

Heart failure and galectin 3

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Abstract: Innovations in medical diagnosis and treatment have led to prolongation of life of patients. Increasing the life expectancy of cardiac patients and thereby increasing the prevalence of heart failure (HF). Currently more than one million hospital admissions per year are due to HF and it has been estimated that the cost is approximately \$39 billion annually in the U.S. There are two pathophysiologic myocardial mechanisms that cause HF: systolic dysfunction and diastolic dysfunction. Normal cardiac aging is characterized by morphological and structural changes that increase cardiomyocyte size, increased number of apoptosis with decreased number in myocytes, increased collagen deposition, and functional changes at cellular level. All these factors contribute to fibrotic remodeling that leads to LV diastolic stiffness, which ultimately leads to impaired diastolic function. At the same time it has been shown that galectin-3, a soluble β -galactoside-binding protein secreted by activated macrophages, promotes cardiac fibroblast proliferation, collagen deposition, and ventricular dysfunction. In this paper we review the prognostic value of galectin-3 as an independent predictor of mortality in patients with moderate to advanced chronic HF (CHF).

Keywords: Galectin 3; systolic heart failure (HF); diastolic HF

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Introduction

More than one million hospital admissions per year are due to heart failure (HF), it has been estimated that the cost is approximately \$39 billion annually in the U.S (1). HF results from structural or functional cardiovascular disorders that cause inadequate systemic perfusion (2). Patients complain of breathlessness (dyspnea) at normal or mild exertion, fatigue, paroxysmal nocturnal dyspnea and peripheral edema (3). It is a common clinical syndrome caused by a variety of diseases such as hypertension, anemia, COPD, cancer, diabetes mellitus, atrial fibrillation, diseases affecting the pericardium, myocardium, endocardium, cardiac valves or cardiac vessels (1-3). Although there is no specific diagnostic test for HF, initial evaluation for patients with symptoms suggestive of HF includes clinical assessment thorough history and physical exam), electrocardiogram, blood tests, and chest X-ray, and measurement of plasma brain natriuretic peptide (BNP) or N-terminal pro-BNP levels is suggested in patients with

suspected HF in whom the diagnosis is uncertain (2). New studies have suggested the measurement of galectin-3 as a marker for cardiac remodeling (4,5).

There are two pathophysiologic myocardial mechanisms that cause HF: systolic dysfunction and diastolic dysfunction.

Systolic dysfunction

Systolic dysfunction is also known as HF with reduced ejection fraction, defined as a left ventricular EF of <40%. Most common causes of systolic dysfunction are ischemic heart disease, idiopathic dilated cardiomyopathy (DCM), hypertension, and valvular disease. Being DCM the most frequent etiology (1,2).

Diastolic dysfunction

Diastolic dysfunction is also known as HF with preserved ejection fraction (HFpEF), defined as a left ventricular >45%

(3,6). Many of the same conditions that lead to systolic dysfunction have been found to cause HFpEF, among the most common are hypertension, ischemic heart disease, hypertrophic obstructive cardiomyopathy, and restrictive cardiomyopathy. Concomitantly to make the diagnosis of HFpEF patients must present abnormal LV relaxation, diastolic distensibility, or diastolic stiffness (3) and no valvular abnormalities detected echocardiographically, as established by the American College of Cardiology/American Heart Association (7). The final effect is the shift of LV filling from early to the latter part of diastole (2).

Pathology

Innovations in medical diagnosis and treatment have led to prolongation of life of patients. Increasing the life expectancy of cardiac patients and thereby increasing the prevalence of HF (2). Normal cardiac aging is characterized by morphological and structural changes that increase cardiomyocyte size, increased number of apoptosis with decreased number in myocytes, increased collagen deposition, and functional changes at cellular level. Which all contribute to fibrotic remodeling that leads to LV diastolic stiffness, which leads to impaired diastolic function (8-10).

