Original Article

Galectin-3 and Cardiac Function in Survivors of Acute Myocardial Infarction

Robin A.P. Weir, MD; Colin J. Petrie, MBChB; C. Aengus Murphy, MD; Suzanne Clements, BSc;
Tracey Steedman, BSc; Ashley M. Miller, PhD; Iain B. McInnes, PhD; Iain B. Squire, MD;
Leong L. Ng, MD; Henry J. Dargie, MBChB; John J.V. McMurray, MD

Background—Galectin-3 is a biomarker associated with inflammation and fibrosis that predicts adverse outcome and relates to biomarkers of extracellular matrix turnover in patients with heart failure, particularly when left ventricular (LV) systolic function is preserved. Whether galectin-3 is related to LV remodeling after acute myocardial infarction is unknown.

Methods and Results—Circulating galectin-3 and various extracellular matrix biomarkers were measured in 100 patients (age, 58.9±12.0 years; 77% men) admitted with acute myocardial infarction and LV dysfunction, at baseline (mean 46 hours) and at 24 weeks, with cardiac MRI at each time-point. LV remodeling was defined as change in LV end-systolic volume index. Relationships among galectin-3, biomarkers, and LV remodeling were analyzed across the entire cohort, then according to median baseline LV ejection fraction. Galectin-3 levels were elevated in 22 patients (22%) at baseline and increased significantly over time from 14.7±5.5 to 16.3±6.6 ng/mL (*P*=0.007). Baseline galectin-3 did not correlate with any LV parameters at baseline or change in any parameter over time. Galectin-3 was positively associated with remodeling in patients with supramedian baseline LV ejection fraction (ie, >49.2%; *r*=0.40; *P*=0.01) but not when LV ejection fraction was ≤49.2%. Galectin-3 correlated significantly with matrix metalloproteinase-3 and monocyte chemoattractant protein-1 at baseline, biomarkers that have been shown to relate to LV remodeling in this cohort.

Conclusions—Galectin-3 correlated significantly with certain biomarkers involved in extracellular matrix turnover, although no definite relationship was identified with LV remodeling. Whether galectin-3 plays a pathological role in remodeling remains unclear but merits further study.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00132093. (***Circ Heart Fail***. 2013;6:492-498.)

Key Words: acute myocardial infarction ■ cardiac magnetic resonance ■ galectin-3 ■ remodeling

With the widespread introduction of optimal reperfusion therapy for the management of ST-segment–elevation acute myocardial infarction (AMI), and significant advances in the treatment of non–ST-segment–elevation acute coronary syndromes, greater numbers of patients survive an acute infarct but remain at risk of developing heart failure. After acute myocardial injury, even if coronary blood flow is promptly restored, a series of mechanical and neurohormonal triggers may precipitate geometric changes that result in progressive left ventricular (LV) dilatation and dysfunction, leading ultimately to heart failure and premature death; this process is termed remodeling.[1–4] Attenuation (or even reversal) of LV remodeling is already a major focus in the management of survivors of acute coronary syndromes.

Clinical Perspective on p 498

Galectin-3 is a β-galactoside–binding lectin secreted by activated macrophages, which has gained interest as at least a marker of, or possibly even a potential mediator in inflammation and fibrosis, processes that are central to the pathophysiology of LV remodeling.[5,6] Upregulation of galectin-3 expression has been demonstrated in murine models of hypertensive heart disease, myocarditis and cardiomyopathy, and in the hypertrophied ventricular myocardium of humans with aortic stenosis and depressed LV systolic function.[7–9] Serum

galectin-3 is increased in patients with acutely decompensated heart failure, whereas elevated serum galectin-3 levels in patients with chronic heart failure (CHF) are associated with higher New York Heart Association class and predict poorer outcome.[10–12] Correlation between serum galectin-3 and echocardiographic measures of diastolic function and right ventricular performance has been demonstrated in patients with dyspnoea with and without acutely decompensated heart failure, but detailed cardiac structural data in relation to galectin-3 levels are lacking.[13] Moreover, there are no human studies examining the role of galectin-3 in LV remodeling after AMI. We measured galectin-3 on plasma samples from a cohort of patients admitted with AMI and enrolled in a randomized trial assessing the effects of aldosterone antagonism on LV remodeling, and present data on the relationships over time of plasma galectin-3 and cardiac structural and functional parameters, using cardiac MRI (CMR).[14]

Methods

Patients

The subjects of this study were participants in a randomized, double-blinded, placebo-controlled clinical trial investigating the effects of eplerenone on LV remodeling after AMI.[14] Inclusion criteria were aged ≥18 years; able to provide written, informed consent; AMI 1 to 14 days before enrollment; screening transthoracic echocardiographic LV ejection fraction (LVEF) <40% (Simpson biplane rule). The main exclusion criteria were clinical or radiological heart failure (Killip score >I), diabetes mellitus, pregnancy, serum creatinine >220 μmol/L (≈2.5 mg/dL), serum potassium >5.0 mmol/L, planned coronary artery bypass surgery, contraindication to CMR. The trial protocol complied with the declaration of Helsinki and was approved by the local ethics committee.

