Optimal Noninvasive Assessment of Left Ventricular Filling Pressures

A Comparison of Tissue Doppler Echocardiography and B-Type Natriuretic Peptide in Patients With Pulmonary Artery Catheters

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Background—Early transmitral velocity/tissue Doppler mitral annular early diastolic velocity (E/Ea) and B-type natriuretic peptide (BNP) have been correlated with left ventricular filling pressures, yet there are no data on how these 2 estimates of left ventricular filling pressures compare.

Methods and Results—Patients admitted to intensive care underwent simultaneous tissue Doppler echocardiography, BNP measurement, and pulmonary capillary wedge pressure (PCWP) determination. The ability of mitral E/Ea and BNP to predict PCWP >15 mm Hg was assessed. Fifty patients were studied. Ln BNP had a correlation of \( r=0.32 \) (\( P=0.02 \)) with PCWP compared with \( r=0.69 \) (\( P<0.001 \)) between E/Ea and PCWP. E/Ea >15 was the optimal cutoff to predict PCWP >15 mm Hg (sensitivity, 86%; specificity, 88%), whereas the optimal BNP cutoff was >300 pg/mL (sensitivity, 91%; specificity, 56%). The correlation between change in PCWP and change in E/Ea at 48 hours was \( r=0.87 \) (\( P=0.003 \)) compared with \( r=-0.59 \) (\( P=0.39 \)) for BNP. In the 36 patients with cardiac disease, E/Ea >15 (sensitivity, 92%; specificity, 91%) appeared more accurate than BNP >400 pg/mL (sensitivity, 92%; specificity, 51%), whereas in patients without cardiac disease, BNP (sensitivity, 81%; specificity, 83%) appeared more accurate than E/Ea >15 (sensitivity, 74%; specificity, 72%) for PCWP >15 mm Hg.

Conclusions—In intensive care unit patients, mitral E/Ea has a better correlation than BNP with PCWP. Both BNP and mitral E/Ea have high sensitivity for PCWP >15 mm Hg; however, E/Ea appears more specific in this patient population. In patients without cardiac disease, BNP appears more accurate than E/Ea for PCWP >15 mm Hg, whereas E/Ea appears more accurate in patients with cardiac disease. (Circulation. 2004;109:2432-2439.)

Key Words: natriuretic peptides ■ hemodynamics ■ echocardiography ■ heart failure

Many critically ill patients have clinical and radiographic findings that cast doubt on left ventricular filling pressures (LVFP). Pulmonary artery catheters have been used to measure LVFP and guide patient management. However, given their cost, their complications, and evidence from recent studies that they either have a neutral\(^1\) or negative\(^2\) effect on intensive care unit (ICU) patient outcome, a reliable noninvasive method for the estimation of LVFP is needed.

B-type natriuretic peptide (BNP) is a 32–amino acid protein that is released from the cardiac ventricles in response to myocyte stretch.\(^3\) BNP has been shown to predict clinical congestive heart failure (CHF) in the emergency room setting\(^4\) and has been correlated to LVFP measured invasively in patients with depressed left ventricular ejection fraction (EF) and CHF.\(^5,6\) There is no information, however, on how BNP performs in patients with mixed disorders (cardiac and noncardiac) in whom the clinical scenario mandates monitoring of LVFP. In addition, there are few data on the accuracy of repeated BNP measurements compared with invasive LVFP estimates in patients undergoing intensive medical therapy.

Tissue Doppler (TD) echocardiography is a novel technique that directly measures myocardial velocities.\(^7\) The early diastolic mitral annular velocity (Ea) has been shown to be a relatively load-independent measure of myocardial relaxation in patients with cardiac disease.\(^7\) When TD is combined with pulsed Doppler transmitral flow in early diastole (E), the resultant E/Ea ratio has been correlated with LVFP measured invasively.\(^7,8\) However, although mitral E/Ea and BNP have both been proposed for the assessment of LVFP, there has been no direct comparison between the 2 modalities in patients with indwelling pulmonary artery catheters. Therefore, the objective of this study was to compare these 2 noninvasive techniques of LVFP estimation in ICU patients.
using pulmonary capillary wedge pressure (PCWP) as the reference standard.

