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Prevalence, Clinical Phenotype, and Outcomes Associated with Normal B-Type Natriuretic Peptide Levels in Heart Failure with Preserved Ejection Fraction

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Abstract

B-type natriuretic peptide (BNP) is used widely to exclude heart failure (HF) in patients with dyspnea. However, most studies of BNP have focused on diagnosing HF with reduced ejection fraction (EF). We hypothesized that a normal BNP (< 100 pg/ml) is relatively common in HF with preserved EF (HFpEF), a heterogeneous disorder commonly associated with obesity. We prospectively studied 159 consecutive patients enrolled in the Northwestern University HFpEF Program. All subjects had symptomatic HF with EF>50% and elevated pulmonary capillary wedge pressure (PCWP). BNP was tested at baseline in all subjects. We compared clinical characteristics, echocardiographic parameters, invasive hemodynamics, and outcomes among HFpEF patients with normal (< 100 pg/ml) vs. elevated (>100 pg/ml) BNP. Of the 159 HFpEF patients, 46 (29%) had BNP < 100 pg/ml. Subjects with normal BNP were younger, more often female, had higher rates of obesity and higher body-mass index, and less commonly had chronic kidney disease and atrial fibrillation. Both EF and PCWP were similar in normal vs. elevated BNP groups (62±7 vs. 61±7% [P=0.67] and 25±8 vs. 27±9 mmHg [P=0.42], respectively). Elevated BNP was associated with enlarged left atrial volume, worse diastolic function, abnormal right ventricular structure/function, and worse outcomes (e.g., adjusted hazard ratio for HF hospitalization = 4.0, 95% confidence interval 1.6-9.7, P=0.003). In conclusion, a normal BNP is present in 29% of symptomatic outpatients with HFpEF who have elevated PCWP, obesity is likely the primary driver of this finding, and although BNP is useful as a prognostic marker in HFpEF, a normal BNP does not exclude the outpatient diagnosis of HFpEF.

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Keywords

B-type natriuretic peptide; diastolic heart failure; obesity; hemodynamics; echocardiography; outcomes

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is common, increasing in prevalence, and associated with high morbidity and mortality.¹ HFpEF, a heterogeneous syndrome more common among elderly, female, and obese patients, is defined by HF symptoms in the presence of a normal left ventricular EF (> 50%).² The diagnosis of HFpEF is challenging because symptoms are non-specific and can be due to several alternative non-cardiac conditions such as anemia, chronic kidney disease, and chronic lung disease. The European Society of Cardiology (ESC) has developed algorithms for both the diagnosis and exclusion of HFpEF based in part on serum natriuretic peptides,³ but the utility of this diagnostic schema in the clinical realm is unknown. Natriuretic peptides (e.g., B-type natriuretic peptide [BNP]) are excellent biomarkers for the diagnosis of HF with reduced EF (HFrEF),⁴ but BNP is less sensitive for the diagnosis of HFpEF, and BNP levels are lower in HFpEF compared to HFrEF.⁵⁻⁸ The ESC guidelines for HFpEF diagnosis recommend the exclusion of HFpEF in the setting of a normal BNP (< 100 pg/mL).³ However, in our clinical practice of the care of a large number of HFpEF patients, we have found that BNP is frequently within the “normal” range (< 100 pg/mL) despite clinical, echocardiographic, and invasive hemodynamic evidence of HFpEF. The reasons for normal BNP in some patients with HFpEF are unclear and may relate to the high prevalence of obesity in this patient population.^{9, 10} We therefore sought to explore the frequency, clinical phenotype, and outcomes of patients with HFpEF and normal BNP.