Methods

At baseline, eligible patients had venous blood collected for measurement of blood chemistry and biomarker concentrations (including galectin-3), after which contrast-enhanced CMR (ceCMR) was performed. Patients were then randomized to double-blind eplerenone or placebo, with repeat ceCMR and measurement of plasma biomarkers at 24 weeks after which study drug was withdrawn and individual patient involvement in the trial ceased.

Measurement of Galectin-3

For galectin-3 measurement, we used an enzyme-linked immunosorbent assay developed by BG Medicine, Inc, Waltham, MA, which quantitatively measures galectin-3 concentrations on plasma samples. At both time-points, blood was collected into chilled tubes containing potassium EDTA (1 mg/mL blood) and aprotinin (50 KIU/mL blood), and centrifuged within 1 hour at 2000 g for 15 minutes at ambient temperature. Plasma was extracted and stored at −70°C until batched blinded analysis after trial completion. Each aliquot was subjected to 2 freeze–thaw cycles. The coefficient of variation (CV) for the assay was <10%, and the limit of detection was 1.13 ng/mL.

Measurement of Other Biomarkers

Blood similarly collected into chilled tubes containing potassium EDTA and aprotinin, and centrifuged within 1 hour before plasma extraction and stored at −70°C was used for quantification of matrix metalloproteinases (MMP-2, -3, and -9), tissue inhibitors of metalloproteinase (TIMP-1, -2, and -4), and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Each aliquot was subjected to 1 freeze–thaw cycle only. The MMPs and TIMPs were measured using commercially available enzyme-linked immunosorbent assay kits (R&D Systems, Abingdon, Oxfordshire, United Kingdom). The

intra- and interassay CV was <10% for each assay. NT-proBNP was measured using a chemiluminescent assay kit (Roche Diagnostics) on an Elecsys 2010 autoanalyzer (CV<2%; limit of detection, 5 pg/mL).

Blood simultaneously collected into plain tubes, allowed to clot, then centrifuged at 2000 g for 15 minutes at ambient temperature before serum extraction and stored at −70°C was used to measure several biomarkers. Serum cytokines were analyzed in a 20-plex human cytokine assay (Biosource, Invitrogen) for simultaneous quantification of interleukin-1 (IL-1) receptor antagonist (IL-1Ra), IL-2 receptor (IL-2R), IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12(p40), IL-15, IL-21, and monocyte chemoattractant protein-1. This assay was run according to the manufacturer's procedure and read on the Bio-Plex suspension array system (CV<5%). Serum soluble ST2 (sST2) was quantified using a human IL-1 R4/ST2 enzyme-linked immunosorbent assay (R&D Systems), with CV<5% and lower limit of detection of 32 pg/mL. Apelin quantification was performed using the Apelin-12 microplate enzyme-linked immunosorbent assay kit (Phoenix Pharmaceuticals) according to the manufacturer's instructions (CV<5%).

ceCMR Protocol and Analysis

ceCMR was performed using a 1.5T Siemens Sonata with a phased-array chest coil, during breath-hold, and gated to the ECG. The sequences used in cine image acquisition and in inversion-recovery imaging after administration of gadolinium diethylenetriaminepentaacetate (GE Healthcare), together with the techniques used in measuring LV volumes, LVEF and infarct volumes, have been described in detail previously.[14]

Statistics

ceCMR measurements were adjusted for total body surface area, creating the following indexed quantities: LV end-systolic volume index (LVESVI), LV end-diastolic volume index (LVEDVI), LV mass index, and LV infarct volume index. Only patients with both a baseline and 24-week follow-up scan were analyzed; patients with an incomplete dataset were excluded. LV remodeling was defined as the change in LVESVI between baseline and 24 weeks because this is more strongly predictive of adverse cardiovascular outcome than change in LVEDVI (or even change in LVEF).[4] All baseline biomarker measurements were taken before randomization, and serial biomarker data were analyzed regardless of parent study treatment allocation; galectin-3 data were then analyzed by treatment group. Normally distributed, continuous data are expressed as mean values (±SD). Non-normally distributed continuous data are expressed as medians (interquartile range). Differences between mean values were analyzed using the Student t test and those between median values by the Mann–Whitney U test. Paired comparisons in biomarker concentrations over time were performed using the Wilcoxon match-pairs signed-rank test. The biomarker data were non-normally distributed and thus were logarithmic-transformed before correlative analysis. Bonferroni post hoc correction was applied to comparisons of mean concentrations of galectin-3 and the sampled biomarkers listed above; where quoted, the P values for such comparisons are (SPSS) Bonferroni-corrected. Spearman correlation coefficients were used to assess the relationships between biomarker values and ceCMR parameters of LV function.

Given that galectin-3 is a more powerful prognostic marker in CHF with preserved LVEF (HF-PEF) than in CHF with reduced LVEF (HF-REF),[12] we categorized LVEF at baseline according to median LVEF, then analyzed the relationship between galectin-3 and remodeling in relation to median baseline LVEF. To test for interaction between baseline galectin-3, LVEF, and remodeling in each of these 2 subgroups (baseline LVEF≤median, baseline LVEF>median), linear regression analysis was performed with baseline LVEF, galectin-3, and an interaction quotient—defined as the product of baseline LVEF and galectin-3—inserted as independent variables to assess the effects on change in LVESVI in each group. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, IL). A P value of <0.05 was considered significant.