There is significant evidence that suggest that the activation of several molecular pathways may contribute to age-related fibrotic cardiac remodeling. Pathways such as transforming growth factor (TGF)- β activation, endothelin-1 and angiotensin II signaling mediate interstitial and perivascular fibrosis in the senescent heart and galectin-3 (8,11,12). Reason for which galectin has been established as a biomarker of cardiovascular diseases, risk stratification, evaluation of therapy response and predictor of short-term and long-term prognosis (8).

Other mechanisms thought to be involved in HF include reduced expression and regulation of proteins involved with calcium cycling into and out of the sarcoplasmic reticulum, depression of β -adrenergic signaling, proteins involved in oxidative stress targeting calcium-handling and reduced recoil of elastic elements compressed during systole (3).

In patients with HFpEF the expression of collagen type I and type III are elevated and are coupled to reduced collagenase and metalloproteinase-1. At the same time cross-linking of collagen including the formation of advanced glycation end products and increased tissue inhibitor of matrix metalloproteinase-1 expression, enhance and promote fibrosis and stiffening (3,13).

Galectin-3

A total of 15 mammalian galectins have been described, these have been subcategorized into three groups based on their carbohydrate-recognition domain (CRD) (14,15). The first group includes galectins-1, -2, -5, -7, -10, -13, -14 and -15. The second group is composed by galectins that contain two-CRD joined by a linker peptide of variable length, these are galectins-4, -6, -8, -9 and -12. The third group is galectin-3, it is the only member of the family of galectins that has three distinct structural motifs: (I) a short NH₂ terminal domain containing a serine phosphorylation site; (II) a repetitive proline-rich collagen- α -like sequence cleavable by matrix metalloproteases; and (III) a globular COOH terminal domain containing a carbohydrate binding motif and a NWGR anti-death motif (14,16,17).

Galectin-3 is a member of the family of soluble b-galactoside-binding lectins and it plays a crucial role in several diverse biological processes and diseases (18). Mainly it is known for its role as a mediator of tumor growth, progression and metastasis (19). At the same time it has also been associated it with increased age, diabetic nephropathy (20), fibrotic conditions such as liver fibrosis (21), renal fibrosis, idiopathic lung fibrosis and chronic pancreatitis (22,23). Recently it has drawn greater attention to its contribution in the pathophysiology of HF since it has been shown that galectin-3 promotes cardiac fibroblast proliferation, collagen deposition, and ventricular dysfunction (24,25).

The mechanism by which galectin-3 is released into the extracellular space is not well understood. Lukyanov *et al.* reported findings that suggested that galectin-3 on its own has the capacity to traverse the lipid bilayer (26).

Galectin-3 has been found to be located in the cytoplasm, nucleus and extracellularly where it has different effects. Cytoplasmic galectin-3 had an anti-apoptotic activity; it is found to regulate several signal transduction pathways. Nuclear galectin-3 has been associated with pre-mRNA splicing and gene expression. It is also able to induce like cell growth, adhesion, migration, invasion, angiogenesis, immune function, apoptosis and endocytosis (17).

Concomitantly, it has been found that exogenously added galectin-3 has been shown to influence the growth of many different cell types, including immune cells (27). On the other hand galectins-1 and -3 induce apoptosis in T cells, including human T-leukemia cell lines, human peripheral blood mononuclear cells (PBMC), and activated mouse T-cells (28,29). Galectin-3 has also been associated with

apoptosis in neutrophils (30).

At the same time, galectin-3 has a direct effect on immune and inflammatory responses by modulating cell adhesion of various immune cell types (31). It has been evidenced that recombinant galectin-3 was found to promote adhesion of human neutrophils to laminin (32) and to endothelial cells (33). At the same time galectin-3 has found to have a suppressive effect on myeloid cells, by inhibiting IL-5 production in human eosinophils (34). To be able to fully understand the functions of galectin-3 *in vivo* will require inhibitors that will be able to differentiate intracellular from extracellular galectin (14).

