Published in final edited form as:
Am Heart J. 2008 December ; 156(6): 1191–1195. doi:10.1016/j.ahj.2008.07.022.

Independent Prognostic Value of Echocardiography and NT-proBNP in Patients with Heart Failure

Alan L. Hinderliter, MD[a], **James A. Blumenthal, PhD**[b], **Christopher O'Conner, MD**[b], **Kirkwood F. Adams, MD**[a], **Carla Sueta Dupree, MD, PhD**[a], **Robert A. Waugh, MD**[b], **Daniel Bensimhon, MD**[b], **Robert H. Christenson, PhD**[c], and **Andrew Sherwood, PhD**[b]

[a]University of North Carolina, Chapel Hill, NC

[b]Duke University Medical Center, Durham, NC

[c]University of Maryland School of Medicine, Baltimore, MD

Abstract

Background—Echocardiographic indices of cardiac structure and function and natriuretic peptide levels are strong predictors of mortality in patients with heart failure. Whether cardiac ultrasound and natriuretic peptides provide independent prognostic information is uncertain.

Methods—Echocardiograms and measurements of N-terminal pro-B type natriuretic peptide (NT-proBNP) were prospectively performed in 211 patients with left ventricular systolic dysfunction who were followed for a median of 4 years. Echocardiographic variables and NT-proBNP were examined as predictors of all-cause mortality in univariable and multivariable proportional hazards models.

Results—Participants averaged 57 (SD 12) years of age and had a mean left ventricular ejection fraction of 32 (SD 11) %. A total of 71 patients (34%) died during the follow-up period. NT-ProBNP was a strong predictor of mortality ($P < 0.001$) as were multiple echocardiographic measures. In models that included age and NT-proBNP, with other clinical variables eligible for entry by stepwise selection, significant predictors of death included left ventricular ejection fraction ($P = 0.013$) and end-diastolic volume ($P < 0.001$), left atrial volume index ($P = 0.005$), right atrial volume index ($P = 0.003$), and tricuspid regurgitation area ($P = 0.015$). In models that also included left ventricular ejection fraction, end-diastolic volume of the left ventricle ($P = 0.019$), left atrial volume ($P = 0.026$), and right atrial volume ($P = 0.020$) remained significant predictors of mortality.

Conclusions—Left ventricular size and function and left atrial and right atrial sizes are significant predictors of all-cause mortality in patients with heart failure, independent of NT-proBNP levels and other clinical variables.

Echocardiography is an important tool in the evaluation of patients with heart failure. A comprehensive two-dimensional and Doppler echocardiogram provides a reliable assessment of left ventricular and right ventricular function and of the severity of associated valvular lesions. In addition to providing insight into the etiology of heart failure,

Corresponding author: Alan L. Hinderliter, Division of Cardiology, University of North Carolina, CB# 7075, Burnett-Womack Building, Chapel Hill, NC 27559-7075, Phone 919-843-5447; fax 919-966-1743, hinderli@med.unc.edu.

echocardiographic data is valuable in assessing prognosis. The degree of left ventricular remodeling[1,2], left ventricular dysfunction[2,3,4], impaired left ventricular filling[1,3], left atrial enlargement[5], right ventricular dysfunction[6,7], and mitral and tricuspid regurgitation[1,8,9] are all predictors of adverse outcomes.

Recent studies have demonstrated that B type natriuretic peptide (BNP) and its precursor, N-terminal proBNP (NT-proBNP), are strong predictors of morbidity and mortality in patients with chronic heart failure.[10] Whether echocardiography provides incremental prognostic information is uncertain. The objective of this study was to assess the prognostic utility of widely available echocardiographic parameters after accounting for age, NT-proBNP levels, and other predictors of mortality in patients with heart failure and severe left ventricular dysfunction.