Results

Baseline characteristics are shown in Table 1. The mean time from AMI to screening transthoracic echocardiographic was 34 hours, and to the first ceCMR scan was 97 hours; biomarker sampling was performed at a mean 46 hours after AMI and again at 24 weeks. Paired analysis of both ceCMR and biomarker results was performed in the 93 patients who completed the entire 24-week follow-up (3 died, 4 withdrew).
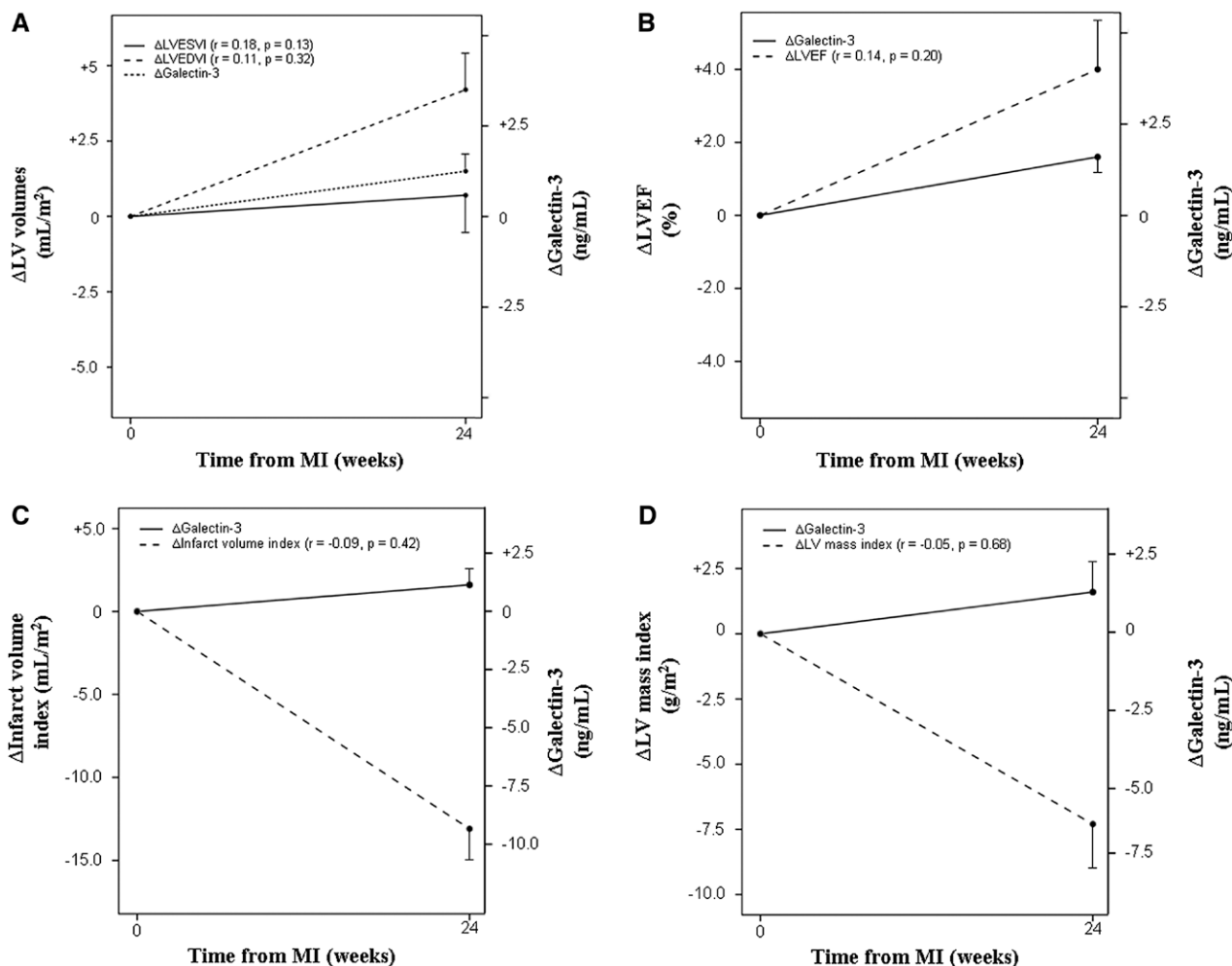
Galectin-3 Levels

For all study subjects (n=100) at baseline, mean plasma galectin-3 concentration was 14.7±5.4 (SD) ng/mL. Twenty-two patients (22%) had galectin-3 levels above the upper limit of normal cut-off value for galectin-3 of 17.7 ng/mL. Higher galectin-3 concentrations were associated with older age ($r=0.29$; $P=0.004$), higher serum creatinine ($r=0.39$; $P<0.001$), and (weakly) with the use of an angiotensin-converting enzyme inhibitor at baseline ($r=0.20$; $P=0.049$). Paired analysis of galectin-3 concentrations in the 93 patients who completed the study revealed a significant increase in plasma galectin-3 between baseline and 24 weeks, from 14.7±5.5 to 16.3±6.6 ng/mL ($P=0.007$). During the same time period, serum creatinine was unchanged (100.0±21.3 μmol/L at baseline; 98.8±21.6 μmol/L at 24 weeks; $P=0.46$).