Molecular effects of galectin-3 in cardiac remodeling

Galectin-3 is a soluble β -galactoside-binding protein secreted by activated macrophages. This leads to progressive inflammation, tumor growth and cardiac fibrosis (5,35). It has been in the last couple of years that galectin-3 has been studied as a new independent biomarker for diagnosis of acute HF and outcome predictor in patients with chronic HF (CHF) (36).

As described above cardiac remodeling is one of the main components of HF. Immune cells are recruited to the myocardium after acute or chronic damage or with age. Galectin-3 is released in the myocardium, via a paracrine effect, stimulating proliferation of myofibroblasts and procollagen-1 deposition (37,38). The activation of fibroblasts and myofibroblasts and the deposition of procollagen into the extracellular matrix is what ultimately lead to cardiac fibrosis (5,25,35,39).

Galectin-3 has been found to be upregulated in the plasma of patients with acute and CHF (5). A study was done using a rat model of HF prone hypertensive hearts, where they were able to demonstrated upregulation of galectin-3 in myocytes (5). Concomitantly, galectin-3 has also been found to be significantly up-regulated in the hypertrophied hearts of patients with aortic stenosis (40).

Sharma *et al.* were able to demonstrate that galectin-3 infusion into the pericardium of normal rats led to the development of cardiac remodeling. Concomitantly their results showed that the highest levels of galectin-3 were among the group of animals that had the highest degree of cardiac fibrosis and had developed HF (5,24). Liu *et al.* also confirmed that galectin-3 infused in pericardial sac leads to cardiac inflammation, remodeling, and dysfunction in adult male rats (37,41).

Prognostic value of galectin-3 in HF

Galectin-3 has been known to affect cell growth and survival, activate or inhibit cellular responses, modulate cell adhesion, and induce cell migration (14). But it has been recently that galectin-3 has been associated with HF. Galectin-3 levels are reliably measured in plasma, for this reason there have been several studies on plasma galectin-3 as a biomarker in HF. However, until now only limited data are available in human HF. There have been several studies on the pathophysiological role for galectin-3 in development and progression of HF, such galectin-3 mediates aldosterone-induced vascular fibrosis by Calvier *et al.* (42), fibrosis in HF subtypes by Toprak *et al.* (43) among others. For these reasons, it is speculated that the blockade of galectin-3 may slow down the progression of HF and reduce the morbidity and mortality associated (23). Due to this, its prognostic value has been evaluated in several studies, some of which are discussed below.

According to Lok, the prognostic value of galectin-3 appears to be high, making galectin-3 an independent predictor of mortality in patients with moderate to advanced CHF. A total of 232 patients with CHF (New York Heart Association functional class III or IV) who participated in the Deventer-Alkmaar HF study were followed up for 6.5 years. In this span of time, 98 patients died. Galectin-3 was adjusted for age and sex, and severity of HF and renal dysfunction, and was found to be a significant predictor of mortality risk. ROC curve analysis revealed an area under the curve (AUC) of 0.612 (0.538-0.685), $P=0.004$ for galectin-3 and 0.611 (0.538-0.685), $P=0.004$ for NT-proBNP. Although the highest product of sensitivity and specificity was seen with gal-3 levels of 17.72 ng/mL, the Kaplan-Meier survival curves showed that there was a gradual increase in all-cause mortality across the galectin-3 quartiles (log-rank $P=0.048$). Concomitantly patients with high baseline levels of both galectin-3 and NT-proBNP were observed to have an approximately 1.5- to 2-fold higher mortality rate compared to patients in other categories ($P=0.036$ for trend) (22).