Methods
The research protocol was approved by the Baylor Institutional Review Board. All participating patients gave informed consent.

Patient Population
Consecutive patients admitted to the ICU or coronary care unit at our institution who had an indwelling pulmonary artery catheter were eligible. Pulmonary artery catheters were inserted by the critical care attending physician for clinical reasons, not for the sole purposes of this study. Exclusion criteria were atrial fibrillation, paced rhythm, severe mitral regurgitation, mitral stenosis, mitral prolapse, severe mitral annular calcification, acute myocardial infarction, unstable angina, and coronary artery bypass surgery within 72 hours.

Patients with cardiac disease were defined as having either clinical evidence of cardiac disease (prior myocardial infarction, angina, heart surgery, percutaneous coronary intervention, known CHF or depressed systolic function, right heart failure) or echocardiographic evidence (enlarged cardiac chambers indexed to body surface area, reduced LV or right ventricular [RV] systolic function, significant valvular disease [any stenosis, regurgitant lesion greater than mild], or significant pericardial or aortic disease).9

Studies
PCWP Determination
Swan-Ganz catheters were positioned in the main pulmonary artery and confirmed by chest radiography. Catheters were then advanced with the distal balloon inflated to an occlusive position identified by characteristic changes in mean pressure values and waveform. Catheters were flushed with normal saline; transducers were positioned at the level of the mid right atrium with patients in the supine position and zeroed before measurement. PCWP determinations were performed at the level of the right atrium with patients in the supine position and confirmed by chest radiography. Catheters were then advanced with the distal balloon inflated to an occlusive position identified by characteristic changes in mean pressure values and waveform. PCWP determinations were performed 3 times consecutively, and measurements were averaged. All invasive hemodynamic data were obtained without knowledge of BNP and echocardiographic data.

BNP Determination
Venous blood (2 mL) was drawn from consenting patients and placed in a Triage B-Type Natriuretic Peptide test slide (Biosite Diagnostics) and analyzed in the Biosite MeterPlus machine, a point-of-care test based on fluorescence immunoassay. The test has a range of 5 to 1300 pg/mL.

Echocardiography and Doppler
Two-dimensional measurements were performed according to recommendations of the American Society of Echocardiography10 and included EF by the previously validated multidiameter method11 and maximal left atrial volume (LAV) by the method of discs.12 An EF <50% was defined as normal; an EF <50% was defined as reduced.13 Pulsed Doppler was used to record transmitral and pulmonary venous flow in the apical 4-chamber view.14 TD velocities were acquired at the septal and lateral annular sites as previously described.7

Studies were analyzed by an echocardiologist blinded to all clinical, hemodynamic, and BNP data. Transmitral flow 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 systolic, diastolic, and atrial reversal (Ar) velocities; systolic filling fraction; and duration of Ar.14 The early diastolic (Ea) velocity by TD at the septal and lateral annular sites was measured and the E/Ea ratio was computed from the average of the septal and lateral Eas because this approach has been shown to yield optimum accuracy in patients with regional wall motion abnormalities.15

Statistical Analysis
Continuous data are presented as mean±SD and categorical data as numbers (percent). Natural log transformation was performed on BNP values because of nonlinear distribution. Sensitivity, specificity, positive and negative predictive values, and accuracy for PCWP >15 mm Hg were computed by use of standard definitions. Receiver-operating characteristic (ROC) curves were constructed to determine optimal sensitivity and specificity. For continuous variables, differences between patients with and without PCWP >15 mm Hg were compared by unpaired t tests. For dichotomous parameters, the χ² test was used. Univariate and multivariate logistic regression analyses were performed on variables included in the echocardiographic and BNP model for prediction of PCWP >15 mm Hg. A value of P<0.05 was significant. Analyses were performed with SigmaStat 3.0.