Galectin-3 and LV Function

Across the cohort, LVEF increased significantly between baseline and 24 weeks, from 48.9 (8.8)% to 52.9 (11.9)%, $P<0.001$. Baseline galectin-3 had no correlation with baseline CMR measurements: LVESVI ($r=0.02$; $P=0.083$), LVEDVI ($r=0.01$; $P=0.95$), LVEF ($r=-0.14$; $P=0.16$), or infarct volume index ($r=0.10$; $P=0.34$). Similarly, there were no significant relationships between baseline galectin-3 and change from baseline to 24 weeks in any CMR measure (ΔLVESVI, ΔLVEDVI, ΔLVEF, or Δinfarct volume index). When analyzed in relation to 24-week values of these CMR parameters, baseline galectin-3 displayed inverse correlation with 24-week LVEF ($r=-0.25$; $P=0.023$) but not with any other parameter. Change in galectin-3 from baseline to 24 weeks had no association with the change in any LV or infarct volume measurement over time (Figure).

Median LVEF was 49.2%. The relationships between galectin-3 and remodeling were analyzed according to whether baseline LVEF was >49.2% or ≤49.2%. In patients with supramedian LVEF at baseline, galectin-3 increased significantly from 13.9±4.3 to 15.5±5.3 ng/mL ($P=0.016$), whereas in those with baseline LVEF≤49.2%, galectin-3 was 15.5±6.4 ng/mL at baseline and 17.0±7.7 ng/mL at 24 weeks ($P=0.11$). There were no significant associations between baseline galectin-3 and ΔLVESVI (ie, remodeling, $r=0.1$; $P=0.46$), ΔLVEDVI ($r=0.02$; $P=0.91$), or change in any other LV parameter over time in patients with LVEF≤49.2%. In those with supramedian LVEF at baseline, however, galectin-3 correlated significantly with both ΔLVESVI ($r=0.40$; $P=0.01$) and ΔLVEDVI ($r=0.42$; $P=0.008$) but not with change in any other parameter. In patients with baseline LVEF≤49.2%, interaction tests revealed no significant relationships between ΔLVESVI and baseline galectin-3 ($β=-2.3$; $P=0.10$), baseline LVEF ($β=-0.45$; $P=0.27$), or the galectin-3/LVEF interaction coefficient ($β=0.26$; $P=0.09$). In the subgroup of patients with baseline LVEF>49.2%, however, galectin-3 remained a significant predictor of ΔLVESVI ($β=2.7$; $P=0.04$); the relationship between ΔLVESVI and the galectin-3/LVEF interaction coefficient was of borderline statistical significance

Table 1.   Baseline Characteristics of Study Patients

	Total Cohort (n=100)	r*	P*
Patient characteristics			
Age, y	58.9 (12.0)	0.29	0.004
Male, %	77 (77%)	0.15	0.13
BMI	30.8 (4.2)	−0.08	0.42
Medical history			
Angina	39 (39%)	0.08	0.43
Smoker	55 (55%)	−0.07	0.49
Previous AMI	7 (7%)	0.02	0.83
Hypertension	35 (35%)	0.11	0.27
Hypercholesterolemia	25 (25%)	−0.11	0.26
Treatment			
Thrombolysis	54 (54%)	−0.13	0.19
Primary PCI	27 (27%)	0.05	0.62
Rescue PCI	26 (26%)	−0.02	0.82
Angiography performed	85 (85%)	−0.10	0.32
PCI performed	74 (74%)	−0.10	0.33
ceCMR measurements			
LVESVI, mL/m²	43.8 (15.2)	0.04	0.68
LVEDVI, mL/m²	84.3 (18.1)	0.03	0.72
ΔLVEF, %	48.9 (8.7)	−0.10	0.33
LVMI, g/m²	74.4 (14.9)	0.10	0.36
Infarct volume, mL/m²	33.2 (20.7)	0.03	0.75
Renal function			
Creatinine, μmol/L	100.1 (21.3)	0.39	<0.001
Admission medication			
Aspirin	25 (25%)	0.17	0.09
β-Blocker	18 (18%)	0.06	0.55
ACE inhibitor/ARB	12 (12%)	0.20	0.049
Statin	15 (15%)	−0.05	0.59
Discharge medication			
Aspirin	96 (96%)	0.22	0.03
Clopidogrel	82 (82%)	0.18	0.07
β-Blocker	93 (93%)	−0.12	0.23
ACE inhibitor/ARB	94 (94%)	0.19	0.05
Statin	98 (98%)	−0.06	0.52
Furosemide	21 (21%)	0.17	0.09

Continuous data are expressed as mean (SD), whereas categorical data are expressed as percentages of the cohort at baseline. ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BMI, body mass index; ceCMR, contrast-enhanced CMR; LVEDVI, LV end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, LV end-systolic volume index; LVMI, LV mass index; and PCI, percutaneous coronary intervention.

*Correlative analysis with baseline galectin-3 (Spearman correlation coefficients for continuous variables, or paired samples correlation for categorical variables).

