ratio computed using the average of the septal and lateral Ea as previously described.\(^6,15\)

**Echocardiographic diagnosis of CHF:** In the presence of a left ventricular ejection fraction \(<50\%\), CHF was diagnosed on 2 of 3 of the following Doppler criteria: (1) mitral inflow (E/A \(>1\) or deceleration time \(<160\) ms, or both),\(^11,16,17\) (2) pulmonary venous flow (systolic filling fraction \(<40\%\) or pulmonary venous atrial Ar duration – mitral A duration \(>30\) ms),\(^7\) and (3) tissue Doppler-derived ratios (E/Ea \(>15\)).\(^6,15\) If pulmonary venous parameters were unavailable and mitral inflow and tissue Doppler parameters were discrepant, left atrial volume \(>30\) ml/m\(^2\) was needed. When ejection fraction was \(\geq 50\%\), CHF was diagnosed using tissue Doppler ratios (E/Ea \(>15\)), and the Ar-A duration \(>30\) ms), because other conventional Doppler indexes have lower diagnostic accuracy in normal ejection fraction.\(^7,18\) In case of discrepancy between tissue Doppler and pulmonary venous parameters, left atrial volume \(>30\) ml/m\(^2\) was needed.

**Statistical analysis:** Continuous data are presented as mean \(\pm\) SD and categorical data as number (percentage). Natural log transformation was performed on BNP values due to nonlinear distribution. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for CHF diagnosis were computed using standard definitions, and differences determined using McNemar’s test. Receiver operating characteristic (ROC) curves were constructed to determine optimal sensitivity and specificity, and area under the curve (AUC) calculated. For continuous variables, differences between patients with and without CHF were compared by unpaired \(t\) test and analysis of variance. For dichotomous parameters, the chi-square test was used. Univariate and multivariate logistic regression was performed on variables included in the echocardiographic and BNP model for prediction of CHF. A \(p\) value \(<0.05\) was significant. Analyses were performed using the SigmaStat 3.0 system (Chicago, Illinois).

### RESULTS

**Clinical characteristics and diagnosis of CHF:** One hundred forty-five consecutive inpatients at our institution with suspected CHF were eligible. Fifteen patients were excluded for nonsinus rhythm, 3 for severe mitral regurgitation, 2 for prosthetic mitral valve, 1 for severe mitral annular calcification, 1 for mitral stenosis, and 1 who refused consent. Thus, 122 patients were studied; clinical characteristics are listed in Table 1.

Seventy patients (57%) had clinical CHF. Of the 52 patients without CHF, the final diagnosis was dyspnea due to pulmonary disease in 14 patients, of whom 10 had an exacerbation of chronic obstructive lung disease, 2 had interstitial lung disease, 1 had a pulmonary embolus, and 1 had pneumonia. The remaining 38 patients did not meet the Framingham criteria for CHF.

Patients with CHF were more likely to have a

<table>
<thead>
<tr>
<th>TABLE 1 Baseline Characteristics of 122 Hospital Inpatients With Suspected Congestive Heart Failure (CHF)</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age (yrs)</td>
</tr>
<tr>
<td>Women</td>
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<tr>
<td>Body surface area [m(^2)]</td>
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<tr>
<td>Etiology of CHF</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>History</td>
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<tr>
<td>Prior CHF*</td>
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<tr>
<td>CHF admission in last year*</td>
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<tr>
<td>Prior myocardial infarction</td>
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<tr>
<td>Prior coronary angioplasty or stent</td>
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<tr>
<td>Prior coronary bypass surgery</td>
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<tr>
<td>Systemic hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Current smoker</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>Chronic obstructive lung disease</td>
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<tr>
<td>Renal failure (creatinine (&gt;2.0) mg/dl)</td>
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</table>

* \(p \leq 0.05\) for comparison between those with and without clinical CHF.

Values are expressed as mean \(\pm\) SD or number (%).
Ejection fraction was lower in patients with CHF, and E/Ea were all significantly different (p < 0.001) in patients with than without CHF (Table 2).

