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Additional value of Galectin-3 to BNP in acute heart failure patients with preserved ejection fraction

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ABSTRACT

Background: Almost half of patients with acute heart failure have preserved ejection fraction (HFpEF). HFpEF is a diagnostic challenge using traditional investigation tools; Galectin-3 (Gal-3) is an emerging biomarker useful in individuals at risk for HF. The aim of our study is to analyse the relation and prognostic value of Gal-3, BNP and renal dysfunction in patients with HFpEF compared to patients with reduced ejection fraction (HFrEF).
Methods: We enrolled 98 patients with acute heart failure (AHF) and measured Gal-3, BNP, and estimated glomerular filtration rate (eGFR) within 12 h of hospital admission. On the basis of echocardiographic findings we divided our sample into two groups: patients with HFrHF (ejection fraction < 50%) or HFpEF (ejection fraction > 50%). Patients were followed up at 6 months.
Results: No differences in Gal-3 levels were found in the two subgroups (HFrEF: 19.5 ± 5.1 ng/mL; HFpEF: 20.5 ± 8.7, $p = 0.56$). Gal-3 was inversely related to renal dysfunction (LogGal-3 vs eGFR: $r = -0.30$, $p = 0.01$) but did not correlate with LogBNP levels ($r = 0.07$, $p = 0.55$). Gal-3 was associated with more advanced diastolic dysfunction in HFpEF ($p = 0.009$). In addition LogGal-3 was related to diastolic LV stiffness (all patients: $r = 0.45$, $p < 0.001$; HFpEF: $r = 0.64$, $p < 0.001$). Cox regression analysis showed that LogGal-3 > 1.30 was related to poor outcome independently from renal dysfunction and other risk factors only in HFpEF (univariate HR 23.98 [3.03–89.45]; $p < 0.001$). Adjusted for renal dysfunction (HR 16.32 [1.98–34.09]; $p = 0.009$).
Conclusions: Gal-3 is not able to distinguish between HFrEF and HFpEF patients. However it is related to diastolic dysfunction severity and LV stiffness in HFpEF. Gal-3 demonstrates a prognostic role independently from renal dysfunction in subjects with HFpEF.

1. Introduction

The wide characteristic spectrum of heart failure (HF) syndrome depends on the heterogeneity of patient population and multiple etiologies. Around half patients with acute heart failure (AHF) have left ventricular ejection fraction (LVEF) > 50% and are classified as heart failure with preserved systolic function (HFpEF). Unfortunately, most interventional trials focused on patients with heart failure and reduced ejection fraction (HFrEF), and there is a paucity of data in patients with HFpEF. These patients are more often old, female, and obese with higher incidence of hypertension and atrial fibrillation (AF) [1]. In this context additional parameters for both diagnostic and prognostic assessment may facilitate HF diagnosis identifying the pathophysiological process responsible for the disease as well as prognostic assessment [2]. Early diagnosis is mandatory for both therapy optimization and risk stratification. For this reason, there is an increasing interest in the development of new biomarkers and a great number of laboratory tests have recently been studied [3]. Galectin-3 (Gal-3) is an emerging biomarker useful in individuals at risk for HF, in both acute and chronic HF, not only in HF management but also in prognostication [4,5]. A recent pooled-meta-analysis in patients with AHF showed that circulating Gal-3 plasma levels are a strong predictor of outcome in terms of death and HF re-hospitalization [6].

Gal-3 is a beta galactoside-binding lectin secreted by macrophages. In response of this activation, galectin-3 initiates a pro-fibrotic process: other macrophages, pericytes, and myofibroblasts are consequentially activated. At the end of the cascade the fibroblasts lead to the deposition of collagen into the extracellular matrix. This process leads to a progressive cardiac fibrosis and consequent pathological remodeling of the myocardium structure [7]. Myocardial fibrosis and extracellular matrix collagen deposition are two major players in HFpEF pathophysiology [2]. However the diagnostic evaluation of HFpEF remains underestimated due to the absence of a universally accepted definition of the disease. Moreover, several studies evaluated Gal-3 in chronic HF

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patients and mainly in subjects with systolic dysfunction [8,9]. Although several studies on Gal-3 as risk factor in HFpEF, less data are available in acute heart failure subject and its diagnostic and prognostic role remains debated in this field. Finally, increased levels of Gal-3 have been recently found in patients with renal dysfunction and chronic kidney disease (CKD), and this condition appears strictly related to protein levels [10]. Based on these concerns, the aim of this study was to investigate the diagnostic role, of Gal-3 and B-type natriuretic peptide (BNP) in patients with HFrEF compared to patients with HFpEF. We also analysed the prognostic value of two biomarkers and the relation between Gal-3 and renal dysfunction.

2. Methods

2.1. Population

We evaluated 103 consecutive patients with AHF admitted to our Department since September 2012 to February 2015. Five patients were subsequently excluded, due to lack of echocardiographic data. In our sample remain 98 patients and we performed echocardiography and measured Gal-3 and BNP within 12 h of hospital admission. Patients were enrolled within 12 h of hospital admission with diagnosis of new onset or exacerbated AHF, with signs and symptoms of acute decompensated HF: dyspnoea, orthopnoea, pulmonary rales, third heart sound, peripheral oedema or exercise intolerance, chest X-ray signs of pulmonary pressure overload, dilated jugular veins, and hepathic-jugular reflux. All these patients were screened for Diur HF trial (NCT01441245).