Δ Normal range 58% to 68%.

Figure. Mean (±SEM) change from baseline in galectin-3 concentration in relation to (**A**) left ventricular end-systolic volume index (ΔLVESVI) and LV end-diastolic volume index (ΔLVEDVI), (**B**) LV ejection fraction (ΔLVEF), (**C**) LV infarct volume index, and (**D**) LV mass index. Correlation coefficients and significance levels are shown for each cardiac magnetic resonance parameter in relation to change in galectin-3.

(β=−2.5; P=0.05). Baseline LVEF was not a significant predictor of ΔLVESVI in this subgroup (β=0.75; P=0.10).

Galectin-3 and Natriuretic Peptides

NT-proBNP fell from 2587 (2732) pg/mL at baseline to 841 (1982) pg/mL at 24 weeks (P<0.001). Baseline galectin-3 correlated with baseline NT-proBNP (r=0.30; P=0.003) and with ΔNT-proBNP (r=−0.24; P=0.022).

Galectin-3 and Biomarkers

Correlative analysis of galectin-3 concentrations and the sampled biomarkers is detailed in Table 2. At baseline, there was significant correlation between galectin-3 and MMP-3, TIMP-1, monocyte chemoattractant protein-1, and IL-8. The only parameter that correlated significantly with change over time in galectin-3 was change in apelin concentration.

Table 2.   Spearman Correlation Coefficients for Biomarkers, Sampled at Baseline and 24 Weeks, and Simultaneous Galectin-3 Concentrations During 24 Weeks Post-AMI in the 93 Patients Who Completed the Study

Gal-3	MMP-2	MMP-3	MMP-9	TIMP-1	TIMP-2	TIMP-4	sST2	Apelin	IL-1Ra	IL-2R	IL-4	IL-5	IL-6	IL-7	IL-8	IL-10	IL-12	IL-15	IL-21	MCP-1
Baseline line	0.05	0.33**	0.18	0.22*	0.15	0.18	−0.15	0.01	0.03	0.18	0.38	0.16	0.05	0.15	0.34**	−0.02	0.18	0.10	0.04	0.23*
24 wk	0.02	0.22*	0.08	0.25*	0.05	0.24*	0.32*	0.18	−0.06	0.03	−0.07	0.04	0.08	0.09	0.29*	−0.10	0.13	0.05	−0.01	0.14
Δ	0.05	−0.11	−0.19	0.02	−0.09	0.12	0.12	0.24*	0.07	−0.06	−0.08	−0.06	−0.08	−0.01	−0.07	−0.01	0.18	−0.07	0.03	−0.03

AMI indicates acute myocardial infarction; Gal-3, galectin-3; IL, interleukin; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinases; sST2, Serum soluble ST2; and TIMP, tissue inhibitors of metalloproteinase.

Δ Change in each biomarker between baseline and 24 weeks. Note: all biomarker data logarithmic-transformed before correlative analysis.

*P<0.05.

**P<0.01 (P values are SPSS Bonferroni-adjusted).

Effect of Eplerenone on Galectin-3

At baseline, serum galectin-3 was 14.0 (4.6) ng/mL in patients randomized to placebo and 15.3 (6.0) ng/mL in those randomized to eplerenone (*P*=0.26). There was a non-significant trend toward increase in galectin-3 in the placebo group (+1.1 [4.4] ng/mL; *P*=0.074), whereas the increase in galectin-3 levels in eplerenone-treated patients reached significance (+2.1 [6.7] ng/mL; *P*=0.039). There was no significant treatment effect of eplerenone on serum galectin-3 levels during the 24-week study period (*P*=0.23). In the parent study, eplerenone had a modest antiremodeling effect, but only after covariate adjustment.[14]

Discussion

A potential role for galectin-3 in the pathophysiology of LV remodeling has been suggested by a variety of animal and human studies, although a causal effect has yet to be proven. Data on circulating levels of galectin-3 in the early post-AMI period in humans are lacking, however, as are detailed cardiac structural data in relation to galectin-3 concentrations in survivors of AMI and in patients with CHF. Galectin-3 has been shown to be elevated in 49% of a cohort of patients with New York Heart Association class III-IV CHF and reduced LVEF; levels of galectin-3 were unchanged over 6 months in a subset of these patients who underwent serial sampling.[15] Galectin-3 was similarly unchanged >18 months in patients with CHF, reduced LVEF, and interventricular conduction defects enrolled in the Cardiac Resynchronization in Heart Failure Trial (CARE-HF) trial.[16] Among the novel findings in this study, we have shown that around one fifth of a cohort of patients admitted with AMI, with reduced LVEF at baseline, had an elevated plasma galectin-3 when sampled on average 2 days after symptom onset. Moreover, despite a high revascularization rate and greater uptake of antiremodeling drug therapy than any other post-AMI trial to date (reflected in the observation that LVEF rose significantly during the study follow-up and LV volumes decreased), plasma galectin-3 was found to increase significantly over time. Although this may suggest an uncoupling of galectin-3 and serial change in LV function, there were interesting observations when galectin-3 levels were analyzed in relation to remodeling in this cohort.