Results
Patient Population
Of the 57 patients screened; 4 were excluded for atrial fibrillation, 2 for severe mitral regurgitation, and 1 for acute

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics</th>
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<tr>
<td>All Patients (n = 50)</td>
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<tr>
<td>CD (n = 35)</td>
</tr>
<tr>
<td>No CD (n = 15)</td>
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<tr>
<td>EF &lt;50% (n = 31)</td>
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<td>EF ≥50% (n = 19)</td>
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<td>Prior PCI, n (%):</td>
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<td>Prior CABG, n (%):</td>
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<td>Intubated, n (%):</td>
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CD indicates cardiac disease; MI, myocardial infarction; CABG, coronary artery bypass grafting surgery; and PCI, percutaneous coronary intervention.

*P<0.05 for comparison between cardiac disease and no cardiac disease.
†P<0.05 for comparison between EF <50% and EF ≥50%.
myocardial infarction. Thus, 50 patients were enrolled in the study. The mean age of the patients was 59.8 years, and 48% were female. The admitting diagnoses were CHF (18 patients), respiratory failure of unknown origin (10 patients), vascular surgery (8 patients), shock (6 patients), abdominal surgery (5 patients), and trauma (3 patients). The baseline characteristics of the study group are listed in Table 1, and the hemodynamic, echocardiographic, and BNP data of the population are displayed in Table 2.

**Correlation Between Echocardiographic Measurements, BNP, and PCWP**

There were significant correlations between PCWP and various echocardiographic and BNP parameters: EF (R = 0.50, P < 0.001), LAV index (R = 0.54, P < 0.001), mitral E/A (R = 0.55, P < 0.001), mitral deceleration time (R = 0.60, P < 0.001), pulmonary venous systolic filling fraction (R = 0.59, P < 0.001), and pulmonary venous Ar duration minus mitral A-wave duration (R = 0.58, P = 0.004). Of these parameters, mitral E/Ea (R = 0.69, P < 0.001) had the best correlation with PCWP, whereas Ln BNP had a correlation of R = 0.32 (P = 0.02) with PCWP (Figure 1). When mitral E/Ea, Ln BNP, and LVEF were included in a multiple logistic regression model for PCWP > 15 mm Hg (other variables were excluded because of significant overlap), mitral E/Ea (OR, 1.5; P = 0.003) performed best. BNP trended toward significance (OR, 2.5; P = 0.06), and LVEF (OR, 1.0; P = 0.5) was not significant.

Pulmonary venous systolic filling fraction had a correlation of R = 0.58 with mitral E/Ea and 0.45 with Ln BNP (P < 0.001 for all). Mitral A-wave duration minus pulmonary venous Ar duration had a correlation of R = 0.63 with mitral E/Ea and 0.51 with Ln BNP (P < 0.001 for all).

**TD Echocardiography and BNP in Patients With Normal and Reduced EF**

The population of 50 patients was divided into those with EF < 50% (31 patients) and EF ≥ 50% (19 patients) and then further subdivided into those with PCWP ≤ 15 mm Hg and > 15 mm Hg (Figure 2A and B). Of the 31 patients with EF < 50%, there were significant differences in E/Ea between those with PCWP ≤ 15 mm Hg (8 patients) and those with EF ≥ 50%.
>15 mm Hg (23 patients), although there were no significant differences in their mean BNP levels. A similar pattern was seen in the 19 patients with EF <50% divided into PCWP ≤15 mm Hg (10 patients) and >15 mm Hg (9 patients).

There were significant BNP elevations in patients with PCWP ≥15 mm Hg and EF ≥50% (mean BNP, 653.0 pg/mL) and PCWP ≤15 mm Hg and EF ≥50% (mean BNP, 388.3 pg/mL).

**Diagnostic Accuracy of BNP and TD for Estimating PCWP ≥15 mm Hg**

The ROC curves for BNP and mitral E/Ea in the prediction of PCWP ≥15 mm Hg are shown in Figure 3. In all 50 patients, the optimal cutoff for BNP was >300 pg/mL (sensitivity, 91%; specificity, 56%), whereas the optimal cutoff for E/Ea was >15 (sensitivity, 85%; specificity, 88%). In the 31 patients with EF <50%, the optimal cutoff for BNP was >400 pg/mL (sensitivity, 96%; specificity, 50%), whereas the optimal cutoff for E/Ea was >15 (sensitivity, 92%; specificity, 90%). In the 19 patients with EF ≥50%, the optimal cutoff for BNP was >250 pg/mL (sensitivity, 89%; specificity, 60%), whereas the optimal cutoff for E/Ea was >11 (sensitivity, 78%; specificity, 80%). In all 50 patients, adding E/Ea >15 to BNP >300 mm Hg (both criteria needed) resulted in a sensitivity of 77% and a specificity of 94% for detection of PCWP >15 mm Hg.

