Plasma N-Terminal Prototype-B Natriuretic Peptide and Restrictive Mitral Flow to Risk-stratify Patients with Stage B Heart Failure

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ABSTRACT

Background: The prognostic role of echocardiography is well established in patients with previous or current symptoms of heart failure (HF). Less is understood about patients with stage B HF, who have structural heart disease but no symptoms at any stage. This study investigated the role of plasma N-terminal prototype-B natriuretic peptide (NT-proBNP) and Doppler-echo parameters of diastolic and systolic function for risk stratification in stage B HF patients.

Hypothesis: We investigated whether plasma NT-proBNP and Doppler-echo parameters of diastolic and systolic function have a role in risk stratification of stage B HF patients.

Methods: Doppler echocardiography was performed in 155 outpatients with asymptomatic left ventricular (LV) dysfunction (ejection fraction [EF] <50%) and comprised conventional diastolic variables, including pulsed-Doppler mitral E-wave deceleration time (EDT). Plasma NT-proBNP was assessed at the time of the echocardiogram. The prespecified end point was cardiac death or HF hospitalization or any new HF episode requiring a change in medication.

Results: Mean EF was $35\% \pm 7\%$. Median NT-proBNP was 745 pg/mL (interquartile range [IQR], 442–1672). Patients with events at follow-up ($n = 46$) had higher prevalence of risk factors for developing HF. Plasma NT-proBNP, EDT, and EF were independently associated with cardiac events at multivariable analysis and receiver operating characteristic curves were used to determine the optimal prognostic cut points for each: NT-proBNP ≥ 831 pg/mL, EDT <145 msec, and EF <37%. When used in combination, event-free survival was incrementally worse with each additional abnormality.

Conclusion: Plasma NT-proBNP, EDT, and EF are independently useful for prognostic stratification of stage B HF patients and suggest an incremental prognostic deficit is associated with the combination of each. This study supports the complementary role of comprehensive echocardiography and natriuretic peptide assay in asymptomatic LV dysfunction.

Introduction

The guidelines of the American College of Cardiology/American Heart Association for the Diagnosis and Management of Chronic Heart Failure in the Adult are based on a staging system that is intended to complement the New York Heart Association (NYHA) functional classification.¹ According to this classification, stage A and B represent asymptomatic patients, the former at high risk for developing heart failure (HF), but with no structural heart disease; the latter with structural disorders of the heart, but with no previous or current symptoms of HF.¹ The prognostic role of Doppler echocardiographic parameters of left ventricular (LV) diastolic dysfunction^{2,3} and plasma natriuretic peptide testing^{4–6} is well established in patients with symptomatic stages of HF. Less is understood about patients with stage B HF. This study investigated

the role of plasma N-terminal prototype-B natriuretic peptide (NT-proBNP) and Doppler-echo parameters of diastolic and systolic function for risk stratification in stage B HF patients.

Methods

Patients

This prospective observational study was performed in consecutive outpatients referred for transthoracic echocardiography at the echo laboratory of the Cardiovascular Unit 2 of the Santa Chiara Hospital, Pisa, Italy, between April 2003 and March 2007 with LV systolic dysfunction (ejection fraction [EF] <50%) diagnosed at echocardiography. Referral for echocardiography was part of the routine follow-up assessment of patients with either a previous myocardial

Figure 1. Event-free survival in patients categorized according to N-terminal protype-B natriuretic peptide (NT-proBNP), E-wave deceleration time (EDT), and left ventricular ejection fraction (LVEF).

infarction, assessment for nonspecific symptoms such as chest pain or dyspnea, electrocardiographic abnormalities such as left bundle branch block, or a history of atherosclerotic vascular disease, diabetes mellitus, or systemic hypertension with associated cardiovascular risk factors. Each participant's medical records were reviewed to determine if any prior diagnosis of HF had been made.