We found that galectin-3 had no correlation with LVEF or LV volumes on the baseline CMR scan. This is consistent with echocardiographic studies in patients with CHF who have consistently failed to demonstrate any relationship between galectin-3 and LVEF; although, galectin-3 has been shown to correlate with parameters of LV stiffness (diastolic function) and right ventricular function in such patients.[13,15] However, subgroup analysis of patients stratified by median baseline LVEF revealed significant relationships between baseline galectin-3 and change in both LVESVI and LVEDVI over time in those with relatively preserved LV function early after AMI (ie, those with LVEF greater than the median) but not in those with median or lower baseline LVEF. This study was underpowered for biomarker analysis, and these findings may simply be spurious, or may simply reflect findings from a recent acute coronary syndromes study and a number of CHF trials that galectin-3 is an adverse prognostic marker.[12,13,15,17] Galectin-3 has, however, been shown to be a more powerful prognostic indicator in patients with HF-PEF than in those with HF-REF.[12] Galectin-3 is related to certain echocardiographic markers of diastolic but not systolic dysfunction.[13] In the failure-prone hypertrophied rat heart, myocardial biopsy before development of overt heart failure showed that galectin-3 expression was highest in the rats that later developed heart failure.[7] We have found a possible association between higher galectin-3 levels and greater remodeling in patients with relatively preserved LV function early after AMI but not in those with more severe LV dysfunction.

Why might galectin-3 seem to be of greater significance prognostically (and perhaps pathophysiologically) in patients with relatively preserved LV function in CHF (and possibly after AMI)? Galectin-3 has been demonstrated to be profibrotic in animal models. It is released by activated macrophages and is required for normal phagocytosis, but in pathological states, such as (experimental) myocarditis and myocardial hypertrophy (in murine and rat models), galectin-3 stimulates macrophage migration and may also stimulate cardiac fibroblastic proliferation.[11,12,18] Infusion of galectin-3 into the pericardium of healthy rats promoted extensive myocardial fibrosis and progressive LV dysfunction, effects that were completely obviated by the antifibrotic agent N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP).[7,19] Although a profibrotic effect in human myocardium has yet to be confirmed, galectin-3 has been shown to correlate significantly with MMP-2, TIMP-1, and PIIINP, all markers of extracellular matrix turnover, in patients with HF-REF.[20] In the current cohort, we have previously demonstrated associations among TIMP-4, MMP-3, monocyte chemoattractant protein-1 and sST2 and remodeling; of these biomarkers, galectin-3 was significantly associated with MMP-3 and monocyte chemoattractant protein-1 at baseline in the current analysis.[14,21–23] Galectin-3 may thus influence a variety of separate pathways of extracellular matrix turnover, and may provide the link between macrophage activation and fibrosis, although this requires further investigation. Whether galectin-3 may activate certain profibrotic, proremodeling pathways in patients with preserved LV function that, perhaps, are already highly activated (via other means) in those with depressed LV function is unknown, but clearly the determination of whether galectin-3 plays a definite role in remodeling merits further study.

NT-proBNP is elevated in symptomatic and asymptomatic LVSD and predicts mortality across all grades of CHF (both HF-REF and HF-PEF).[24–26] It also predicts major adverse cardiac events after AMI.[27] NT-proBNP was elevated early after AMI in the present study, and although it decreased significantly over time, remained elevated at 24 weeks. We found that galectin-3 correlated significantly with NT-proBNP at baseline. Similar findings have been reported after acute coronary syndromes and in patients with CHF.[15,17,28] Baseline galectin-3 also correlated inversely with ΔNT-proBNP, although galectin-3 subsequently rose over time. This presumably reflects the difference between the profibrotic effects of galectin-3 and the load-dependent nature of natriuretic peptide release, NT-proBNP (and BNP) tending to fall with reduction in myocardial stretch and in the presence of off-loading therapies, such as angiotensin-converting enzyme inhibitors and

diuretics. Indeed, in patients with advanced CHF requiring LV assist device (LVAD) support, galectin-3 and BNP were significantly elevated at baseline, but while BNP fell significantly after LVAD implantation, galectin-3 did not (although galectin-3 was highest in those who died).[11]

The present study is the first to date that has assessed the effect of antiremodeling drug therapy on galectin-3 levels—in either AMI or CHF—in a randomized, controlled manner. We analyzed whether 24 weeks of therapy with eplerenone influenced plasma galectin-3 levels after AMI. The study was powered for CMR end points rather than drug effects on biomarkers. Within these confines, we found that galectin-3 increased over 24 weeks in patients treated with eplerenone but not in those receiving placebo; although, overall the treatment effect did not reach statistical significance. In a recent substudy of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), use of an aldosterone antagonist was associated with higher concentrations of galectin-3 in patients with chronic systolic heart failure.[29] These data may suggest potential interplay between galectin-3 and the aldosterone pathway, although such findings would need to be explored in a larger, appropriately powered study. That the profibrotic effects of galectin-3 were blocked by Ac-SDKP in an experimental model of cardiac remodeling suggest that further research is warranted into both the development and possible clinical applications of galectin-3-modifying therapy in the attempt to ameliorate remodeling in CHF and after AMI.[19]