METHODS

Consecutive patients were prospectively enrolled from March 2008 to October 2009 from the outpatient clinic of the Northwestern University HFpEF Program as part of a systematic observational study of HFpEF (ClinicalTrials.gov identifier #NCT01030991). Patients with possible HF were initially identified by an automated daily query of the inpatient electronic medical record at Northwestern Memorial Hospital as described previously.¹¹ The list of patients generated was screened daily, and only those patients who had LV ejection fraction (LVEF) > 50% and who met Framingham criteria for HF were offered post-discharge follow-up in a specialized HFpEF outpatient program. Once evaluated as an outpatient in the HFpEF clinic, the diagnosis of HF was confirmed by a board-certified HF specialist. The diagnosis of HFpEF was based on previously published criteria, which requires both an LVEF > 50% and an LV end-diastolic volume index < 97 mL/m².³ As in prior studies,¹² patients with significant valvular disease (defined as greater than moderate in severity), prior cardiac transplantation, prior history of reduced LVEF < 40%, or a diagnosis of constrictive pericarditis were excluded.

Blood samples for BNP measurement were collected by venipuncture into EDTA tubes upon initial outpatient HFpEF clinic evaluation (at the time of study enrollment). Blood samples were kept at room temperature and analyzed within 4 hours using the Triage BNP assay (Biosite Inc, San Diego, Calif). The Triage meter was used to measure the BNP concentration by detecting a fluorescent signal that reflected the amount of BNP in the sample. The precision, analytical sensitivity, interferences, and stability have all been previously described.¹³

We collected and analyzed the following clinical characteristics of the study participants: demographics, ethnicity, New York Heart Association (NYHA) functional class, HF symptoms, comorbidities, vital signs, physical findings, and laboratory data which included hemoglobin, serum sodium, blood urea nitrogen (BUN), and creatinine. Estimated glomerular filtration rate (eGFR) was calculated using the Modified Diet in Renal Disease (MDRD) equation.

Hypertension was defined by systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, physician documented history of hypertension, or use of antihypertensive medications. Diabetes was defined by the presence of physician-documented history of diabetes or use of oral hypoglycemic agents or insulin for the treatment of hyperglycemia. Coronary artery disease (CAD) was defined by the presence of physician documented history of CAD, known coronary stenosis $> 50\%$, prior history of myocardial infarction, percutaneous intervention, coronary artery bypass grafting, or abnormal stress test consistent with myocardial ischemia. Obesity was defined by a body mass index > 30 kg/m². Chronic kidney disease was defined as eGFR < 60 ml/m². Chronic obstructive pulmonary disease (COPD) and asthma were defined by physician-documented history or pulmonary function testing results, which were consistent with obstructive lung disease.

All study participants underwent comprehensive 2-dimensional echocardiography with Doppler and tissue Doppler imaging. All standard echocardiographic views were obtained. Echocardiography was performed using commercially available ultrasound systems with harmonic imaging (Philips iE33 or 7500, Philips Medical Systems, Andover, MA; or Vivid 7, GE Healthcare, General Electric Corp., Waukesha, WI). Cardiac structure and function (including LV systolic and diastolic function and right heart structure/function) were quantified as recommended by the American Society of Echocardiography.¹⁴⁻¹⁶ All echocardiographic measurements were made by an experienced research sonographer blinded to all other clinical data using ProSolv 4.0 echocardiographic analysis software (ProSolv CardioVascular; Indianapolis, IN) and verified by a board-certified echocardiographer.

Within 30 days of the initial outpatient HFpEF clinic evaluation (date of study enrollment), right heart and pulmonary arterial (PA) catheterization was performed from either the right internal jugular or right femoral vein approach using standard Seldinger technique under fluoroscopic guidance. Participants underwent recording of invasive hemodynamics (mean RA pressure; systolic, diastolic, and mean PA pressure [mPAP]; and PCWP) using a fluid-filled, 6F PA catheter (Edwards Lifesciences, Irvine, CA) and a properly zeroed pressure transducer. Pressure recordings were analyzed off-line using a WITT Hemodynamic Workstation (Philips Medical Systems, Andover, MA) at a 50 mm/s paper speed with adjustment of pressure (mmHg) scale as needed. All hemodynamic pressure measurements were made at end-expiration and in duplicate using a standardized measurement protocol, by a physician blinded to all clinical data. Cardiac output was calculated using the thermodilution method.