**Mitral E/Ea Between 8 and 15**

Because mitral E/Ea from 8 to 15 can be a “gray zone” for the estimation of LVFP, we analyzed this group separately. Of the 50 patients in the study, 14 (28%) had E/Ea of 8 to 15. Compared with the 5 patients in this group with PCWP >15 mm Hg, the 9 patients with PCWP ≤15 mm Hg had the following variables: BNP, 473.5±445.1 versus 723.7±283.1 pg/mL (P=0.30); deceleration time, 181.5±35.8 versus 132.2±26.1 cm/s (P=0.04); mitral E/A, 0.9±0.2 versus 2.1±0.2 (P=0.02); and pulmonary venous systolic filling fraction, 0.67±0.18 versus 0.47±0.16 (P=0.19). When mitral inflow, pulmonary venous, and LAV parameters (comprehensive echo Doppler) were considered in patients with E/Ea of 8 to 15, patients with PCWP >15 mm Hg were detected with 79% sensitivity and 90% specificity.

**BNP Elevations in Patients With Normal LVFP**

The determinants of elevated BNP in patients without elevated LVFP were analyzed. Of the 50 patients in the study, 16 (32%) had PCWP ≤15 mm Hg. In these patients, Ln BNP had the best correlation with TD systolic annular velocity (Sa; R=0.53, P=0.04), LV mass (R=0.50, P=0.05), LVEF (R=0.49, P=0.05), and RV fractional area change (R=0.45, P=0.10). These correlations are displayed in Figure 4.
The population was divided into patients with (35 patients; mean age, 61.3±12.9 years) and without (15 patients; 55.8±14.7 years, P=0.21) cardiac disease. The final diagnoses in the patients without cardiac disease were adult respiratory distress syndrome (5 patients), sepsis (4), trauma (3), abdominal surgery (2), and volvulus (1). There were significant differences in several variables between patients with and without cardiac disease: EF (32.8±16.8% versus 64.5±7.4%, P<0.001), BNP (956.8±428.0 versus 417.4±408.1 pg/mL, P<0.001), E/Ea (18.1±6.1 versus 12.3±5.7, P=0.006), LV volume (155.7±45.9 versus 114.8±22.2 mL, P=0.006), and Ea (6.0±1.7 versus 7.5±2.6 cm/s, P=0.01).

In patients without cardiac disease, BNP >250 pg/mL had a sensitivity of 81%, a specificity of 83%, and an accuracy of 82% for PCWP >15 mm Hg compared with 74%, 72%, and 67%, respectively, for E/Ea >11. In patients with cardiac disease, BNP >400 pg/mL had a sensitivity of 90%, a specificity of 57%, and an accuracy of 83% for PCWP >15 mm Hg compared with 92%, 81%, and 89%, respectively, for E/Ea >15.

**Repeated Measurements**

Nine patients underwent repeated simultaneous measurement of BNP, mitral E/Ea, and PCWP 48 hours after the initial assessment. Of these patients, 8 of 9 (89%) were undergoing treatment with intravenous inotropes, and 5 of 9 (56%) were being treated with intravenous diuretics. The mean EF of this group was 47.3±17.5%. At 48 hours, the correlation of absolute change in PCWP and corresponding change in Ln BNP was r=−0.59 (P=0.39) compared with a correlation of change in PCWP with change in E/Ea of r=0.87 (P=0.003) (Figure 5).

