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Comparative study of galectin-3 and B-type natriuretic peptide as biomarkers for the diagnosis of heart failure

Qiu-Sheng YIN, Bing SHI, Lan Dong, Lei BI

Department of Geriatric Cardiology, General Hospital of Beijing Command of PLA, Beijing 100700, China

Abstract

Background Heart failure (HF) is a common disease with complex pathophysiological causes. The diagnosis of HF commonly relies on comprehensive analyses of medical history and symptoms, and results from echocardiography and biochemical tests. Galectin-3, a relatively new biomarker in HF, was approved by the US Food and Drug Administration in 2010 as a marker in the stratification of risk for HF. We assessed galectin-3 as a biomarker for HF diagnosis in patients with preserved ejection fraction (pEF) and compared its performance with that of B-type natriuretic peptide (BNP). **Methods** Thirty-five pEF patients with HF (HFpEF group) and 43 pEF patients without HF (control group) were enrolled. Plasma levels of galectin-3 and BNP in HFpEF and control subjects were determined. Sensitivity, specificity, predictive values, and accuracy of galectin-3 and BNP as markers for HF diagnosis were calculated and compared. **Results** Levels of galectin-3 and BNP were 23.09 ± 6.97 ng/mL and 270.46 ± 330.41 pg/mL in the HFpEF group, and 16.74 ± 2.75 ng/mL and 59.94 ± 29.93 pg/mL in the control group, respectively. Differences in levels of galectin-3 and BNP between the two groups were significant ($P < 0.01$). As a biomarker for HF diagnosis in study subjects, galectin-3 showed sensitivity and specificity of 94.3% and 65.1%, respectively, at a cutoff value of 17.8 ng/mL. BNP showed sensitivity and specificity of 77.1% and 90.7%, respectively, at a cutoff value of 100 pg/mL. Galectin-3 was a significantly more sensitive ($P < 0.05$) but less specific ($P < 0.01$) biomarker compared with BNP. Differences in positive predictive value, negative predictive value, and accuracy between galectin-3 and BNP markers were not significant ($P > 0.05$). Areas under the receiver operating characteristic curve (95% confidence interval) were 0.891 (0.808–0.974) and 0.896 (0.809–0.984) for galectin-3 and BNP, respectively, with no significant difference between the two values ($P > 0.05$). **Conclusions** The level of galectin-3 is significantly elevated in patients with HF. Galectin-3 and BNP are useful biomarkers for the diagnosis of HF in patients with pEF.

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Keywords: Heart failure; Preserved ejection fraction; Galectin-3; B-type natriuretic peptide; Diagnosis

1 Introduction

Heart failure (HF) is a common cardiovascular disease in the elderly. HF affects about 10% of people aged > 65 years of age in the United States. About 40%–50% patients with HF have preserved ejection fraction (HFpEF).[1] Despite advances in HF therapy, treatment outcomes remain poor, with 5-year mortality approaching 50% in symptomatic patients. Therefore, early diagnosis and treatment are very important in improving life expectancy and the quality of life of HF patients.

Galectin-3 is a soluble β-galactoside-binding lectin. Before 2006, it had been studied mainly for its role in the proliferation, invasion, and transformation of tumors.[2] Later studies showed that galectin-3 expression is up-regulated in HF patients, and that galectin-3 may be used as a biomarker for the diagnosis and prognosis of HF.[3,4] Galectin-3 was approved by the US Food and Drug Administration (FDA) in 2010 as a new biomarker in stratification of the risk of HF risk.

In the present study, we determined levels of galectin-3 and B-type natriuretic peptide (BNP) in pEF patients with or without HF. We then compared their values for the diagnosis of HF in pEF patients.

2 Methods

2.1 Patients

The study protocol was approved by the Ethics Committee of the General Hospital of the Beijing Command of the PLA (Beijing, China). All patients provided written informed consent to be included in the study.

Correspondence to: Qiu-Sheng Ying, PhD, Department of Geriatric Cardiology, General Hospital of Beijing Command of PLA, Beijing 100700, China. E-mail: yinqiusheng2001@aliyun.com

Telephone: +86-10-66721873 **Fax:** +86-10-84014381

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Thirty-five HFpEF and 43 pEF patients without HF (control) were recruited. All patients were enrolled in the Department of Geriatric Cardiology of the General Hospital of the Beijing Command of the PLA from January 2013 to May 2013.

Of the 35 HFpEF patients, 29 had hypertension, 25 had coronary heart disease, 10 had infarction, and 17 had diabetes mellitus. Of the 43 pEF patients without HF, 35 had hypertension, 9 had coronary heart disease, and 16 had diabetes mellitus. The average age was 82.31 ± 6.72 years in HFpEF patients and 63.36 ± 11.14 years in control patients. Most patients were males: 85.71% in the HFpEF group and 90.70% in the control group.