Limitations

The main limitation of this study is that the clinical trial on which the current analysis is based was powered for CMR end points, not biomarker effects.[14] The results are, therefore, hypothesis-generating only. It is, however, the only study using serial CMR scanning—the current gold standard imaging modality for LVEF and LV volume measurement (and that allows significant sample size reduction compared with echocardiography and other modalities)—in relation to galectin-3. We measured galectin-3 only once at baseline, on average 2 days after AMI. It is not known whether galectin-3 levels fluctuate in plasma early after AMI, or indeed during the 24-week period that served as follow-up in our study. Similar limitations are relevant to studies of galectin-3 in CHF.[12,13] Our findings are applicable to patients with AMI and depressed LV function on echocardiography performed within 48 hours of infarction, and without clinical heart failure, and, therefore, cannot be extrapolated to all patients with AMI. We measured galectin-3 concentrations in plasma only, which provide no information on tissue levels. Finally, the correlations reported do not necessarily indicate direct biological relationships but do provide directions for further study.

Conclusions

This is, to our knowledge, the first study reporting serial galectin-3 concentrations in human plasma after AMI. Galectin-3 was elevated in only around one fifth of survivors of AMI with reduced LVEF. Higher galectin-3 concentrations at baseline were significantly associated with lower LVEF at 24-week follow-up, although there

was no significant relationship between galectin-3 and remodeling per se. Whether a relationship does exist between galectin-3 and remodeling after AMI remains unclear and will require to be analyzed further in larger, appropriately powered studies. Galectin-3 seems to be related to natriuretic peptides after AMI similar to findings from CHF trials, and correlated significantly with certain biomarkers involved in the inflammation-fibrosis cascade, although it remains unclear whether galectin-3 plays a direct role in remodeling. We found no significant effect of therapy with the aldosterone antagonist eplerenone on serum galectin-3 levels over 24 weeks after AMI in this (underpowered) study, but further projects assessing the effects on remodeling (and indeed on cardiovascular outcomes) of specific galectin-3-modifying therapies are undoubtedly warranted as we continue to target remodeling as a therapeutic strategy in both AMI and CHF.

References

1. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation*. 1990;81:1161–1172.
2. Rouleau JL, de Champlain J, Klein M, Bichet D, Moyé L, Packer M, Dagenais GR, Sussex B, Arnold JM, Sestier F. Activation of neurohumoral systems in postinfarction left ventricular dysfunction. *J Am Coll Cardiol*. 1993;22:390–398.
3. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling–concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol*. 2000;35:569–582.
4. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation*. 1987;76:44–51.
5. Dumic J, Dabelic S, Flögel M. Galectin-3: an open-ended story. *Biochim Biophys Acta*. 2006;1760:616–635.
6. Yang RY, Rabinovich GA, Liu FT. Galectins: structure, function and therapeutic potential. *Expert Rev Mol Med*. 2008;10:e17.
7. Sharma UC, Pokharel S, van Brakel TJ, van Berlo JH, Cleutjens JP, Schroen B, André S, Crijns HJ, Gabius HJ, Maessen J, Pinto YM. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. *Circulation*. 2004;110:3121–3128.
8. Reifenberg K, Lehr HA, Torzewski M, Steige G, Wiese E, Küpper I, Becker C, Ott S, Nusser P, Yamamura K, Rechtsteiner G, Warger T, Pautz A, Kleinert H, Schmidt A, Pieske B, Wenzel P, Münzel T, Löhler J. Interferon-gamma induces chronic active myocarditis and cardiomyopathy in transgenic mice. *Am J Pathol*. 2007;171:463–472.
9. Thandavarayan RA, Watanabe K, Ma M, Veeraveedu PT, Gurusamy N, Palaniyandi SS, Zhang S, Muslin AJ, Kodama M, Aizawa Y. 14-3-3 protein regulates Ask1 signaling and protects against diabetic cardiomyopathy. *Biochem Pharmacol*. 2008;75:1797–1806.
10. van Kimmenade RR, Januzzi JL Jr, Ellinor PT, Sharma UC, Bakker JA, Low AF, Martinez A, Crijns HJ, MacRae CA, Menheere PP, Pinto YM. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and

apelin for the evaluation of patients with acute heart failure. *J Am Coll Cardiol*. 2006;48:1217–1224.

11. Milting H, Ellinghaus P, Seewald M, Cakar H, Bohms B, Kassner A, Körfer R, Klein M, Krahn T, Kruska L, El Banayosy A, Kramer F. Plasma biomarkers of myocardial fibrosis and remodeling in terminal heart failure patients supported by mechanical circulatory support devices. *J Heart Lung Transplant*. 2008;27:589–596.

12. de Boer RA, Lok DJ, Jaarsma T, van der Meer P, Voors AA, Hillege HL, van Veldhuisen DJ. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. *Ann Med*. 2011;43:60–68.

13. Shah RV, Chen-Tournoux AA, Picard MH, van Kimmenade RR, Januzzi JL. Galectin-3, cardiac structure and function, and long-term mortality in patients with acutely decompensated heart failure. *Eur J Heart Fail*. 2010;12:826–832.