METHODS

This is a prospective observational study of clinically stable patients with heart failure and left ventricular dysfunction. Baseline demographic and clinical parameters, NT-proBNP levels, and echocardiographic measures were examined as predictors of all-cause mortality and other adverse outcomes over a median follow-up interval of 4 years. The study was approved by the Institutional Review Board at Duke University Medical Center, and written informed consent was obtained from all participants prior to their participation.

Patients

The study sample consisted of 211 consecutive patients recruited from the heart failure clinics at Duke University Medical Center and the University of North Carolina at Chapel Hill from January, 2000 through December, 2002. Inclusion criteria included left ventricular ejection fraction ≤ 40% by angiography, radionuclide ventriculography, or echocardiography within the past year; and clinically stable heart failure (i.e., not requiring hospitalization or medication adjustment for decompensation for at least 3 months). Exclusion criteria included myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery in the past 3 months; and uncontrolled hypertension. Baseline assessments, measurement of NT-proBNP, and echocardiography were performed at the time of enrollment on a single visit to the research laboratory.

Baseline assessments

Demographic and clinical characteristics and medication use were determined by interview and examination of the medical record. Height, weight, and blood pressure were measured on the visit to the research laboratory. Blood specimens were acquired for measurement of serum sodium, hematocrit, and creatinine; glomerular filtration rate was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula.

NT-proBNP

Blood was collected from the antecubetal vein in a phlebotomy tube containing EDTA, centrifuged at 1000Xg for 10 minutes, and stored at −80°C. Samples were thawed within 12 months of collection for measurements of NT-proBNP using an electrochemiluminescence immunoassay (Elecsys proBNP, Roche Diagnostics Corporation, Indianapolis, IN). According to the manufacturer, NT-proBNP values are 10% lower in samples collected in EDTA tubes compared to serum or heparinized plasma.

Echocardiography

Echocardiograms were performed by a single sonographer using a defined imaging protocol, and were stored as digital loops. Two-dimensional images and Doppler flow tracings were

subsequently analyzed by an experienced echocardiographer who had no knowledge of patient clinical outcomes, using customized offline software (Access Point 2000, Freeland Systems, LLC, Westfield, Indiana). Measurements were made on 3 representative beats and the results were averaged.

The following indices of left ventricular and right ventricular size and function, left atrial and right atrial sizes, left ventricular filling, and mitral and tricuspid regurgitation were measured: 1) left ventricular ejection fraction was determined using the biplane Simpson's rule from apical 4-chamber and 2-chamber images of the heart.[11] In patients in whom poor endocardial definition precluded quantification of left ventricular volumes (n = 43), ejection fraction was estimated visually. 2) Left ventricular end-diastolic volume was determined by the biplane Simpson's rule, as described above. 3) Right ventricular function was quantified as the tricuspid annulus systolic excursion, measured as the difference between the distances from the right ventricular apex to the lateral tricuspid annulus at end-diastole and at end-systole.[6] 4) Left atrial volume was estimated by using the biplane area-length formula after determining the end-systolic areas and long axis lengths of the left atrium in the apical 4-chamber and 2-chamber views.[11] 5) Right atrial volume was calculated using the single-plane area-length method after right atrial area and long-axis length were measured in the apical 4-chamber view.[11] 6) Mitral regurgitation severity was quantified as the maximum area of the regurgitant color flow Doppler jet in the apical 2-chamber and 4-chamber views. 7) Tricuspid regurgitation severity was estimated as the maximum area of the regurgitant color flow Doppler jet in the apical 4 chamber view. 8) Deceleration time of early left ventricular filling was measured by pulsed wave Doppler, with the sample volume located at the tip of the mitral valve leaflets. Left ventricular end-diastolic volume and left atrial and right atrial volumes were indexed for body size by dividing by body surface area (BSA).

Follow-up

Each patient's medical record was reviewed annually on anniversaries of the baseline assessment by trained research assistants. Deaths were verified through hospital and Emergency Medical Service records, and the cause of death was determined by consensus of at least 3 study physicians. The median follow-up was 4 years with a range of 3–6 years. Follow-up data were available for all participants.

