

EDITORIAL COMMENT

Evolving Role of Galectin-3 as a Cardiac Biomarker



Heart Failure With Preserved Ejection Fraction and Renal Function, Important Pieces of the Puzzle*

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For more than a decade, galectin-3 (Gal-3) has been known to be an important mediator in the pathophysiology of heart failure (HF) predominantly by promoting fibrosis (1). Several years after that finding, levels of Gal-3 in the blood were recognized to be prognostic for death or recurrent acute HF in patients with acute decompensated HF, and additive to a natriuretic peptide level (2). Subsequently, there has been development and U.S. Food and Drug Administration approval of a commercial assay and discussion of the assay with a class IIb indication for additive risk stratification in patients with established HF in the most recent version of American Heart Association/American College of Cardiology Foundation HF guidelines (3,4). A recent review summarizing prognostic studies showed that Gal-3 concentrations remain prognostic for subjects with acute and chronic HF but that the association with outcomes is often attenuated or absent when adjusted for cardiac-specific biomarkers or renal function (5).

Gal-3 has long been known to be a mediator of fibrosis in multiple organs including the kidney (6). The absence of a cardiac contribution to systemic levels of Gal-3 has been recognized in patients

supported by a ventricular assist device, where the amount of Gal-3 in the extracted myocardial tissue correlates poorly with the systemic levels (7). In patients with chronic heart failure with reduced ejection fraction (HFrEF) undergoing biventricular pacemaker implantation, coronary sinus levels were actually found to be lower than systemic levels of Gal-3, suggesting the negligible contribution of cardiac sources to systemic levels (8). Recently, there has been more insight into cardiac-renal interaction with Gal-3. First, Meijers et al. (9) showed that despite sera levels of Gal-3 that were higher in HF patients than in controls, urine levels were similar, demonstrating that HF patients had a lower fractional renal extraction than controls, explaining one possible cause of elevated levels in patients with HF. Second, aldosterone-salt-treated rats showed both increased cardiac and renal expression levels of Gal-3 mRNA and protein, as well as protein synthesis of collagen type I and histologic evidence of fibrosis in both organs. Cotreatment with spironolactone prevented these changes, as did modified citrus pectin, a Gal-3-specific inhibitor (10). Clinical support for a strong association between renal function and Gal-3 has been shown in predominantly chronic HFrEF and general population cohorts (11-13). The association of Gal-3 levels and risk of new-onset HF no longer achieved statistical significance after accounting for patients with prevalent chronic kidney disease (CKD) in the Framingham Heart Study (14). However, in that same cohort, higher levels of Gal-3 were predictive of incident CKD even in extensively adjusted models, suggesting that Gal-3 might perform better as a marker for the progression of renal rather than cardiac disease in general population cohorts (15).

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Despite the initial enthusiasm, Gal-3 levels are not consistently predictive of progression to incident HF in community-based cohorts as was recently found in the large PREVENT (Prevention of Vascular and Renal Endstage Disease) study (16). Furthermore, in that study, the only biomarker to predict progression to HFpEF was the marker of renal function, cystatin C (16).

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous disorder with myocardial fibrosis as the major component (17). In the COACH (Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure) study of hospitalized HF patients, progressively higher levels of Gal-3 were associated with a greater risk of hospitalization and death in those with HFpEF but not in those with HFrEF, seemingly consistent with an association between systemic Gal-3 levels and extent of cardiac fibrosis (18). Until recently, there has been a paucity of clinical data in HFpEF patients, exploring the association of Gal-3 with cardiac structure and function, patient functional status, and potential interaction with therapy to provide insight into which subjects with this heterogeneous disorder may best respond to therapy. Substudies from the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) and Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) trials effectively filled that gap but, in the course of doing so, highlight the heterogeneity of patients classified as having HFpEF (19,20). Each study is a randomized controlled trial evaluating sildenafil and spironolactone, respectively, versus placebo with a surrogate endpoint of improving exercise capacity (21,22). Both studies were negative for this endpoint.

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The RELAX substudy by AbouEzzeddine et al. (20) published in this issue of *JACC: Heart Failure* shows that Gal-3 is not associated with measures of cardiac structure and function other than relative wall thickness. Gal-3 is inversely associated with peak oxygen consumption (V_{O_2}), peak heart rate, and 6-min walk distance. All these associations become insignificant when adjusting for renal function as measured by cystatin C. Furthermore, significant baseline associations with systemic biomarker measurements of fibrosis as well as N-terminal pro-B-type natriuretic peptide (NT-proBNP) all become insignificant once adjusted for renal function. There is also no significant interaction between sildenafil and Gal-3 levels (20). The authors have

nicely demonstrated through the loss of statistical associations with adjustment for cystatin C that Gal-3 levels are integrally linked to renal function. The Aldo-DHF investigators also found few associations among Gal-3 and cardiac structure and function as measured by echocardiography (left atrial diameter and the early peak mitral diastolic inflow velocity to early peak mitral diastolic annular velocity ratio [E/e']) are significant in a univariate analysis).

In contrast to the RELAX substudy, the Aldo-DHF study showed that even after adjustment for renal function, Gal-3 levels were significantly inversely associated with 6-min walk distance and almost remained associated with peak V_{O_2} . In Aldo-DHF, there was no significant interaction between spironolactone and Gal-3 levels, and baseline levels did not predict all-cause mortality and hospitalization (19). Thus, although both studies of carefully selected HFpEF patients are consistent in their absence of association of structural and functional cardiac findings, Gal-3 levels appear to be linked to renal function with respect to overall exercise capacity more in the RELAX study than in the Aldo-DHF study. This would have implications as to whether Gal-3 may have a role as a biomarker surrogate for overall functional status in patients with HFpEF. However, there are marked differences between the characteristics of the patients enrolled in each study. The RELAX patients had a higher median Gal-3 level (18.5 ng/ml, adjusted to commercial assay used in the Aldo-DHF study, versus 12.1 ng/ml) than in Aldo-DHF. The median NT-proBNP concentration was 700 pg/ml (reported for the complete RELAX cohort) and only 159 pg/ml in the Aldo-DHF substudy (19,22). The median estimated glomerular filtration rate (eGFR) was 64 ml/min/1.73 m² versus a mean of 78.7 ml/min/1.73 m² and the mid-tertile for the 6-min walk distance was 325 m versus a mean walk distance of 530 m for RELAX and Aldo-DHF patients, respectively (19,20). As others have suggested, the Aldo-DHF patients have modest objective findings of HFpEF (23). Last, the methodology for measuring renal function might also have played a role in the differences in the findings from these studies, where cystatin C has been shown to be a superior predictor of cardiac and renal events compared to creatinine-determined eGFR in the range of eGFR reported for RELAX (24). Cystatin C has also been shown to have a closer association with Gal-3 versus creatinine based eGFR (18).

It is noteworthy that 2 different assays for measurement of Gal-3 were used in the studies; in RELAX,

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