In the study by van Kimmenade *et al.*, researchers investigated the utility of galectin-3 alone or together with natriuretic peptide testing for diagnosis and short-term prognosis estimation in subjects with acute HF. Galectin-3 was measured in 599 patients with acute dyspnea who presented to the emergency department, of whom 209 (35%) were diagnosed as "acute HF". The NT-proBNP was superior to galectin-3 for diagnosis of acute HF, the ROC curve of galectin-3 for the diagnosis of HF was 0.72

($P=0.001$) as compared to a ROC curve for NT-pro BNP of 0.94 ($P=0.001$; difference with galectin-3 $P=0.001$). Concomitantly, galectin-3 levels were higher in those with acute HF than in those who did not (9.2 vs. 6.9 ng/mL; $P=0.001$). The analysis for mortality prediction showed that, for 60-day prognosis, galectin-3 had the greatest AUC at 0.74 ($P=0.0001$), whereas NT-proBNP had an AUC of 0.67 ($P=0.009$). At the same time, a multivariate logistic regression analysis showed that the elevation of galectin-3 was the best independent predictor of 60-day mortality (odds ratio 10.3, $P<0.01$) or the combination of death/recurrent HF within 60 days (odds ratio 14.3, $P<0.001$). The Kaplan-Meier analyses done in this study showed that the combination of an elevated galectin-3 with NT-proBNP was a better predictor of mortality than either of the two markers alone (44).

The study by Milting *et al.* analyzed several biomarkers for myocardial remodeling in plasma among them galectin-3, from 55 end stage HF patients who needed mechanical circulatory support (MCS). Subsequently, this data was compared to 40 healthy controls. Plasma biomarkers were analyzed pre- and 30 days post-implantation of a MCS. Galectin-3 levels were higher in HF patients than in controls (11 vs. 4.1 ng/mL, $P=0.05$), but galectin-3 remained elevated or even increased further 30 days after MCS in contrast to BNP levels that decreased after the MCS. However, patients who died or in whom multi-organ failure developed, had significantly higher galectin-3 levels, in comparison to those that had a successful procedure (45).

In the study by de Boer *et al.*, 592 patients that were hospitalized for HF were followed for 18 months. They found that a doubling of galectin-3 levels was associated with a hazard ratio (HR) of 1.97 (1.62-2.42) for the primary outcome ($P<0.001$). Galectin-3 levels were correlated with higher IL-6 and CRP levels ($P<0.002$). The ROC analysis of galectin-3 for the prediction of the primary outcome showed an AUC of 0.67 ($P<0.004$), while the AUC of BNP was 0.65 ($P<0.001$). The combination of both galectin-3 and BNP was 0.69 ($P<0.05$ versus BNP or galectin-3 alone) while the AUC of 6-month galectin-3 was 0.66 ($P<0.04$). The predictive value of galectin-3 was stronger in patients with preserved LVEF ($n=114$) compared to patients with reduced LVEF ($P<0.001$). Galectin-3 shows being an independent marker for outcome in HF particularly in HF patients with preserved LVEF. In conclusion, they found that the interaction with LVEF much stronger in the subset of HF patients with preserved LVEF, in comparison to HF

patients with reduced LVEF and that base-line galectin-3 levels were enough to predict outcome (39).

Chen *et al.* studied the predictive value of plasma galectin-3 in 62 patients with CHF. They found that the level of galectin-3 was significantly higher in NYHA functional class III and IV compared with that in control ($P<0.05$ and $P<0.01$, respectively). At the same time level of plasma galectin-3 was positively correlated with LAD ($r=0.271$, $P<0.05$) and LVEDD ($r=0.480$, $P<0.01$), but negatively correlated with LVEF ($r=-0.683$, $P<0.01$). In contrast the levels of plasma NT-pro BNP was positively correlated with LAD ($r=0.481$, $P<0.01$) and LVEDD ($r=0.270$, $P<0.05$), but negatively correlated with LVEF ($r=-0.516$, $P<0.01$). AUC was 0.798 when the level of plasma galectin-3 was more than 7.52 ng/mL and the sensitivity to predict CHF was 62.9%, and the specificity was 90%. On the other hand, the AUC was 0.901 when the level of plasma NT-pro BNP was more than 1,143 pg/mL and the sensitivity to predict CHF was 92.8% and the specificity was 85%. Indicating that specificity of galectin-3 to predict CHF is higher than NT-pro BNP, but not as sensitive (46).

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