Patients with atrial fibrillation, primary valvular heart disease, mechanical valve prosthesis, hypertrophic cardiomyopathy, unstable angina, recent myocardial infarction within the previous 3 months, advanced renal disease requiring hemodialysis, or coexisting malignant disease were excluded. A total of 423 patients with LV systolic dysfunction were identified: of these, 124 were excluded because of a previous HF hospitalization and 144 patients were excluded because of prior or current symptoms of HF (according to Framingham criteria).⁷ This study was approved by the hospital ethics committee and all patients gave written informed consent to participate in the study.

Echocardiographic Evaluation

Comprehensive transthoracic echocardiography was performed with an Acuson Sequoia C256 ultrasound instrument (Siemens, Mountain View, CA) with second-harmonic imaging and a 3.5-MHz transducer. The 2-dimensional and Doppler recordings were made in standard parasternal and apical views. M-mode and 2-dimensional measurements, including LV mass and volumes and maximal left atrial (LA) end-systolic area, were measured according to recent recommendations.⁸ LV ejection fraction (LVEF) was obtained by biplane Simpson's rule. Pulsed wave Doppler mitral velocity curves, including E wave deceleration time (EDT), and pulmonary vein flow velocity tracings were obtained as previously described.⁹ From the 4-chamber view, tissue Doppler longitudinal velocities were recorded with the sample volume placed at the junction between the septal LV wall and the mitral annulus. Analyses were performed for the ratio of mitral to myocardial early velocities (E/Em ratio).¹⁰ Abnormalities in LV diastolic function

were classified according to the Canadian Consensus Guidelines.¹¹

Measurement of Amino-Terminal Pro-Type B Natriuretic Peptide

Venous blood was collected at the time of the index echocardiogram in EDTA-containing tubes (Roche Diagnostics, Grenach-Whylen, Germany). NT-proBNP plasma levels were measured by an Elecsys 2010 analyzer (measuring range, 5–35 000 pg/mL) using a chemiluminescent immunoassay kit (Roche Diagnostics, Grenach-Whylen, Germany).

Follow-up Data

Study patients were followed for 24 ± 15 months after the index Doppler echocardiogram. A cardiac event (cardiac death, hospital admission for HF, or any episode of HF requiring a change in medication) was considered the combined study end point. The follow-up data were obtained monthly by regular visits, telephone calls, from local authority registry, and hospital records.

Statistical Analyses

Continuous variables are expressed as mean $\pm$ standard deviation or median (interquartile range [IQR]) as appropriate. Differences in clinical comorbidities, echocardiographic variables, and plasma NT-proBNP between those with and without an event were assessed with the unpaired student *t* test, Wilcoxon rank sum test, or χ^2 test as appropriate. Variables with independent significance in their association with a cardiac event were identified using the Cox proportional hazards approach, creating 2 models that incorporated different diastolic parameters. Model 1 included plasma NT-proBNP, LVEF, EDT, age, gender, and indexed LA area, whereas Model 2 replaced the indexed LA area with E/E_m. Variables that were significantly associated with cardiac events on Cox hazard analysis were then assessed with a receiver operating characteristic (ROC) curve analysis to determine the optimal cut point for each. The effect of dichotomizing by the optimal cut point, as determined by the Youden index,¹² in estimating event-free survival up to 4 years is displayed using the Kaplan-Meier method and compared using the log-rank test. The incremental risk associated with a combination of the significant abnormalities, using the ROC-defined cut points, was examined using the Kaplan-Meier method by dividing the patients into 4 groups: no abnormality, any 1 abnormality, any 2, or any 3 abnormalities. Procedures of SAS v9.1 (SAS Institute, Cary, NC) were employed. A *P* value <0.05 was considered significant.