Analysis of Data

All analyses were performed using SAS statistical software, version 9.1. Data were summarized as mean (SD) for continuous variables and number of patients (%) for categorical variables.

The primary endpoint was all-cause mortality. Secondary endpoints included death from progressive heart failure, sudden cardiac death, and a composite endpoint of death or cardiac transplant. Cox proportional hazards modeling was used for univariable analyses of echocardiographic variables as predictors of endpoints. Each echocardiographic variable was then examined in multivariable models that included age and NT-proBNP; other variables of potential explanatory value, including gender, body mass index, etiology of heart failure (ischemic or nonischemic), history of atrial fibrillation, New York Heart Association functional class, diabetes, systolic blood pressure, heart rate, glomerular filtration rate, serum sodium, hematocrit, and QRS duration, were eligible for entry into the models by stepwise selection (significance level for entry into the model = 0.1). Echocardiographic variables that were independently predictive of adverse outcomes in these multivariable models were further evaluated in models incorporating the same variables plus left ventricular ejection fraction. Hazard ratios (HR) and their corresponding 95% confidence intervals (95% CI) were produced from the parameter estimates and

standard errors obtained from the proportional hazards models. For Cox proportional hazards models, NT-proBNP values were trimmed at the 95th percentile.

RESULTS

Baseline demographic and clinical characteristics of the patients have been described previously[12] and are summarized in Table I. Mean values for echocardiographic parameters are shown in Table II. The average age of study participants was 57 (SD 12) years, with a range of 27–88 years. Heart failure was due to coronary artery disease in 43%. Most had New York Heart Association functional class II or III heart failure at enrollment. Hypertension and diabetes were common co-morbidities. The vast majority were treated with a beta blocker and either an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. The mean NT-proBNP was 1675 (SD 2657) pg/ml, with a median value of 693 pg/ml. The left ventricular ejection fraction averaged 32 (SD 11)%. Seventeen subjects (8%) had an implantable defibrillator at the time of enrollment, and an additional 63 (30%) had a device implanted during the follow-up period.

During the follow-up period, 71 patients (34%) died; 23 died of progressive heart failure, 31 died suddenly, 2 died of other cardiac causes, and 15 died of noncardiac causes. Twelve (6%) underwent a cardiac transplant.

As shown in Table III, when examined as univariable predictors, left ventricular volume and ejection fraction, deceleration time, right ventricular function, left atrial and right atrial volumes, and severity of mitral regurgitation and tricuspid regurgitation were all significantly associated with all-cause mortality. NT-proBNP was also a strong predictor of mortality (HR = 2.02, 95% CI = 1.65 – 2.48, $P < 0.001$, for a 2,000 pg/ml change in NT-proBNP). To determine if echocardiographic measures added incremental prognostic value, models including age, NT-proBNP, and individual echocardiographic parameters, with other clinical variables eligible for entry by stepwise selection, were examined (Table IV). Left ventricular ejection fraction and end-diastolic volume, left atrial and right atrial volumes, and tricuspid regurgitation area were significant predictors of death. In models that also included left ventricular ejection fraction, end-diastolic left ventricular volume (HR = 1.22, 95% CI = 1.04–1.43, $P = 0.019$ for an increase of 25 ml/m^2), left atrial volume (HR = 1.29, 95% CI = 1.03–1.62, $P = 0.026$ for an increase of 20 ml/m^2), and right atrial volume (HR = 1.41, 95% CI = 1.06–1.89, $P = 0.020$ for an increase of 20 ml/m^2) remained significant predictors of mortality.

Echocardiographic measures were stronger predictors of death from heart failure than of sudden cardiac death. When death from heart failure was considered as the endpoint, left ventricular ejection fraction, left ventricular end-diastolic volume index, deceleration time, mitral regurgitation area, left atrial volume index, and right atrial volume index were all significant predictors of an adverse outcome in multivariable analyses, while only left ventricular ejection fraction and right atrial volume index were independent predictors of sudden cardiac death. When a composite endpoint of death or cardiac transplant was considered, all echocardiographic variables except the tricuspid annular excursion were significant predictors in multivariable models.