**Discussion**

In this study, the correlation between E/Ea and PCWP in ICU patients with indwelling pulmonary artery catheters appears...
to be better than the correlation between BNP and PCWP. Second, patients with depressed EF yet PCWP ≤15 mm Hg had significant BNP elevations, as did patients with normal EF and PCWP ≤15 mm Hg. Third, temporal changes in PCWP were better tracked by changes in mitral E/Ea than changes in BNP. Finally, although E/Ea appeared to have better accuracy than BNP for PCWP ≤15 mm Hg in patients with cardiac disease, BNP appeared to have better accuracy in patients without cardiac disease.

B-Type Natriuretic Peptide

Previous studies have demonstrated that BNP correlates with PCWP and LV end-diastolic pressure in CHF patients with depressed EF. Kazanegra et al demonstrated a correlation (R=0.72) between BNP and PCWP in CHF patients with depressed EF. Although some patients had a reduction in BNP with PCWP reduction with therapy, others did not have a change in BNP. Furthermore, patients with a reduction in BNP still had significant elevation of BNP despite normalization of PCWP. Maeda et al demonstrated similar findings correlating LV end-diastolic pressure with BNP in patients with systolic heart failure.

In the present study, the correlation between BNP and PCWP was lower than in the studies cited above. This difference is likely due to the heterogeneity of the current population: patients with normal and abnormal EF, cardiac and noncardiac disease, and various admitting diagnoses and a “sicker” population (42% intubated). However, our findings with respect to repeated measurements are in keeping with these prior studies. All 3 studies (including the present study) demonstrate that in a significant number of patients (“nonresponders”), BNP does not change despite a significant reduction in PCWP in patients undergoing treatment. Even in “responders,” BNP, although decreasing, remains elevated despite a PCWP ≤15 mm Hg.

Potential reasons for this apparent “BNP memory” include the findings in the present study of significant correlations between BNP and LV mass, LVEF, RV fractional area change, and LV Sa in patients with PCWP ≤15 mm Hg. These features, suggestive of LV and RV myocardial disease, may be associated with BNP elevations regardless of filling pressures, a finding that is supported by recent studies. In addition, because BNP has a lower affinity for natriuretic peptide clearance receptor-C, it has a longer half-life than ANP, which may contribute to its memory.

TD Imaging

We have previously demonstrated that mitral E/Ea correlates with PCWP in patients with indwelling pulmonary artery catheters. We have also previously demonstrated that Dopp-
Accuracy of BNP and TD Echocardiography in Patients With and Without Cardiac Disease

BNP appeared to be more accurate than E/Ea in predicting PCWP >15 mm Hg in patients without cardiac disease, whereas E/Ea appeared to be more accurate in patients with cardiac disease. It has been shown that BNP is elevated by increased LV mass and decreased LVEF, independent of LVFP.16,17 Thus, its specificity for determining PCWP >15 mm Hg in such patients appears limited. However, in patients without cardiac disease, BNP appeared more accurate than E/Ea. It has been shown that Ea is relatively load independent in patients with cardiac disease but load dependent in patients without cardiac disease.20 Thus, E/Ea had lower accuracy in patients without cardiac disease because Ea itself is altered by volume shifts, adversely influencing E/Ea.

Study Limitations

The number of patients in the present study was relatively small; however, we were able to reach several significant observations. This study included a heterogeneous population of patients admitted to the ICU who had indwelling pulmonary artery catheters. Thus, the findings may vary if only patients with depressed EF and a diagnosis of CHF are included. However, this study likely better reflects the utility of BNP and E/Ea in a “real-world” ICU population with a mix of cardiac and noncardiac disorders in whom there is a clinical indication for pulmonary artery catheters.

Conclusions

TD-derived mitral E/Ea has a better correlation than BNP with PCWP in critically ill patients with indwelling pulmonary artery catheters. Although BNP has high sensitivity for PCWP >15 mm Hg, the specificity was lower because of BNP elevations from depressed EF and myocardial disease, in the absence of elevated PCWP. Because E/Ea is less affected by these variables, it appears to have better diagnostic accuracy than BNP for detecting PCWP >15 mm Hg in unselected ICU patients. However, in ICU patients with neither clinical nor echocardiographic evidence of cardiac disease, BNP appears to have better diagnostic accuracy than TD echocardiography for estimation of LVFP.

References

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