2.2 Criteria for HF diagnosis

Criteria for HF diagnosis in pEF patients were overt symptoms of HF, left ventricular ejection fraction (LVEF) > 45%, normal size of the left ventricular cavity, and left ventricular diastolic dysfunction as confirmed by echocardiography. Patients with valvular heart disease, cardiomyopathy, or cardiac hypertrophy were excluded. Patients with HF were associated with New York Heart Association (NYHA) classes II–IV.

2.3 Measurement of galectin-3 level

Galectin-3 levels in plasma were determined by Kindstar Global (Beijing, China) using an enzyme-linked immunosorbent assay (ELISA) from BG Medicine (Waltham, MA, USA). Venous blood (4 mL) was collected into tubes containing potassium EDTA (1 mg/mL blood) and aprotinin (50 KIU/mL blood) early in the morning on the day of hospitalization. Blood samples were centrifuged within 1 h at 2000 r/min at 4°C for 15 min. Plasma was collected and stored at −70°C until analyses. Cutoff value of galectin-3 in the present study was set at 17.8 ng/mL (the concentration used in HF risk stratification by the US FDA). BNP levels in plasma were determined in the laboratory of our hospital using an ELISA. The cutoff value of BNP was set at 100 pg/mL.

2.4 Statistical analyses

Data were analyzed using SPSS v13.0 (SPSS, Chicago, IL, USA). Levels of galectin-3 and BNP are the mean ± SD. Differences between groups were analyzed using the independent-sample *t*-test. Differences in proportions between groups were tested using the χ^2 test. Sensitivity, specificity, predictive values, accuracy, and 95% confidence intervals (CIs) for proportions were calculated using standard methods for binomial distribution. Receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) values of galectin-3 and BNP were calculated and compared. $P < 0.05$ was considered significant.

3 Results

3.1 Levels of galectin-3 and BNP in HFpEF and control groups

Concentrations of galectin-3 and BNP in the HFpEF group were significantly higher than those in the control group ($P = 0.000$ and $P = 0.001$, respectively) (Table 1).

Table 1. Levels of galectin-3 and BNP in HFpEF and control groups.

Group	*n*	Galectin-3 (ng/mL)	BNP (pg/mL)
HFpEF	35	23.09 ± 6.97	270.46 ± 330.41
Control	43	16.74 ± 2.75	59.94 ± 29.93
t		–5.477	–3.757
P		0.000	0.001

BNP: B-type natriuretic peptide; HFpEF: heart failure with preserved ejection fraction.

3.2 Sensitivity and specificity of galectin-3 and BNP for HF diagnosis

At a galectin-3 cutoff value of 17.8 ng/mL, 33 out of the 35 patients in the HFpEF group were diagnosed as having HF. Using a BNP cutoff value of 100 pg/mL, 27 out of the 35 patients in the HFpEF group were diagnosed as having HF. Of the 43 patients in the control group, 15 were diagnosed as having HF according to galectin-3 level, and 4 were diagnosed as having HF according to BNP level. The sensitivity of HF diagnosis by galectin-3 level was significantly higher than that by BNP ($P = 0.04$). However, the specificity of HF diagnosis by galectin-3 level was significantly lower than that by BNP ($P = 0.004$). Differences in the positive predictive value (PPV), negative predictive value (NPV), and accuracy between galectin-3 and BNP were not significant ($P > 0.05$), (Table 2).

Table 2. Sensitivity, specificity, and predictive values of galectin-3 and BNP (%).

Method	Sensitivity	Specificity	PPV	NPV	Accuracy
Galectin-3	94.3	65.1	68.8	93.3	78.2
BNP	77.1	90.7	87.1	83.0	84.6
χ^2	4.20	8.174	3.741	1.737	1.059
P	0.04	0.004	0.062	0.187	0.303

BNP: B-type natriuretic peptide; PPV: positive predictive value; NPV: negative predictive value.

3.3 Evaluation of galectin-3 and BNP as markers for HF diagnosis

Values of ROC and AUC curves for galectin-3 and BNP were calculated. There were no significant differences between the two methods ($P > 0.05$) (Figure 1, Table 3).

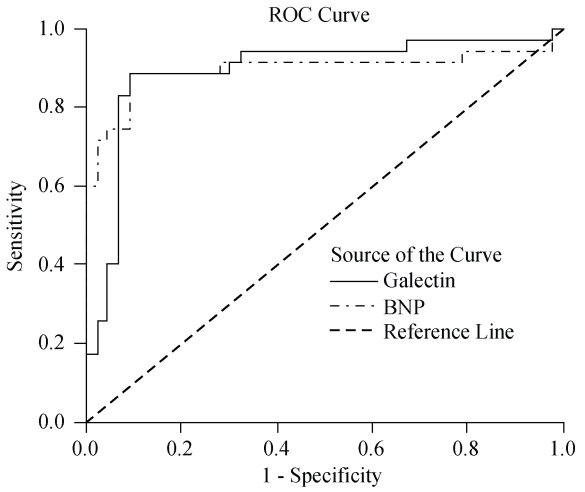

Figure 1. ROC curves of galectin-3 and BNP. BNP: B-type natriuretic peptide; ROC: receiver operating characteristic.

