Galectin-3: a potential biomarker for diagnostics of heart failure

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ABSTRACT

Heart failure is a dysfunction with varied etiology; one of possible causes is anticancer treatment with anthracyclines. Rapid diagnosis is important because the disease is associated with high mortality and morbidity. The only biomarkers fully approved for diagnostics of heart failure are natriuretic peptides. They are secreted by ventricular muscle cells in response to volume and pressure overload. However, their concentration can be influenced by other factors, such as age or gender. A potential marker, not affected by these issues might be galectin-3. Current studies showed that galectin can play particularly significant role in myocardial fibrosis and inflammation. Elevated galectin-3 concentration has been observed in such cardiovascular diseases as heart failure, atherosclerosis, stroke and myocardial infarction. The review summarizes results of studies which indicate the role of galectin-3 in inducing fibrosis and cardiac remodelling (processes which influence disease progression and prognosis) and showed its potential diagnostic value.

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Galectins are family of proteins with characteristic carbohydrate recognition domain (CRD), consisting of 130 amino acids. CRD is responsible for recognizing β-galactosides, especially glycans with N-acetylgalactosamine. 15 proteins from this family has been discovered so far. They were divided, according to their structure, to [1]:

1. Prototypical galectins: one CRD domain; two subunits may form dimer; galectins with this structure are: Gal-1, -2, -5, -7, -10, -11, -13, -14, -15.
2. Tandem galectins: two CRD domains joined by a sequence of 70 amino acids; galectins with this structure are: Gal-4, -6, -8, -9, -12.
3. Chimeric galectins: single CRD fused to N-terminal sequence of 120 amino acids; they can form pentamers; Gal-3 is the only member of this group.

Galectins can be found in many different cells (skeletal muscles, neurons, kidneys, placenta, active macrophages, mastocytes, epithelial cells of gastrointestinal tract, respiratory system). Their location and intracellular function depends on type and condition of cells [1]. Galectin-3 (Gal-3) expression was observed in neutrophils, macrophages, fibroblasts, mast cells, os-

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teoclasts, cancer cells. Typical tissues for galectin-3 presence include lungs, spleen, stomach, colon, adrenal glands, uterus, ovaries. In lesser amounts, galectin-3 can be found in heart, kidneys, brain, pancreas, liver [2]. Current studies showed that galectin can play particularly significant role in myocardial fibrosis and inflammation. It was also found, that galectin can contribute to tumour growth, angiogenesis, and metastatic progression. Elevated galectin-3 concentration has been observed in such cardiovascular diseases as heart failure, atherosclerosis, stroke and myocardial infarction [3–5].

Heart failure is a dysfunction with varied etiology; one of possible causes is anticancer treatment with anthracyclines. Rapid diagnosis is important because the disease is associated with high mortality and morbidity. The only biomarkers fully approved for diagnostics of heart failure are natriuretic peptides (especially BNP and NT-proBNP) which are secreted by ventricular muscle cells in response to volume and pressure overload. However, their concentration can be influenced by other factors, such as age, gender, renal function, anaemia, overweight, atrial fibrillation, and volume status showing that it reflects haemodynamic condition rather than structural abnormalities of the heart [6, 7]. A potential marker, not affected by these issues might be galectin.

Of all galectins, galectin-3 is particularly interesting as it has effect on cardiac fibrosis and remodelling: both mechanisms influencing the development and progression of heart failure [7]. Animal studies confirmed upregulation of Gal-3 expression in myocardial biopsies of rats with cardiac hypertrophy [8]. Myocardial level of Gal-3 is nearly undetectable in myocytes while increasing significantly in fibroblasts [9]. A very important feature of Gal-3 is its influence on fibrosis, fibroblasts proliferation and synthesis of type 1 collagen which forms rigid protein fibers resistant to stretching [2]. It was found out in animal studies that pathologic mechanism of collagen accumulation and myocardial remodelling is associated with rapid increase in Gal-3 concentration [9]. Analysis of rats cardiovascular biopsies revealed that severe heart fibrosis and clinical diagnosis of heart failure is preceded by increased Gal-3 level [10]. These results indicated the role of Gal-3 in inducing fibrosis and cardiac remodelling (processes which influence disease progression and prognosis) and showed its potential diagnostic value.