Results

Patient Characteristics

The study included 155 patients with a mean age of 69 ± 11 years (range, 33–86 y; median 70 y, 20% women). Mean LVEF was $35\% \pm 7\%$. There were 37 patients with

restrictive mitral flow (24%), 25 with pseudonormal flow (16%), and 21 with mild-to-moderate diastolic dysfunction (14%) according to the Canadian Consensus Guidelines. Feasibility of acquiring pulmonary vein flow signals was 98% for forward wave velocities and 97% for retrograde wave velocity. The median plasma NT-proBNP was 745 pg/mL (IQR, 442–1672). When compared with patients in the nonrestrictive group, patients with restrictive mitral flow had higher plasma NT-proBNP levels (1389 pg/mL [IQR, 961–2834] vs 602 pg/mL [IQR, 310–1326], $P < 0.0001$).

Outcome Analyses

During the follow-up, a total of 46 events (11 deaths, 25 HF-related hospitalizations, and 10 new episodes of HF requiring an increase in medication) occurred. Tables 1 and 2 show differences in clinical and Doppler echocardiographic parameters of patients with or without cardiac events. Patients with cardiac events were more likely to be male and had higher prevalence of diabetes, coronary artery disease, and chronic renal failure.

Irrespective of the multivariable model (using either indexed LA area or E/E_m) only plasma NT-proBNP, EDT, and LVEF were significantly associated with a cardiac event (Table 3). Receiver operating characteristic curve analyses of each of these 3 significant predictors suggested optimal cut points of 831 pg/mL for NT-proBNP, 145 ms for EDT, and 37% for LVEF. Event-free survival on the basis of each of these optimized univariate predictors is shown in Figure 1. Patients with restrictive mitral flow exhibited a worse event-free survival at 4 years (41%) than those without (84%). In patients categorized according to NT-proBNP plasma levels, the outcome at 4 years was worse in patients with plasma NT-proBNP at or above 831 pg/mL (56%) than in patients with NT-proBNP below 831 pg/mL (91%). The outcome at 4 years was 66% in patients with EF below the cut point and 88% in those with EF at or above the cut point.

The incremental risk of cardiac event increased as the number of abnormalities increased: those patients who did not meet any of the ROC-defined cut points for either NT-proBNP, LVEF, or EDT had the best event-free survival. There was an incremental increase in event rate as the number of these abnormalities increased in any combination (Figure 2).

Discussion

The ability of echocardiographic parameters and plasma NT-proBNP levels to risk stratify patients with asymptomatic LV dysfunction (stage B HF) based on the outcome of cardiac events was evaluated. This study showed that NT-proBNP, EF, and EDT were independently associated with cardiac events and identified optimal cut points for these variables to achieve risk stratification.

Table 1. Demographic and Clinical Factors in Patients Grouped According to the Occurrence of Cardiac Events

Variable	Total (n = 155)	Patients With Events (n = 46)	Patients Without Events (n = 109)	P Value
Age, yrs	69 ± 11	69 ± 10	68 ± 11	0.69
Women, %	20	15	22	0.33
HR, beats/min	71 ± 13	75 ± 14	69 ± 12	0.01
SBP, mm Hg	132 ± 21	128 ± 19	135 ± 22	0.1
DBP, mm Hg	78 ± 10	76 ± 10	79 ± 10	0.11
NT-proBNP, pg/mL	745 (442–1672)	1374 (708–2884)	602 (310–1250)	<0.0001
Etiology				
Prior myocardial infarction, %	59	67	55	0.15
Dilated cardiomyopathy, %	25	26	25	0.86
Hypertensive heart disease, %	15	7	18	0.06
Unknown origin, %	1	0	2	0.36
Associate disorders				
History of hypertension, %	55	52	57	0.59
Diabetes, %	17	24	15	0.17
Renal insufficiency, % ^a	12	15	10	0.36
COPD, %	10	11	10	0.88

Abbreviations: COPD, chronic obstructive pulmonary disease; DPB, diastolic blood pressure; HR, heart rate; NT-proBNP, N-terminal protype-B natriuretic peptide; SBP, systolic blood pressure.

Continuous data are mean ± SD or median (IQR).