DISCUSSION

In our cohort of outpatients with stable heart failure, echocardiographic measurements of ejection fraction, left ventricular end-diastolic volume, left and right atrial volumes, and severity of tricuspid regurgitation were predictive of mortality after adjusting for NT-

proBNP and other clinical variables; and left ventricular, left atrial, and right atrial volumes remained significant predictors in models that also included left ventricular ejection fraction.

These findings reaffirm decades of research demonstrating the prognostic importance of left ventricular function and geometry in patients with heart failure. Although ejection fraction is influenced by loading conditions and is difficult to measure, an inverse relationship between this index of systolic function and cardiovascular mortality has been demonstrated over a wide range of severities of heart failure.[2,3,4] Similarly, the degree of left ventricular remodeling has consistently correlated with mortality in cohorts of patients with heart failure.[1,2]

More recently, left atrial enlargement has been recognized as a robust predictor of adverse cardiovascular outcomes.[5,13] Left atrial size increases in response to chronically elevated left ventricular filling pressures. As a reflection of left ventricular diastolic function over time, left atrial volume has theoretical advantages over load-dependent Doppler indices of instantaneous filling properties and the “snap-shot” view of left ventricular stretch provided by natriuretic peptides. Our observations suggest that right atrial volume may similarly be predictive of death in patients with heart failure.

Several previous studies have compared the prognostic values of natriuretic peptides and cardiac ultrasound in patients hospitalized with heart failure. Gackowski, et al,[14] performed serial echocardiograms and measurements of BNP in patients hospitalized with acute heart failure. Serial BNP measurements were more informative than repeated echocardiograms in predicting adverse cardiac events over the 60 days following admission. Dokainish, et al,[15] measured BNP and two-dimensional echocardiographic parameters in patients at the time of hospital discharge. A BNP >250 pg/ml predicted 41 of 54 cardiovascular deaths or hospitalizations for heart failure over a mean follow-up of 527 days, while high risk echocardiographic features predicted 51 of 54 events ($p = 0.51$). BNP was more cost effective than echocardiography. Dokainish, et al,[16] also reported that predischarge BNP and mitral annular tissue Doppler velocities were independent predictors of death or rehospitalization, while other more conventional echocardiographic parmeters, such as ejection fraction, left ventricular end-diastolic volume, left atrial volume, and deceleration time, were not predictive of adverse events in multivariable analyses. We are not aware of previous studies that have examined the incremental prognostic values of echocardiography and natriuretic peptide levels in outpatients with stable heart failure.

In summary, cardiac ultrasound and natriuretic peptide levels provide important prognostic information in patients with stable, advanced heart failure. Echocardiographic measures of left ventricular size and function and of left atrial and right atrial sizes are significant predictors of mortality, independent of NT-proBNP levels and other clinical variables.

Acknowledgments

This study was supported by Grant HL61784 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, and grant M01-RR-30 from the General Clinical Research Center program, National Center for Research Resources, National Institutes of Health.

The authors gratefully acknowledge the assistance of Rosamond Hylton in preparation of the manuscript.