It was observed in PRIDE and COACH clinical studies that Gal-3 was a prognostic marker for 60-day and 18-month mortality and rehospitalization of patients with acute heart failure [11, 12]. Long-term (up to 4 years) predictive value of Gal-3 was found by Shah et al. in the group of patients with acutely decompensated heart failure; prediction was independent of echocardiographic markers of disease severity [8]. Similar findings, concerning association of increased Gal-3 level with increased probability of death or rehospitalization, were described in patients with chronic heart failure [13–16]. Gal-3 prognostic value was negated in some studies corrected with renal function parameters and natriuretic peptide level. Therefore, despite the results of huge metanalysis (> 8,000 patients with acute or chronic heart failure) confirming the association between Gal-3 and increased risk of all-cause mortality and cardiovascular mortality, the role of Gal-3 measurement in patients with renal dysfunction remained a subject of doubt [17]. Predictive value of Gal-3 in the assessment of heart failure risk was evaluated in 2-year study on 100 patients with acute coronary syndrome. The study confirmed the association between increased Gal-3 level and development of heart failure. In patients, whose initial Gal-3 concentration was higher than median

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value the risk of heart failure was two times higher compared to the control group. Also, a poor but statistically significant negative correlation between Gal-3 and LVEF (left ventricular ejection fraction) was observed. The authors of the study applied for justifying the use of Gal-3 as marker of heart remodelling leading to heart failure [18].

The results of the study on general population, in a group of nearly 8,000 patients, with average observation period of 10 years, provided evidence that Gal-3 correlated with multiple cardiovascular risk factors, including lipid levels, diabetes mellitus, blood pressure, BMI, kidney function and NT-proBNP level. There was a strong association between Gal-3 levels and age and a particularly strong correlation between Gal-3 levels and the risk of cardiovascular disease in women. It was shown that in general population the marker concentration correlated with the risk of death and was a predictor of all-cause mortality [12].Another study on 4000 patients with similar follow up also confirmed that elevated Gal-3 level was an independent predictor of cardiac failure and death from any cause, even after correction of renal function and BNP measurements [19]. In the elderly population with unknown cardiovascular diseases, elevated Gal-3 level was associated with an increased risk of cardiovascular death in the 11-year period [20]. A study on 120 patients with hypertension with or without clinically apparent heart failure has recently been carried out on Polish population. There was no significant difference in initial Gal-3 concentration between heart failure and non-heart failure patients. Although increased Gal-3 concentration was not shown to influence the risk of apparent heart failure in patients with hypertension, the authors stated that addition of Gal-3 measurement to NT-proBNP assessment provided better diagnosis of heart failure [21].Potential prognostic value of galectin was recently observed by Imran *et al.* and Miro *et al.* [22, 23], they found that galectin level was associated with all-cause mortality, cardiovascular mortality and heart failure.

Based on the results of clinical trials, recommendations for use of Gal-3 in routine clinical practice have been formulated. According to the ACC/AHA (American College of Cardiology/American Heart Association) guidelines, monitoring of Gal-3 level is recommended in acute and chronic heart failure, to predict hospitalization or death risk, and as an addition to natriuretic peptides for risk stratification and disease progression [24]. Different opinion was presented by the ESC (European Society of Cardiology) experts who, according to the studies' findings, did not allow Gal-3 to be included in routine clinical practice [6].