All study participants were evaluated clinically in the Northwestern HFpEF Program after enrollment into the study as clinically indicated but no less frequently than every 6 months. At each clinic visit, inter-current hospitalizations were documented. For each reported hospitalization, chart review was performed to categorize the hospitalization as due to HF, cardiovascular (including HF), or non-cardiovascular. Every 6 months, participants (or their proxy) were also contacted to determine vital status. Finally, the Social Security Death Index was also queried for additional verification of vital status. Enrollment date was defined as

the date of first visit to the outpatient HFpEF clinic, and date of last follow-up was defined as date of death or date of last HFpEF clinic visit. Follow-up was complete in all patients.

We dichotomized participants into 2 groups based on the clinical cut-off for abnormal BNP (> 100 pg/ml). Clinical characteristics, laboratory data, echocardiographic parameters, and invasive hemodynamic data were compared between groups using t-tests for normally distributed continuous variables (or non-parametric equivalent when appropriate). Chi-squared tests (or Fisher's exact test when appropriate) were used to compare categorical variables between groups. A two-sided p-value < 0.05 was considered statistically significant. Continuous data with a normal distribution were displayed as mean $\pm$ standard deviation. Right-skewed data were log-transformed and presented as median and 25th-75th percentile. To determine the independent association of clinical parameters with normal BNP, we performed multiple logistic regression with normal BNP as the dependent variable. We first investigated which demographic, clinical, physical examination, and laboratory variables were associated with normal BNP on univariate analysis. Variables associated with BNP ≥ 100 pg/ml on univariate analysis ($P < 0.05$) were carried forward to a multivariable model to determine the clinical factors independently associated with BNP ≥ 100 pg/ml. Finally, adjusted Cox proportional hazards regression analyses and Kaplan-Meier curves were used to examine the association between BNP ≥ 100 pg/ml and outcomes. All analyses were done in Stata v.10.1 (StataCorp, College Station, TX).

RESULTS

A total of 159 patients were prospectively enrolled into our invasive hemodynamic study of BNP in HFpEF. All patients met criteria for HFpEF: all were previously hospitalized for HF, all had preserved EF ($> 50\%$), and all had elevated pulmonary capillary wedge pressure (> 15 mmHg) at time of cardiac catheterization. In addition, at the time of post-HF hospitalization outpatient follow-up in the Northwestern University HFpEF Program (i.e., date of enrollment into the present study), the majority still had symptoms and physical signs of HF: 91% had exertional dyspnea, 48% had orthopnea, 29% had paroxysmal nocturnal dyspnea, 72% had elevated jugular venous pressure (mean 10.4 ± 2.8 cm H₂O), 28% had crackles, and 66% had lower extremity edema. Study patients also had echocardiographic abnormalities consistent with HFpEF: LV mass index (mean 53 ± 22 g/m^{2.7}) and left atrial volume index (mean 34 ± 15 ml/m²) were elevated, and the majority (83%) had evidence of moderate or greater diastolic dysfunction. Median BNP in the entire cohort was 234 pg/ml (25th-75th percentile 71-603 pg/ml; mean $\pm$ SD BNP = 521 ± 852 pg/ml). Despite having symptoms and signs of HF, abnormal cardiac structure and function on echocardiography, and elevated filling pressures on invasive hemodynamic testing, 46/159 study patients (29%) had a "normal" BNP (≤ 100 pg/ml).

Patients with a normal BNP were younger, more often female, and more frequently had obesity, but had lower rates of chronic kidney disease, atrial fibrillation, and coronary artery disease (Table 1). Although obesity was more prevalent in patients with normal BNP, there were some patients in our cohort ($N=5/34$ [15%]) with normal BMI (< 25 kg/m²) who had normal BNP and HFpEF, thereby showing that normal BNP can occur even in HFpEF patients who are not obese. HF symptoms were similar across the two groups. LV size, ejection fraction, and mass were also similar between patient groups (Table 2). Diastolic function was worse in patients with elevated BNP, with a higher frequency of severe diastolic dysfunction grade, higher E/e' ratio, higher E/A ratio, and larger left atrial volume. HFpEF patients with elevated BNP also had larger RV size, increased RV wall thickness, larger right atrial size, and worse RV systolic function compared to those with a normal BNP. Table 3 illustrates lower RA pressure, mPAP, and pulmonary vascular resistance among patients with normal BNP. PCWP and cardiac index were similar among both

groups. However, pulmonary artery saturation, a marker of cardiac output independent of body size, was higher in the normal BNP group.

