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Incremental Predictive Power of B-Type Natriuretic Peptide and Tissue Doppler Echocardiography in the Prognosis of Patients With Congestive Heart Failure

Hisham Dokainish, MD, FACC, William A. Zoghbi, MD, FACC, Nasser M. Lakkis, MD, FACC, Eunice Ambriz, RN, MPH, Rajnikant Patel, MD, Miguel A. Quinones, MD, FACC, Sherif F. Nagueh, MD, FACC

Houston, Texas

OBJECTIVES This study was designed to determine how novel indexes of left ventricular (LV) filling pressure—transmitral early diastolic velocity/tissue Doppler mitral annular early diastolic velocity (E/Ea) and B-type natriuretic peptide (BNP)—compare to conventional predictors of outcome in patients with congestive heart failure (CHF).

BACKGROUND It is known that E/Ea can predict LV filling pressure in patients with cardiac disease, including, in contrast to conventional Doppler indexes, in normal ejection fraction. B-type natriuretic peptide has also been correlated to LV filling pressure, but appears to provide more global cardiac information than E/Ea. It is unknown, however, how these novel indexes compare to conventional predictors of CHF patient outcome.

METHODS A total of 116 consecutive patients hospitalized with CHF underwent simultaneous clinical assessment, BNP, and comprehensive echo-Doppler study once ready for discharge. The ability of these variables to determine the primary end point (cardiac death or re-hospitalization for CHF) was determined.

RESULTS Follow-up was complete on 110 of 116 patients at a mean of 527 days after hospital discharge. There were 54 patients (50%) with the primary end point (37 re-hospitalizations for CHF and 17 cardiac deaths). On Cox univariate analysis, E/Ea (chi-square = 13.6, $p = 0.0001$) and BNP (chi-square = 17.0, $p < 0.0001$) were significant predictors of the primary end point. In stepwise analysis, BNP ≥250 pg/ml and mitral E/Ea ≥15 had incremental predictive power (chi-square = 23.1, p for increment = 0.02), to which conventional predictors did not add further prognostic information.

CONCLUSIONS In patients admitted to hospital with CHF, pre-discharge BNP and E/Ea are incremental predictors of outcome, to which conventional predictors do not significantly add. (J Am Coll Cardiol 2005;45:1223–6) © 2005 by the American College of Cardiology Foundation

Conventional predictors for congestive heart failure (CHF) prognosis include clinical variables, two-dimensional echocardiographic parameters (left ventricular [LV] ejection fraction [EF]), and conventional Doppler indexes of LV filling pressure (mitral inflow) (1). Newer parameters used in the diagnosis of heart failure include B-type natriuretic peptide (BNP), a neurohormone secreted from the cardiac ventricles in response to myocyte stretch (2), and transmitral early diastolic velocity/tissue Doppler (TD) early diastolic mitral annular velocity (E/Ea), a method of estimating LV filling pressures (3,4). However, it is unknown how these novel indexes compare to conventional predictors of outcome in patients with CHF.

From the Department of Medicine, Section of Cardiology, Baylor College of Medicine, Houston, Texas. Dr. Dokainish is supported by the Harry B. Graf Career Development Award in Cardiac Disease Prevention from the American College of Cardiology Foundation, and by the Methodist Hospital Foundation Grant.

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METHODS

The study was approved by the Baylor College of Medicine Institutional Review Board.

Patient population. Consecutive inpatients admitted for CHF were eligible. The diagnosis of CHF was made using the Framingham criteria (5). After treatment with appropriate medications, and within 24 h of hospital discharge as determined by the attending physician, subjects underwent simultaneous (<20 min apart) echo-Doppler examination and BNP measurement. Patients were excluded if they had non-sinus rhythm, significant mitral valve disease, unstable angina, acute myocardial infarction, or coexisting terminal diseases.

Studies. BNP DETERMINATION. Two milliliters of venous blood were placed within 30 min on a Triage BNP test slide (Biosite Diagnostics, San Diego, California) and analyzed in the Biosite MeterPlus machine.

ECHOCARDIOGRAPHY AND DOPPLER. Two-dimensional measurements were performed according to recommendations of the American Society of Echocardiography (6) and indexed to body surface area. Ejection fraction was

Abbreviations and Acronyms

AUC = area under curve
BNP = B-type natriuretic peptide
CHF = congestive heart failure
DT = deceleration time
E/Ea = transmitral early diastolic velocity/tissue Doppler early diastolic annular velocity
EF = ejection fraction
LAVi = left atrial volume index
Ln = natural log
LV = left ventricular
TD = tissue Doppler

calculated by the multidiameter method. Pulsed Doppler was used to record transmitral and pulmonary venous flow in the apical four-chamber view (7). Tissue Doppler velocities were acquired at the septal and lateral annular sites and averaged as previously described (3,4). Studies were analyzed by an echocardiologist blinded to all clinical data (including patient outcome) and BNP values.