^a Renal insufficiency was defined as a calculated creatinine clearance rate of less than 60 mL per minute as determined by the Cockcroft-Gault equation.

Echocardiography and Plasma Natriuretic Peptides for Risk Assessment of Stage B Heart Failure

The negative impact of asymptomatic LV dysfunction on patients' outcome has been clearly demonstrated,¹³ but little is known about the interaction between Doppler-echo parameters of LV dysfunction and natriuretic peptide concentrations in the prognostic stratification of asymptomatic LV dysfunction.

Development of the clinical syndrome of HF is gradual and many patients remain asymptomatic or mildly asymptomatic owing to the compensatory mechanisms acting through the autonomic nervous system and neurohormones.¹⁴ Therefore, the early identification of LV dysfunction by echocardiography may be corroborated by the laboratory findings of increased plasma natriuretic peptide concentration.^{14,15}

In a recent study, we assessed the prognostic value of natriuretic peptides and Doppler diastolic variables in NYHA class I and II patients with a history of HF,⁹ but to our knowledge no study specifically addressed the question whether natriuretic peptides and restrictive mitral flow

affect the outcome of asymptomatic patients with structural cardiac disease but without current or prior evidence of HF. In this investigation, we examined the relationship between LV systolic and diastolic dysfunction and plasma NT-proBNP levels and subsequent cardiovascular events in patients with structural heart disease without HF symptoms, 60% of them with a history of coronary artery disease.

Clinical and Therapeutic Implications

Complete history and physical examination are the first steps in evaluating patients considered at high risk of developing structural heart disease (stage A HF). Recent reports have demonstrated that evaluation of plasma natriuretic peptide concentrations is a useful strategy to screen for asymptomatic LV dysfunction in population and community-based studies and that only patients with altered natriuretic peptide levels should be referred to echocardiography.^{16,17}

Although, the widespread application of echocardiography for screening large populations is limited by availability and cost,^{16–18} proper identification of high risk patients

Table 2. Doppler Echocardiographic Variables in Patients Grouped According to the Occurrence of Cardiac Events

Variable	Total (n = 155)	Patients With Events (n = 46)	Patients Without Events (n = 109)	P Value
LVEDVi, mL/m ²	110 ± 29	120 ± 35	106 ± 25	0.014
LVESVi, mL/m ²	72 ± 24	82 ± 26	68 ± 21	0.002
LVEF, %	35 ± 7	32 ± 6	36 ± 7	0.002
LV mass index, g/m ²	159 ± 36	169 ± 39	155 ± 35	0.038
LA diameter index, mm/m ²	25 ± 3	26 ± 3	25 ± 3	0.284
LA area index, mm ² /m ²	13 ± 3	14 ± 3	13 ± 3	0.013
E wave, cm/sec	74 ± 24	84 ± 30	70 ± 20	0.006
A wave, cm/sec	78 ± 28	73 ± 32	80 ± 26	0.165
E/A ratio	1.3 ± 1.3	1.7 ± 2.0	1.1 ± 0.8	0.032
EDT, msec	178 ± 51	155 ± 50	187 ± 49	0.0004
S wave, cm/sec	50 ± 16	42 ± 16	54 ± 15	<0.0001
D wave, cm/sec	46 ± 18	52 ± 20	44 ± 16	0.031
S:D	1.2 ± 0.5	1.0 ± 0.6	1.3 ± 0.5	0.001
dAR-dAd	30 ± 32	40 ± 26	26 ± 34	0.004
Em	9 ± 3	8 ± 3	10 ± 3	0.023
E/Em	9 ± 4	11 ± 6	8 ± 4	0.002

Abbreviations: dAR-dAd, difference in duration of pulmonary vein flow and mitral flow velocity at atrial contraction; Em, early myocardial wave velocity; EDT, E-wave deceleration time; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; LA, left atrial; LV, left ventricular; SF, systolic fraction.

could be potentially valuable for selecting the right patients for echocardiography. Plasma natriuretic peptide measurements, for example, plasma NT-proBNP testing, in conjunction with Doppler echocardiographic parameters of diastolic function¹⁵ may be especially important in asymptomatic patients with structural heart disease who should be the appropriate targets for more aggressive screening.