Multiple logistic regression analysis of normal BNP (< 100 pg/ml) in HFpEF (Table 4) demonstrated that 3 clinical factors are independently associated with normal BNP levels. Obesity was associated with a higher likelihood of normal BNP whereas chronic kidney disease and atrial fibrillation were associated with a lower likelihood of a normal BNP. During a median follow-up time of 14 months (25th-75th percentile 5-23 months; maximum follow-up time 24 months), we observed lower rates of HF hospitalization, cardiovascular hospitalization, and mortality in HFpEF patients with a normal BNP level at baseline (Table 5 and Figure 1). On Cox proportional hazards analysis, elevated BNP was a potent predictor of outcomes for future HF hospitalization (univariate hazard ratio [HR] 4.4, 95% CI 1.9-10.4, $P=0.001$; adjusted HR 4.0, 95% CI 1.6-9.7, $P=0.003$ after adjustment for age, sex, obesity, chronic kidney disease, and atrial fibrillation). Elevated BNP (> 100 pg/ml) was also an independent predictor of the combined endpoint of cardiovascular hospitalization (which included HF hospitalization) and death: univariate HR 3.6, 95% CI 1.8-7.0, $P<0.001$; adjusted HR 3.7, 95% CI 1.8-7.7, $P<0.001$ after adjusting for age, sex, obesity, chronic kidney disease, and atrial fibrillation.

DISCUSSION

Our data from the Northwestern University HFpEF Program indicate that up to 30% of patients with confirmed HFpEF have normal BNP values despite a high prevalence of HF signs and symptoms, abnormal cardiac structure and diastolic dysfunction on echocardiography, and elevated LV filling pressures on invasive hemodynamic testing. In comparison to HFpEF patients with an elevated BNP, HFpEF patients with a normal BNP were younger, more obese, had better renal function, and less often had atrial fibrillation. These patients also had less evidence of right heart structural and functional abnormalities on echocardiography. Importantly, although BNP was found to be normal in a large number of patients with HFpEF in our study, baseline BNP level was still a powerful, independent predictor of future cardiovascular events.

Prior studies (in both the inpatient and outpatient settings) have shown that patients with HFpEF can have normal BNP levels,^{5-8,17} and that BNP levels are lower in HFpEF compared to HFrEF.⁶⁻⁸ BNP values in these prior studies were similar to ours (e.g., Bursi et al. showed that in outpatients with HFpEF, median BNP was 183 pg/ml [25th-75th percentile 88-351 pg/ml]). However, ours is the few studies to systematically recruit patients hospitalized with HFpEF, measure BNP, and confirm the diagnosis of HFpEF by physical exam, echocardiography, and invasive hemodynamic testing. Confirmation of the HFpEF diagnosis in our study with invasive hemodynamic testing is critical, as some have argued that patients with HFpEF and normal BNP levels do not truly have the HF syndrome.¹⁸

The decrease in circulating natriuretic peptide levels in obese patients suffering from HF has already been well established.^{9,10,19} The mechanism behind reduced serum BNP levels and obesity still remains unclear. Debate exists regarding whether natriuretic peptides are cleared by receptors on adipocytes or if obese patients have a predisposition that does not allow them to generate and/or release BNP from the myocardium.²⁰ Insulin resistance and increased visceral adiposity, independent of BMI, correlates with lower concentrations of peripheral natriuretic peptide thus implying that metabolic syndrome may mediate the association between obesity and decreased natriuretic peptides.²¹ Although an important mediator of normal BNP levels in HFpEF, obesity is not the sole contributing factor. We found that although infrequent, patients with normal BMI and HFpEF can have normal BNP levels. In addition, our study is in accordance with prior studies which have demonstrated

associations between BNP and chronic kidney disease in HF²² and BNP and atrial fibrillation in patients with preserved EF.²³ Based on our results, the presence of abnormal right heart structure and function also appears to influence BNP levels in HFpEF, a finding which is supported by other studies which have found that conditions associated with increased right-sided cardiac pressures can result in elevated BNP.^{24, 25}