END POINTS AND DEFINITIONS. The primary end point was the combined risk of cardiac mortality or re-hospitalization for CHF. Only one event was considered in each patient.

STATISTICAL ANALYSIS. For dichotomous parameters, the chi-square test was used, and for continuous variables, the Student *t* test was used. Univariate Cox proportional hazards analysis was used to adjust for time-to-event, and stepwise Cox proportional hazards analysis was used to determine the incremental prognostic power of predictors of outcome, commencing with predictors with the most variability. Natural log (Ln) transformation was performed on BNP values because of skewed distribution. A p value of ≤ 0.05 was significant. Analyses were performed using SigmaStat 3.0 (Chicago, Illinois) and GB Stat 6.5 (London, United Kingdom).

RESULTS

Prognosis of patients with CHF. Of the 145 patients admitted to our institution with a clinical diagnosis of CHF, 116 met the inclusion criteria for the study. Thirteen patients were excluded for non-sinus rhythm, five for myocardial infarction, four for unstable angina, four for coexisting terminal disease, and three for severe mitral regurgitation. Follow-up was complete on 110 of 116 patients (95%) (mean time from hospital discharge to follow-up of 527 ± 47 days). There were 54 of 110 patients (50%) who reached the primary end point (17 cardiac deaths, 37 re-admissions for CHF). The only difference in baseline clinical characteristics (Table 1) between patients who reached the primary end point and patients who did not was an admission to hospital in the preceding year for CHF (45% vs. 18%, respectively, p = 0.03).

The echocardiographic and BNP values in patients with and without an event are depicted in Table 2. There were 54 of 110 patients (49%) with an EF <35%, and 69 of 110 patients (63%) with an EF <50%. Mitral E/Ea (19.2 ± 6.5 vs. 14.2 ± 6.6, p = 0.0003) and BNP (506.2 ± 352.7 vs. 293.3 ± 362.2 pg/ml, p = 0.005) were higher in patients with an event compared to patients without an event.

Table 1. Baseline Characteristics

Variable, n (%)	Event (n = 54)	No Event (n = 56)	p Value
Age (yrs)	58.6 ± 13.0	56.1 ± 11.8	0.30
Gender (male)	26 (49)	32 (56)	0.96
Diabetes	26 (49)	23 (40)	0.93
Hypertension	44 (83)	41 (72)	0.75
Current smoker	25 (47)	20 (35)	0.76
History of CHF	35 (66)	22 (39)	0.08
CHF admission in previous year	24 (45)	10 (18)	0.03
Previous myocardial infarction	14 (26)	12 (21)	0.97
Previous angioplasty/stent	2 (0.4)	7 (1.4)	0.61
Previous CABG	4 (0.8)	3 (0.5)	0.99
Beta-blocker on discharge	26 (50)	30 (53)	0.98
ACE inhibitor on discharge	42 (79)	44 (77)	0.90
Diuretic on discharge	49 (93)	52 (91)	0.95
Digoxin on discharge	7 (14)	9 (15)	0.96

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; CHF = congestive heart failure.

In univariate Cox proportional hazards analysis using continuous data, mitral E/Ea (chi-square = 13.6, p = 0.0001) and Ln BNP (chi-square = 17.0, p < 0.0001) were among the significant predictors of re-hospitalization for CHF or cardiac death (Table 3). By receiver-operating characteristic analysis, E/Ea ≥15 (area under curve [AUC] = 0.73, p < 0.0001) and BNP ≥250 pg/ml (AUC = 0.71, p = 0.0001) were the optimal cutoffs to predict the primary end point. The Kaplan-Meier curves for E/Ea ≥15 and BNP ≥250 pg/ml are displayed in Figures 1A and 1B, respectively. Compared to individual echo-Doppler variables, BNP did not have significantly different predictive power from E/Ea or left atrial volume index (LAVi) (p = NS for both comparisons), but had higher predictive power than EF (p = 0.02) and mitral deceleration time (DT) (p = 0.01).

Stepwise analysis for incremental predictive power of variables. Having the highest variability for predicting the primary end point, BNP ≥250 pg/ml was applied in the first step of multivariate analysis (chi-square = 17.0, p = 0.001). To this was added the variable with the next highest variability, E/Ea ≥15, resulting in a chi-square of 23.1 (p for increment 0.02). The remaining significant predictors with highest variability in the dataset (LAVi, TD mitral annular late diastolic velocity, EF) did not incrementally add to BNP ≥250 pg/ml plus E/Ea ≥15.

DISCUSSION

To our knowledge, this is the first study to demonstrate the incremental predictive power of pre-discharge BNP and E/Ea in determining CHF patient outcome and to show that adding conventional predictors to these novel indexes does not significantly increase that power.