References

1. Grayburn PA, Appleton CP, DeMaria AN, et al. Echocardiographic predictors of morbidity and mortality in patients with advanced heart failure. J Am Coll Cardiol. 2005; 45:1064–1071. [PubMed: 15808765]

2. St John Sutton M, Pfeffer MA, Moye L, et al. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. Circulation. 1997; 96:3294–3299. [PubMed: 9396419]
3. Rihal CS, Nishimura RA, Hatle LK, et al. Systolic and diastolic dysfunction in patients with clinical diagnosis of dilated cardiomyopathy. Relation to symptoms and prognosis. Circulation. 1994; 90:2772–2779. [PubMed: 7994820]
4. Parameshwar J, Keegan J, Sparrow J, et al. Predictors of prognosis in severe chronic heart failure. Am Heart J. 1992; 123:421–426. [PubMed: 1736580]
5. Rossi A, Cicoira M, Zanolla L, et al. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. J Am Coll Cardiol. 2002; 40:1425–1430. [PubMed: 12392832]
6. Ghio S, Recusani F, Klersy C, et al. Prognostic usefulness of tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol. 2000; 85:837–842. [PubMed: 10758923]
7. Meluzin J, Spinarova L, Dusek L, et al. Prognostic importance of the right ventricular function assessed by Doppler tissue imaging. Eur J Echocardiogr. 2003; 4:262–271. [PubMed: 14611821]
8. Blondheim DS, Jacobs LE, Kotler MN, et al. Dilated cardiomyopathy with mitral regurgitation: decreased survival despite a low frequency of left ventricular thrombus. Am Heart J. 1991; 122:763–771. [PubMed: 1877453]
9. Koelling TM, Aaronson KD, Cody RJ, et al. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. Am Heart J. 2002; 144:524–529. [PubMed: 12228791]
10. Doust JA, Pietrzak E, Dobson A, et al. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ. 2005; 330:625–633. [PubMed: 15774989]
11. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18:1440–1463. [PubMed: 16376782]
12. Sherwood A, Blumenthal JA, Trivedi R, et al. Depression and antidepressant medication use affect mortality and hospitalization in patients with congestive heart failure. Arch Int Med. 2007; 167:367–373. [PubMed: 17325298]
13. Moller JE, Hillis GS, Oh JK, et al. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. Circulation. 2003; 107:2207–2212. [PubMed: 12695291]
14. Gackowski A, Isnard R, Golmard J-L, et al. Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure. Eur Heart J. 2004; 25:1788–1796. [PubMed: 15474693]
15. Dokainish H, Zoghbi WA, Ambriz E, et al. Comparative cost-effectiveness of B-type natriuretic peptide and echocardiography for predicting outcome in patients with congestive heart failure. Am J Cardiol. 2005; 97:400–403. [PubMed: 16442404]
16. Dokainish H, Zoghbi WA, Lakkis NM, et al. Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. J Am Coll Cardiol. 2005; 45:1223–1226. [PubMed: 15837253]

Table I

Clinical features of the study cohort

Age (yrs)	57 (12)
Male gender (n [%])	144 (69)
Ethnicity	
African American (n [%])	101 (48)
Caucasian (n [%])	98 (47)
Other (n [%])	12 (6)
Body mass index (kg/m^2)	31.2 (7.2)
Ischemic cardiomyopathy (n [%])	91 (43)
New York Heart Association class	
I (n [%])	6 (3)
II (n [%])	119 (56)
III (n [%])	82 (39)
IV (n [%])	4 (2)
Diabetes (n [%])	93 (44)
Hypertension (n [%])	162 (77)
Hypercholesterolemia (n [%])	104 (49)
History of atrial fibrillation (n [%])	40 (19)
Current smoker (n [%])	36 (17)
Systolic blood pressure (mmHg)	100 (18)
Diastolic blood pressure (mmHg)	61 (11)
Heart rate (bpm)	67 (12)
Glomerular filtration rate (ml/min per 1.73 m^2)	67 (28)
Serum sodium (mEq/dl)	139 (3)
Hematocrit (%)	40 (5)
NT-proBNP (pg/ml)	1675 (2657)
QRS duration (ms)	120 (31)
Implantable defibrillator (n [%])	17 (8)
Medications	
ACE inhibitor (n [%])	182 (86)
Angiotensin receptor blocker (n [%])	16 (8)
Beta adrenergic receptor blocker (n [%])	184 (88)
Aldosterone antagonist (n [%])	66 (31)
Hydralazine (n [%])	10 (5)
Long-acting nitrate (n [%])	41 (19)
Digoxin (n [%])	147 (70)
Statin (n [%])	98 (46)
Aspirin (n [%])	110 (52)

Values are expressed as mean (SD) or n (%). ACE = angiotensin converting enzyme; NT-proBNP = N-terminal pro-B type natriuretic peptide.