Prior studies have already established that patients with HFpEF and HFrEF both have poor outcomes.¹² However, a greater percentage of HFpEF patients die from non-cardiac causes compared to HFrEF patients because of the high frequency of comorbidities such as anemia, chronic kidney disease, and diabetes.^{26, 27} Furthermore, as these comorbid conditions become more severe, BNP levels rise and correlate with worse outcomes. Our results confirm other studies which have demonstrated the prognostic value of natriuretic peptides in HFpEF. In a subgroup analysis from the I-PRESERVE trial, Anand et al., recently found a similar correlation with elevated NT-proBNP levels and poor outcomes in HFpEF.²⁸ Patients with normal NT-proBNP levels had better outcomes, but also were more likely to improve with irbesartan therapy. This finding has led some to question the diagnosis of HF in these patients with preserved EF.¹⁸ Importantly, our study supports Anand et al. by showing that up to one-third of patients with HFpEF have a normal BNP despite symptoms of HF and invasive hemodynamic evidence of elevated LV filling pressures.

The high morbidity and mortality of HFpEF patients is a significant problem, given the growing prevalence of this challenging clinical syndrome. In contrast to HFrEF, few clinical trials are available to guide the treatment of HFpEF patients.²⁹ Therefore, more clinical trials must be conducted and will require increasing enrollment of HFpEF patients to evaluate possible therapeutic options. If these studies use elevated BNP as an enrollment criteria (as some have proposed³⁰), a large number of symptomatic HFpEF patients with high LV filling pressures may be excluded from clinical trials. Excluding such patients may be beneficial given the higher number of adverse outcomes in HFpEF patients with elevated BNP (which would lower the number of trial patients needed to achieve statistical power).¹⁸ However, a BNP-guided enrollment strategy may be harmful because patients with HFpEF and normal BNP, which we have shown to be quite prevalent, will be left with no proven treatment options.

The results of the present study should be interpreted in the context of certain limitations. Serum BNP levels were measured at the time of the first post-hospitalization outpatient clinic visit, which preceded the date of invasive hemodynamic testing. However, symptoms, physical findings, and echocardiography on the date of enrollment show that these patients had the HF syndrome when BNP levels were measured. Nevertheless, our findings should be interpreted in the context of the outpatient evaluation of patients with HFpEF.

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Figure 1. Kaplan-Meier Curves Stratified by B-type Natriuretic Peptide Levels
 (A) Heart failure hospitalization; (B) Combined endpoint (all-cause cardiovascular hospitalization [including heart failure hospitalization] or death). CV = cardiovascular; BNP = B-type natriuretic peptide.

Table 1
Baseline Clinical, Demographic, Physical Examination, and Laboratory Characteristics of Patients with Heart Failure and Preserved Ejection Fraction: Normal versus Elevated B-type Natriuretic Peptide