Table 3. AUC values of galectin-3 and BNP.

Method	AUC (95% CI)	*P*
Galectin-3	0.891 (0.808–0.974)	0.000
BNP	0.896 (0.809–0.984)	0.000

AUC: area under the receiver operating characteristic curve; BNP: B-type natriuretic peptide.

4 Discussion

HF occurs if the heart fails to provide a sufficient pumping action to maintain blood flow to meet bodily needs, and is characterized by systolic and diastolic dysfunction. The clinical diagnosis is commonly made by comprehensive analyses of medical history and symptoms, and results from echocardiography and biochemical tests. The diagnosis of HF in patients with pEF is more difficult than that in patients with abnormal ejection fraction owing to the lack of specific markers. Therefore, new diagnostic biomarkers are needed urgently for HF diagnosis in pEF patients.

Galectin-3 is a soluble β-galactoside-binding lectin released by activated macrophages in the heart. It functions as a potential mediator in the inflammation, macrophage migration, fibroblastic proliferation, and pathophysiological processes of HF. Before 2006, studies on galectin-3 focused on its role in the growth and metastasis of tumors. In recent years, galectin-3 expression has been demonstrated to be up-regulated in patients with acute decompensated HF. Elevated serum levels of galectin-3 in patients with chronic HF are associated with higher NYHA class and worse treatment outcome.[5,6] Additionally, increased galectin-3 levels in patients with HF are associated with significantly longer hospitalization and greater mortality.[7] Galectin-3 is strongly linked to the multiple clinical manifestations of HF (especially myocardial fibrosis).

We found the average level of galectin-3 in the plasma of HFpEF patients to be 23.09 ± 6.97 ng/mL, which was higher than that in control patients without HF ($P < 0.01$). Similar findings have been reported in patients with HF.[8] Plasma levels of galectin-3 in patients with HFpEF in the present study were slightly higher than that reported previously in HF patients with LVEF <45% (20.2 ng/mL).[7] Moreover, the plasma level of BNP (an important biomarker in the clinical diagnosis of HF) was also higher in HFpEF patients than in control patients without HF ($P < 0.01$). It has been reported that galectin-3 levels are significantly correlated with BNP levels.[9] Our data suggest that galectin-3 levels are elevated in pEF patients with HF and, similar to BNP, galectin-3 may be a valuable biomarker for the diagnosis and prognosis of HF in patients with pEF.

BNP is the most validated biomarker for HF diagnosis. It is recommended in guidelines for HF diagnosis in patients with acute dyspnea as well as for risk stratification of patients with chronic HF. Galectin-3 has little or no response to volume unloading,[8] whereas BNP responds directly to volume overload and unloading. What causes the changes in galectin-3 level remains speculative. Recently, it has been shown that galectin-3 is modulated by genetic variances.[10] Galectin-3 levels may signal different aspects of pathophysiologic processes in HF than BNP so galectin-3, as a novel biomarker for HF, could provide additional information in the diagnosis and prognosis of HF.

We determined galectin-3 and BNP levels in HFpEF patients and control patients without HF. We then assessed the sensitivity, specificity, predictive values, and accuracy of galectin-3 and BNP as biomarkers for HF diagnosis in pEF patients. Moreover, we compared the diagnostic performance of galectin-3 and BNP by statistical analysis. Our data suggest that galectin-3 is a more sensitive ($P < 0.05$) but less specific ($P < 0.01$) biomarker than BNP. However, galectin-3 and BNP have no differences in accuracy, PPV, or NPV ($P > 0.05$) in HF diagnosis. Interestingly, a recent report by Chen *et al*.[11] suggested that galectin-3 has higher specificity, but not higher sensitivity, than the N-terminal of the prohormone brain natriuretic peptide for the diagnosis of chronic HF. In the report by Chen *et al*.[11], galectin-3 and BNP showed AUC values of 0.891 and 0.896, respectively,

suggesting that they both performed well as biomarkers for the diagnosis of chronic HF in pEF patients. Specifically, AUC values of galectin-3 and BNP were not significantly different ($P > 0.05$). In another recent report, galectin-3 showed an AUC of 0.68 for the diagnosis of advanced chronic HF in pEF patients.[12] Other frequently used biomarkers such as BNP, high-sensitivity C-reactive protein (hs-CRP), and high-sensitivity troponin T have AUC values of 0.63, 0.66, and 0.68, respectively, for HF diagnosis. Therefore, galectin-3 may be superior to BNP and hs-CRP for HF diagnosis.

Our results suggest that galectin-3 is more sensitive whereas BNP is more specific in HF diagnosis. Galectin-3 and BNP are important biomarkers for HF diagnosis. If used together, they could provide an accurate clinical diagnosis.

The main limitation of the present study was the relatively small sample size. Further assessment of galectin-3 as a biomarker for HF diagnosis in patients with pEF should be conducted with a larger study cohort.

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