Table II

Echocardiographic variables in the study cohort

LV ejection fraction (%)	32 (11)
LV end-diastolic volume index (ml/m^2)	70 (39)
Deceleration time (ms)	221 (81)
MR area (cm^2)	4.6 (5.1)
LA volume index (ml/m^2)	49 (23)
Tricuspid annular excursion (cm)	1.5 (0.6)
TR area (cm^2)	2.4 (3.4)
RA volume index (ml/m^2)	35 (16)

Values are expressed as mean (SD). LA = left atrial; LV = left ventricular; MR = mitral regurgitation; RA = right atrial; TR = tricuspid regurgitation.

Table III

Results of univariable proportional hazards models predicting all-cause mortality: hazard ratios, 95% confidence intervals, and P values for selected clinical and echocardiographic variables

	HR (95% CI)	P value
Age (10 yr)	1.17 (0.97–1.42)	0.098
NT-pro BNP (2000 pg/ml)	2.02 (1.65–2.48)	<0.001
LV ejection fraction (10%)	0.63 (0.50–0.79)	<0.001
LV end-diastolic volume index (25 ml/m^2)	1.40 (1.23–1.60)	<0.001
Deceleration time (100 ms)	0.65 (0.45–0.95)	0.020
MR area (5 cm^2)	1.42 (1.17–1.73)	<0.001
LA volume index (20 ml/m^2)	1.66 (1.41–1.95)	<0.001
Tricuspid annular excursion (0.5 cm)	0.70 (0.57–0.87)	0.001
TR area (5 cm^2)	2.00 (1.49–2.75)	<0.001
RA volume index (20 ml/m^2)	1.78 (1.41–2.24)	<0.001

Hazard ratio and confidence interval calculations were based on changes of approximately 1 SD (indicated in parentheses) for continuous variables.

CI = confidence interval; HR = hazard ratio; LA = left atrial; LV = left ventricular; MR = mitral regurgitation; RA = right atrial; TR = tricuspid regurgitation.

Table IV

Results of multivariable proportional hazards models predicting all-cause mortality: hazard ratios, 95% confidence intervals, and P values for models that incorporate age and NT-proBNP, with other clinical characteristics eligible for entry by stepwise selection

	HR (95% CI)	P value
LV ejection fraction (10%)[a]	0.71 (0.54–0.93)	0.013
LV end-diastolic volume index (25 ml/m^2)[a,b,c]	1.39 (1.18–1.64)	<0.001
Deceleration time (100 ms)[a,d]	0.65 (0.42–1.02)	0.059
MR area (5 cm^2)[a,b]	1.15 (0.91–1.45)	0.237
LA volume index (20 ml/m^2)[d]	1.38 (1.10–1.72)	0.005
Tricuspid annular excursion (0.5 cm)[a]	0.82 (0.64–1.06)	0.123
TR area (5 cm^2)[a]	1.57 (1.09–2.25)	0.015
RA volume index (20 ml/m^2)[a,d]	1.54 (1.16–2.05)	0.003

Hazard ratio and confidence interval calculations were based on changes of approximately 1 SD (indicated in parentheses) for continuous variables.

CI = confidence interval; HR = hazard ratio; LA = left atrial; LV = left ventricular; MR = mitral regurgitation; RA = right atrial; TR = tricuspid regurgitation.

[a] Glomerular filtration rate was selected for inclusion in the model.

[b] Heart rate was selected for inclusion in the model.

[c] Etiology of heart failure was selected for inclusion in the model.

[d] Serum sodium was selected for inclusion in the model.