The mean E/Ea in patients without CHF was 12 ± 5 compared with 20 ± 6 in patients with CHF (p < 0.0001). The mean BNP level in patients with CHF was 652 ± 406 pg/ml compared with 179 ± 219 pg/ml in patients without CHF (p < 0.001). There were significant correlations (p for all < 0.001) between natural log of BNP and the following echo-Doppler parameters: mitral E/Ea (r = 0.57), ejection fraction (0.55), mitral E/A (0.49), mitral deceleration time (0.47), left atrial volume index (0.45), pulmonary venous systolic filling fraction (0.45), tissue Doppler systolic annular velocity (0.41), and mitral A-pulmonary venous Ar (0.37). Figure 1 illustrates a significant increase in BNP level as mitral E/Ea increases.

**Accuracy of BNP and echocardiography in the diagnosis of CHF:** The ROC curves for BNP and mitral E/Ea in the detection of CHF are shown in Figure 2. The sensitivity and specificity of BNP, mitral E/Ea, and comprehensive echo-Doppler for clinical CHF are displayed in Figure 3. The optimal BNP cutoff for clinical CHF was >250 pg/ml (AUC 0.87, p < 0.0001), with a sensitivity of 86%, a specificity of 77%, and an accuracy of 82%. The optimal E/Ea cutoff was >15 (AUC 0.87, p < 0.0001), with a sensitivity of 84%, specificity of 83%, and accuracy of 84%. Comprehensive echo-Doppler had a sensitivity of 95%, a specificity of 88%, and an accuracy of 92% for CHF (AUC 0.91, p < 0.0001). Adding BNP >250 pg/ml to comprehensive echo-Doppler did not improve the diagnostic accuracy of echocardiography (sensitivity 89%, specificity 92%, accuracy 90%).

On univariate analysis, left atrial volume index >30 ml/m², BNP >250 pg/ml, E/Ea >15, and comprehensive echo-Doppler were predictive of clinical CHF (for all, p < 0.001). On multiple logistic regression of these univariate predictors, BNP >250 pg/ml (odds ratio [OR] 12.3, p = 0.002), and comprehensive echo-Doppler (OR 205.9, p < 0.001) were significant predictors of clinical CHF. When comprehensive echo-Doppler was excluded from the model (significant overlap with E/Ea [r = 0.78], p < 0.001), BNP >250 pg/ml (OR 6.4, p = 0.001), and E/Ea >15 (OR 18.3, p < 0.001) were significant independent predictors of clinical CHF.

**Accuracy of BNP and echocardiography for CHF according to ejection fraction:** Of the 46 patients (38%) with normal ejection fraction, 19 (41%) had a diagnosis of clinical CHF. In patients with normal ejection fraction, BNP (456 ± 415 vs 99 ± 176 pg/ml,
p < 0.001) and mitral E/Ea (17 ± 5 vs 10 ± 3, p < 0.001) were higher in patients with than without CHF. Of the 76 patients (62%) with reduced ejection fraction, 51 (67%) had CHF. In the patients with reduced ejection fraction, BNP (725 ± 381 vs 265 ± 230 pg/ml, p < 0.001) and E/Ea (21 ± 6 vs 14 ± 5, p < 0.001) were higher in patients with than without CHF.

The ROC curves for BNP and E/Ea to predict clinical CHF in patients with normal and reduced ejection fraction are shown in Figure 2. The optimal BNP cutoff for clinical CHF was >150 pg/ml in patients with normal ejection fraction (AUC 0.89, p < 0.0001) and >300 pg/ml in patients with reduced ejection fraction (AUC 0.84, p < 0.0001). BNP >150 pg/ml had a specificity of 85% in patients with normal ejection fraction, whereas BNP >300 pg/ml had a specificity of 60% in patients with reduced ejection fraction. The optimal E/Ea cutoff for clinical CHF was 15 in patients with reduced (AUC 0.84, p < 0.0001)
and normal (AUC 0.87, p <0.0001) ejection fraction. E/Ea >15 had a specificity of 93% in those with normal ejection fractions compared with 72% in those with reduced ejection fractions. Comprehensive echo-Doppler had a specificity of 96% for clinical CHF in patients with normal ejection fraction (AUC 0.93, p <0.0001) compared with 80% in patients with reduced ejection fraction (AUC 0.86, p <0.0001). In patients with reduced ejection fraction, comprehensive echo-Doppler trended (p = 0.08) toward higher specificity than BNP in the diagnosis of CHF.