Characteristic	BNP (pg/ml)		P value
	100 (N=46)	> 100 (N=113)	
B-type natriuretic peptide (pg/ml) *	37 (21-63)	379 (205-789)	
Age (years)	62 ± 11	66 ± 12	0.038
Female	33 (72%)	62 (55%)	0.049
European American	21 (46%)	65 (58%)	0.17
African American	20 (43%)	38 (34%)	0.24
Other	5 (11%)	10 (8%)	0.77
New York Heart Association functional class			0.63
I	4 (9%)	8 (7%)	
II	22 (48%)	46 (41%)	
III	20 (43%)	57 (50%)	
IV	0	2 (2%)	
Exertional dyspnea	43 (93%)	102 (90%)	0.52
Orthopnea	22 (48%)	54 (48%)	0.99
Paroxysmal nocturnal dyspnea	13 (28%)	33 (29%)	0.91
Coronary artery disease *	13 (28%)	51 (45%)	0.049
Systemic hypertension *	37 (80%)	89 (79%)	0.81
Hyperlipidemia *	30 (65%)	61 (54%)	0.19
Chronic kidney disease	13 (28%)	75 (66%)	<0.0001
Diabetes mellitus	15 (33%)	37 (33%)	0.99
Atrial fibrillation	5 (11%)	44 (39%)	0.001
Current smoker	8 (17%)	15 (13%)	0.50
Obesity *	32 (70%)	53 (47%)	0.009
Chronic obstructive pulmonary disease or asthma	19 (42%)	49 (43%)	0.90
Obstructive sleep apnea	21 (47%)	44 (39%)	0.37
Heart rate (beats/min)	71 ± 16	71 ± 14	0.97
Systolic blood pressure (mmHg)	124 ± 17	125 ± 21	0.71
Diastolic blood pressure (mmHg)	71 ± 11	69 ± 12	0.30
Pulse pressure (mmHg)	53 ± 15	57 ± 18	0.26
Body mass index (kg/m ²)	35 ± 9	31 ± 9	0.005
Jugular venous pressure (cm H ₂ O)	9 ± 2	11 ± 3	0.002
Pulmonary crackles	13 (28%)	32 (28%)	0.99
Lower extremity edema	30 (65%)	75 (66%)	0.89
Serum sodium (mEq/L)	139 ± 3	138 ± 3	0.14
Blood urea nitrogen (mg/dl)	20 ± 14	28 ± 19	0.012

Characteristic	BNP (pg/ml)		P value
	100 (N=46)	> 100 (N=113)	
Serum creatinine (mg/dl) [†]	1.0 (0.8-1.2)	1.2 (1.0-1.8)	0.0001 [‡]
Estimated glomerular filtration rate (ml/min/1.73 m ²)	70 ± 25	53 ± 27	0.0002
Hemoglobin (g/dl)	12.2 ± 1.4	11.6 ± 1.9	0.08

BNP = B-type natriuretic peptide

* Coronary artery disease was defined by the presence of physician documented history of coronary artery disease, known coronary stenosis > 50%, prior history of myocardial infarction, percutaneous intervention, coronary artery bypass grafting, or abnormal stress test consistent with myocardial ischemia; systemic hypertension was defined as blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, physician-documented history of hypertension, or current use of antihypertensive medications; hyperlipidemia was defined as physician-documented history of hyperlipidemia or current use of lipid-lowering medications; obesity was defined as body-mass index > 30 kg/m².

[†] Median (25th-75th percentile)

[‡] Wilcoxon rank-sum test

Table 2
Echocardiographic Characteristics of Patients with Heart Failure and Preserved Ejection Fraction: Normal versus Elevated B-type Natriuretic Peptide