The role of Gal-3 in apoptosis and cell cycle regulation is widely known [9]. Gal-3 levels are considered to be associated with the potential for tumour progression and spread, inhibition of breast cancer cell apoptosis, and resistance to treatment [25–27]. Available data indicate Gal-3 as a potential predictor of oncological mortality [9]. It seems that measurement of this marker may be important in the diagnosis of breast cancer, due to the relatively high level of Gal-3 expression in triple negative breast cancer [26, 27]. The results of studies in patients with breast cancer did not confirm that monitoring of Gal-3 levels was relevant for risk assessment or early diagnosis of anthracycline-induced cardiotoxicity. In the group of nearly 80 patients treated with doxorubicin and trastuzumab, no statistically significant changes were observed in Gal-3 levels within 3 months after starting treatment while troponin I and myeloperoxidase have been found to be useful in the early diagnosis of cardiotoxicity [28]. Quarterly monitoring of changes in Gal-3 level over a longer 15-month time period did not change this result. In a group of

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Table 1. Pros and cons for routine Gal-3 measurements in cardio-oncological patients

Pros	Cons
They are considered adequate in routine clinical practice in United States in patients with acute and chronic heart failure (American College of Cardiology/ /American Heart Association)	They are considered inadequate in routine clinical practice in Europe in patients with acute and chronic heart failure (European Society of Cardiology)
They are useful for assessment of severity of heart failure, the risk of death, re-hospitalization and better planning for the care of a diagnosed patient	Gal-3 is not a specific cardiac marker
Routine diagnosis of cardiac patients is supported by outcomes of clinical trials	Elevated level of Gal-3 may be associated with renal dysfunction accompanying the heart failure
Gal-3 plays a particularly significant role in myocardial fibrosis and inflammation; it is nearly undetectable in myocytes while increasing significantly in fibroblasts	Data available for the oncologic population is insufficient as Gal-3 can also contribute to tumour growth, angiogenesis, and metastatic progression
Gal-3 plays a role in other cardiovascular diseases as atherosclerosis, stroke and myocardial infarction	Results of studies in patients with breast cancer did not confirm that monitoring of Gal-3 levels was relevant for risk assessment or early diagnosis of anthracycline-induced cardiotoxicity
It is a potential heart failure marker, not affected by age, gender, anaemia, overweight, atrial fibrillation, and volume status	Gal-3 concentration was not shown to influence the risk of apparent heart failure in patients with hypertension
It correlates with multiple cardiovascular risk factors, including lipid levels, diabetes mellitus, blood pressure, BMI, kidney function and NT-proBNP level	
There is a negative correlation between Gal-3 and LVEF	

78 patients treated with doxorubicin and trastuzumab, no increase in Gal-3 was seen in three-month intervals. Similarly to the authors of the earlier study, the greatest chance for early diagnosis of cardiotoxicity was seen in the monitoring of changes in the level of myeloperoxidase [29]. The results of another analysis of 55 patients with breast cancer, one year after doxorubicin, docetaxel and cyclophosphamide treatment showed elevated levels of Gal-3 in only a small proportion of patients. Additionally, no statistically significant correlation with LVEF was found. It was considered that Gal-3 was not useful in the early diagnosis of cardiotoxicity, and further research should focus on NT-proBNP [30]. Summary of pros and cons for routine Gal-3 measurements in cardio-oncological patients is presented in Table 1.

US and European experts disagree on the introduction of routine Gal-3 measurements in patients with heart failure to clinical practice. The results of many studies indicated that Gal-3 may be a useful new tool for assessing the severity of the disease, the risk of death and re-hospitalization, and thus better planning for the care of a diagnosed patient [31, 32]. There is a great interest in the use of Gal-3 measurement in patients with heart failure and preserved ejection fraction [17]. Doubts are raised, among other things, by the fact that Gal-3 is not a specific cardiac marker, and some studies suggested that its elevated level was associated with renal dysfunction accompanying the heart failure [9]. Gal-3 profibrotic properties have been observed in liver, blood and kidney fibrosis and in the differentiation of myofibroblasts [9, 31]. The

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potential for Gal-3 for routine diagnosis of cardiac patients is supported by a number of clinical trials, but there is still insufficient data available for the oncologic population, hence the need for further studies and the unambiguous determination of the usefulness of Gal-3 in these patients.

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