We previously excluded patients with poor acoustic window on echocardiography, respiratory dyspnoea due to bronchial asthma, interstitial lung disease (ILD) or chronic obstructive pulmonary disease (COPD). We excluded patients with acute or recent myocardial ischemia (<6 months) by anamnestic investigation, serial electrocardiographic (ECG) and troponin and myoglobin measurement. We also excluded patients with severe renal insufficiency (eGFR ≤ 15 mL/min/1.73 m^2) in haemodialysis and renal replacement treatment, neoplastic, hematologic and immune diseases with systemic involvement. (Fig. 1).

The echocardiography was performed using HP Sonos 5500 machine. All the examinations were performed by two experienced cardiologists according to the instructions provided by the American Society of Echocardiography [11]. Therefore principal measurements were recorded and independently reviewed by two distinct physicians. Standard echocardiographic M-mode measurements were used for the determination of left ventricle (LV) diameters and wall dimensions. The systolic and diastolic volumes and ejection fraction were determined using apical two- and four chamber views by Simpson biplane formula. We evaluated three consecutive cardiac cycles to obtain average pulsed Doppler transmitral flow velocity during early diastole velocity (E wave) and late diastole velocity (A wave) ratio (E/A) and the deceleration time (DT) of E. The isovolumetric relaxation time (IVRT) was obtained in the apical five chambers view placing the pulsed Doppler between the LV outflow tract and the mitral inflow tract.

We estimated the systolic pulmonary artery pressure (PAPs) by continuous Doppler at tricuspid valve level. The Tricuspidal Anular Plane Systolic Excursion (TAPSE) was obtained by placing the M-mode cursor laterally to the tricuspid annulus. Each result was normalized for body surface area (in m^2), calculated by the weight and height of each patient.

We assessed the diastolic pattern by the following cut-off: impaired relaxation pattern [diastolic dysfunction type I (E/A < 0.8, DT > 200 ms, IVRT > 100 ms, E/e′ < 8 septal and lateral)]; pseudo-normal filling pattern [diastolic dysfunction type II (E/A 0.8–1.5 and decreases by 50% during the Valsalva maneuver, DT 160–200 ms, IVRT < 90 ms, 9 > E/e′ > 12)]; restrictive filling pattern [diastolic dysfunction type III (E/A > 2, DT < 160 ms, IVRT < 60 ms and average E/e′ ratio > 13)]. The ratio of peak early diastolic filling velocity and septal TDI early diastolic

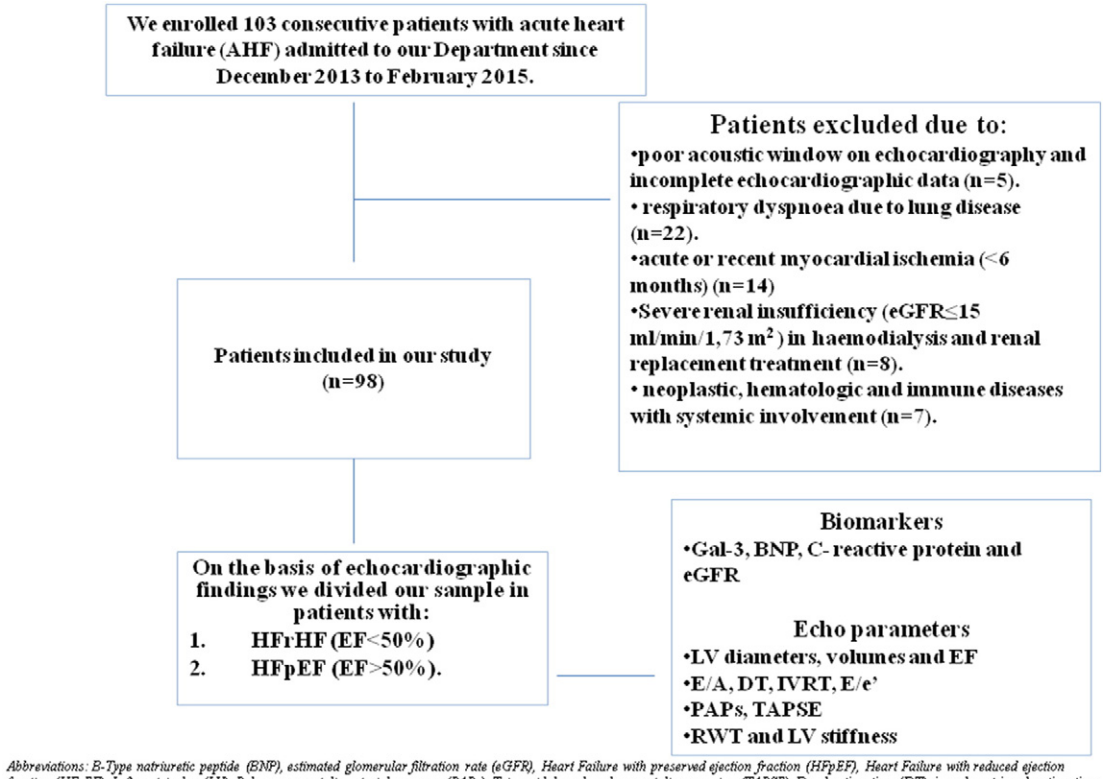

Fig. 1. Flow-chart describing patients screened in our study.