**DISCUSSION**

This study demonstrated that tissue Doppler-derived E/Ea and BNP have similar diagnostic accuracy for clinical CHF in this patient population. In patients with reduced ejection fraction, comprehensive echo-Doppler trended toward higher specificity than BNP for clinical CHF.

BNP has been studied in diagnosing CHF in outpatients and the emergency setting. Cowie et al demonstrated that BNP had a sensitivity of 97% and a specificity of 84% for predicting clinical CHF in the primary care setting. In the emergency room setting, BNP >100 pg/ml had a sensitivity of 90% and a specificity of 76% for CHF determined by Framingham criteria. The sensitivity of BNP >100 pg/ml in the present study was similar, but the specificity was lower. One explanation is that patients with reduced ejection fraction but without clinical CHF have elevated BNP levels. Furthermore, other causes of structural heart disease (left ventricular hypertrophy, cor pulmonale) are associated with elevated BNP levels, independent of left ventricular filling pressures.

Two-dimensional echocardiographic variables, such as ejection fraction, have been shown to be weak indicators of clinical CHF. A significant proportion (30% to 50%) of patients with clinical CHF have normal systolic function, and a reduced ejection fraction does not necessarily imply clinical CHF. Accordingly, ejection fraction was a relatively weak predictor of clinical CHF in the present study. Left atrial volume has been shown to correlate with left ventricular filling pressures and clinical CHF. In the present study, left atrial volume had reasonable sensitivity for CHF, but had low specificity, consistent with previous data indicating that patients with reduced ejection fraction may have enlarged atria independent of left ventricular filling pressure.

Previous studies have demonstrated the value of conventional Doppler (mitral inflow and pulmonary venous parameters) in detecting elevated left ventricular filling pressures. Yamamoto et al and Ommanon et al demonstrated that conventional Doppler is accurate in patients with reduced ejection fraction, but inaccurate in patients with normal ejection fraction. We previously demonstrated that tissue Doppler-derived mitral E/Ea correlates with left ventricular filling pressure measured invasively in patients with normal and reduced ejection fraction. Ommen et al demonstrated that, whereas E/Ea correlates with left ventricular filling pressure, comprehensive echo-Doppler was the most accurate test.

Although BNP and conventional Doppler have been assessed in the detection of CHF, the impact of ejection fraction on the accuracy of BNP has not been assessed. Maisel et al demonstrated that BNP cannot reliably differentiate nonsystolic CHF from systolic CHF. In the present study, BNP was less specific for clinical CHF in patients with reduced ejection fraction, although it was specific for CHF in patients with normal ejection fraction (i.e., because BNP is elevated by reduced ejection fraction alone), its utility in such patients for identifying clinical congestion is limited. Accordingly, different cutoffs for diagnosing CHF were needed for patients with normal ejection fraction (150 pg/ml) than with reduced ejection fraction (300 pg/ml). Although the specificity of E/Ea was lower in patients with reduced ejection fraction, the same cutoff for E/Ea (>15) was needed. Finally, comprehensive echo-Doppler was sensitive and specific for CHF in any ejection fraction, and trended toward higher specificity (80%) than BNP (60%) in patients with reduced ejection fraction.

The determination of CHF in this study was clinical using Framingham criteria. It may be argued that a better reference standard for CHF is invasive measurements. However, it is not feasible in the clinical setting to subject all hospital inpatients with suspected CHF to catheterization, and CHF is ultimately a clinical diagnosis. Furthermore, the Framingham criteria were shown to be highly predictive (90%) of elevated left ventricular filling pressure measured invasively, and have been shown to predict prognosis in patients with CHF. Although comprehensive Doppler echocardiography trended toward higher specificity than BNP for the detection of CHF in patients with reduced EF, this study was not sufficiently powered to detect a difference at a significance of p <0.05 in that subgroup. Finally, the present study assessed BNP and comprehensive Doppler echocardiography in the diagnosis of clinical CHF in hospitalized patients with suspected CHF who were undergoing treatment with diuretics; thus, the results may not apply to the primary care (outpatient or emergency room) settings where patients may be treatment-naive.

**Conclusions:** BNP and tissue Doppler-derived mitral E/Ea have similar diagnostic accuracy for clinical CHF in hospitalized patients. In patients with reduced ejection fraction, comprehensive Doppler echocardiography trended toward higher specificity than BNP in detecting CHF.