Parameter	BNP (pg/ml)		P value
	100 (N=46)	> 100 (N=113)	
LV end-diastolic volume index (ml/m ²)	38 ± 10	42 ± 12	0.21
LV end-systolic volume index (ml/m ²)	15 ± 6	16 ± 7	0.28
LV ejection fraction (%)	62 ± 7	61 ± 7	0.67
LV mass index (g/m ² .7)	49 ± 17	55 ± 23	0.17
Left atrial volume index (ml/m ²)	27 ± 11	36 ± 16	0.002
Early mitral inflow (E) velocity (cm/s)	97 ± 30	112 ± 43	0.059
Late (atrial) mitral inflow (A) velocity (cm/s)	84 ± 23	77 ± 31	0.28
E/A ratio	1.2 ± 0.6	1.6 ± 0.7	0.020
Early mitral inflow deceleration time (ms)	212 ± 43	239 ± 79	0.059
Isovolumic relaxation time (ms)	78 ± 18	85 ± 21	0.06
Tissue Doppler e' velocity (cm/s)	9.9 ± 4.2	8.9 ± 3.5	0.19
E/e' ratio	11 ± 5	14 ± 8	0.017
LV diastolic function			0.010
Normal	7 (15%)	4 (4%)	
Impaired relaxation (Grade 1)	5 (11%)	5 (4%)	
Pseudonormal (Grade 2)	15 (33%)	32 (28%)	
Restrictive (Grade 3)	9 (20%)	46 (41%)	
Indeterminate	10 (22%)	26 (23%)	
RV end-diastolic area index (cm ² /m ²)	12.1 ± 2.0	14.6 ± 4.2	0.001
RV end-systolic area index (cm ² /m ²)	6.5 ± 1.3	8.7 ± 3.1	0.0001
RV fractional area change	0.46 ± 0.06	0.41 ± 0.07	0.0003
Tricuspid annular plane systolic excursion (cm)	2.2 ± 0.6	1.9 ± 1.7	0.001
RV wall thickness index (cm/m ²)	0.23 ± 0.04	0.26 ± 0.06	0.012
Right atrial area index (cm ² /m ²)	8.8 ± 2.8	11.6 ± 4.2	0.0002

BNP = B-type natriuretic peptide; LV = left ventricular; RV = right ventricular

Table 3
Invasive Hemodynamic Characteristics of Patients with Heart Failure and Preserved Ejection Fraction: Normal versus Elevated B-type Natriuretic Peptide

Hemodynamic parameter	BNP (pg/ml)		P value
	100 (N=46)	> 100 (N=113)	
Right atrial pressure (mmHg)	12 ± 5	15 ± 6	0.02
Pulmonary artery systolic pressure (mmHg)	46 ± 11	55 ± 18	0.008
Pulmonary artery diastolic pressure (mmHg)	27 ± 8	29 ± 9	0.37
Mean pulmonary artery pressure (mmHg)	33 ± 8	37 ± 11	0.045
Pulmonary capillary wedge pressure (mmHg)	25 ± 8	27 ± 9	0.42
Cardiac index (L/min/m ²)	3.1 ± 0.8	2.9 ± 0.9	0.28
Pulmonary artery saturation (%)	71 ± 7	67 ± 9	0.002
Systemic vascular resistance (dyne-s/cm ⁵)	1227 ± 507	1292 ± 566	0.55
Pulmonary vascular resistance (dyne-s/cm ⁵) *	87 (64-112)	142 (90-229)	0.0005 [†]

* Median, 25th-75th percentile

[†] Wilcoxon rank-sum test

Table 4
Clinical Predictors of Normal B-type Natriuretic Peptide 100 pg/ml in Patients with Heart Failure and Preserved Ejection Fraction

Predictor	Univariate			Multivariate*		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	0.73	0.54-0.99	0.042	0.95	0.67-1.35	0.77
Female gender	2.09	0.99-4.38	0.052	—	—	—
Chronic kidney disease	0.20	0.09-0.42	<0.001	0.22	0.10-0.49	<0.001
Atrial fibrillation	0.19	0.07-0.52	0.001	0.28	0.09-0.82	0.020
Coronary artery disease	2.02	0.96-4.26	0.063	—	—	—
Obesity	2.59	1.25-5.36	0.011	2.38	1.07-5.32	0.034

OR = odds ratio; CI = confidence interval

* Multivariate model included age, chronic kidney disease, coronary artery disease, and obesity

Table 5
Outcomes of Patients with Heart Failure and Preserved Ejection Fraction: Normal versus Elevated B-type Natriuretic Peptide

Outcome	BNP (pg/ml)		P-value
	100 (N=46)	> 100 (N=113)	
Heart failure hospitalization	6 (13%)	49 (43%)	<0.001
Cardiovascular hospitalization *	10 (22%)	58 (51%)	0.001
Death	0	16 (14%)	0.006
Cardiovascular hospitalization or death *	10 (22%)	62 (55%)	<0.001

* Includes heart failure hospitalization