Study Limitations

The major limitation of this study is the likelihood of selection bias in the patient population. Although our study sample represents a consecutive series of patients referred to the echo laboratory and prospectively followed up, it is not a random sample of community-dwelling individuals. Compared to previous reports, this study involved a rather small sample of asymptomatic LV systolic dysfunction patients followed up for a relatively short period of time. Our purpose, however, was to evaluate patients with a LVEF <50% with a high prevalence of risk factors for the development of HF, while other studies first focused on the prevalence of asymptomatic LV systolic dysfunction

among large populations—including a minority of patients with depressed EF—and then examined the prognostic implications of asymptomatic LV systolic dysfunction. However, further studies are needed to test the portability of these results in larger cohorts of patients with stage B HF.

In this study, eligible patients had to have LV dysfunction with the exclusion of patients with prior HF diagnosis and current presence of Framingham criteria. As known clinical scoring systems have a low accuracy for HF diagnosis in patients with prior LV systolic dysfunction. Moreover, in this population the median NT-proBNP level was 747 pg/mL and 25% had >1672 pg/mL. However, it is now clear that NT-proBNP may increase in settings other than the HF syndrome, including chronic renal dysfunction, the presence and severity of such NT-proBNP release is often significantly associated with risk for adverse outcome. Accordingly, elevation of NT-proBNP in asymptomatic LV dysfunction should be considered with regard to the serious adverse outcomes associated with the elevation.¹⁹

Table 3. Predictors of Cardiac Event at Multivariable Analysis

Model 1: Cardiac Event = NT-proBNP, LVEF, EDT, Age, Gender, LA Area Index		
Variable	Hazard Ratio (95% Confidence Interval)	P Value
Log _e (N-terminal proBNP), pg/mL	1.45 (1.04–2.02)	0.029
EDT, ms	0.99 (0.98–1.00)	0.014
LVEF, %	0.95 (0.91–1.00)	0.036
Age, yrs	0.99 (0.96–1.03)	0.711
Gender, M = 1	1.11 (0.49–2.53)	0.798
LA area index, mm ² /m ²	1.04 (0.95–1.12)	0.482
Model 2: Cardiac Event = NT-proBNP, LVEF, EDT, Age, Gender, E/E _m		
Variable	Hazard Ratio (95% Confidence Interval)	P Value
Log _e (N-terminal proBNP), pg/mL	1.46 (1.05–2.04)	0.026
EDT, ms	0.99 (0.98–1.00)	0.016
LVEF, %	0.95 (0.91–1.00)	0.046
Age, yrs	0.99 (0.96–1.03)	0.666
Gender, M = 1	1.14 (0.51–2.59)	0.748
E/E _m	1.00 (0.94–1.07)	0.991

Abbreviations: EF, ejection fraction; Em, early myocardial wave velocity; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal prototype-B natriuretic peptide.

Figure 2. Event-free survival in patients categorized according to the receiver operating characteristic curve-derived optimal cut points: NT-proBNP ≥ 831 pg/mL, EDT < 145 msec, and EF $< 37\%$. Survival was best in patients with no abnormality and worsened as the number of abnormalities increased.

Conclusion

The present study has shown that in patients with LV systolic dysfunction without previous or current symptoms of HF Doppler-derived parameters of advanced diastolic dysfunction, low EF, or elevated plasma NT-proBNP concentration were significantly associated with the risk of cardiac death or new onset HF symptoms. The prognostic impact of these factors is indeed cumulative and each factor has an additional value in predicting cardiac events, thus supporting a complementary role for comprehensive echocardiography and natriuretic peptides assessment in such patients.

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