14. Weir RA, Mark PB, Petrie CJ, Clements S, Steedman T, Ford I, Ng LL, Squire IB, Wagner GS, McMurray JJ, Dargie HJ. Left ventricular remodeling after acute myocardial infarction: does eplerenone have an effect? *Am Heart J*. 2009;157:1088–1096.

15. Lok DJ, Van Der Meer P, de la Porte PW, Lipsic E, Van Wijngaarden J, Hillege HL, van Veldhuisen DJ. Prognostic value of galectin-3, a novel marker of fibrosis, in patients with chronic heart failure: data from the DEAL-HF study. *Clin Res Cardiol*. 2010;99:323–328.

16. Lopez-Andrès N, Rossignol P, Iraqi W, Fay R, Nuée J, Ghio S, Cleland JG, Zannad F, Lacolley P. Association of galectin-3 and fibrosis markers with long-term cardiovascular outcomes in patients with heart failure, left ventricular dysfunction, and dyssynchrony: insights from the CARE-HF (Cardiac Resynchronization in Heart Failure) trial. *Eur J Heart Fail*. 2012;14:74–81.

17. Grandin EW, Jarolim P, Murphy SA, Ritterova L, Cannon CP, Braunwald E, Morrow DA. Galectin-3 and the development of heart failure after acute coronary syndrome: pilot experience from PROVE IT-TIMI 22. *Clin Chem*. 2012;58:267–273.

18. Sano H, Hsu DK, Apgar JR, Yu L, Sharma BB, Kuwabara I, Izui S, Liu FT. Critical role of galectin-3 in phagocytosis by macrophages. *J Clin Invest*. 2003;112:389–397.

19. Liu YH, D'Ambrosio M, Liao TD, Peng H, Rhaleb NE, Sharma U, André S, Gabius HJ, Carretero OA. N-acetyl-seryl-aspartyl-lysyl-proline prevents cardiac remodeling and dysfunction induced by galectin-3, a mammalian adhesion/growth-regulatory lectin. *Am J Physiol Heart Circ Physiol*. 2009;296:H404–H412.

20. Lin YH, Lin LY, Wu YW, Chien KL, Lee CM, Hsu RB, Chao CL, Wang SS, Hsein YC, Liao LC, Ho YL, Chen MF. The relationship between serum galectin-3 and serum markers of cardiac extracellular matrix turnover in heart failure patients. *Clin Chim Acta*. 2009;409:96–99.

21. Weir RA, Murphy CA, Petrie CJ, Martin TN, Clements S, Steedman T, Wagner GS, McMurray JJ, Dargie HJ. Monocyte chemoattractant protein-1: a dichotomous role in cardiac remodeling following acute myocardial infarction in man? *Cytokine*. 2010;50:158–162.

22. Weir RA, Miller AM, Murphy GE, Clements S, Steedman T, Connell JM, McInnes IB, Dargie HJ, McMurray JJ. Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. *J Am Coll Cardiol*. 2010;55:243–250.

23. Weir RA, Clements S, Steedman T, Dargie HJ, McMurray JJ, Squire IB, Ng LL. Plasma TIMP-4 predicts left ventricular remodeling after acute myocardial infarction. *J Card Fail*. 2011;17:465–471.

24. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J*. 2003;24:1735–1743.

25. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456–2467.

26. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J*. 2006;27:2338–2345.

27. Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton C, Turner J, Crozier IG, Yandle TG. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation*. 2003;107:2786–2792.

28. Felker GM, Fiuzat M, Shaw LK, Clare R, Whellan DJ, Bettari L, Shirolkar SC, Donahue M, Kitzman DW, Zannad F, Piña IL, O'Connor CM. Galectin-3 in ambulatory patients with heart failure: results from the HF-ACTION study. *Circ Heart Fail*. 2012;5:72–78.

29. Gullestad L, Ueland T, Kjekshus J, Nymo SH, Hulthe J, Muntendam P, Adourian A, Böhm M, van Veldhuisen DJ, Komajda M, Cleland JG, Wikstrand J, McMurray JJ, Aukrust P; CORONA Study Group. Galectin-3 predicts response to statin therapy in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA). *Eur Heart J*. 2012;33:2290–2296.

CLINICAL PERSPECTIVE

A major consequence of improved treatment of acute coronary syndromes is the emergence of an increasing cohort of survivors at high risk of progressive left ventricular (LV) remodeling and heart failure, with its attendant morbidity and (premature) mortality. Attenuation, or even reversal, of LV remodeling is a major focus of disease management in such patients, with significant resources spent identifying not only biomarker predictors, but also potential mediators of the process. Galectin-3 has been demonstrated to predict adverse outcome in human chronic heart failure studies; intriguingly, data from animal studies suggest that it may also be integral to remodeling because of its profibrotic properties. Data on galectin-3 after acute coronary syndromes in humans are scarce. Our article describes the relationships among galectin-3, LV function, remodeling, and a variety of biomarkers related to remodeling in a cohort of survivors of acute myocardial infarction. Our findings, that galectin-3 increases over time post–acute myocardial infarction (in contrast to stable chronic heart failure cohorts), that galectin-3 is related to lower medium-term LV ejection fraction, and that galectin-3 may potentially predict greater remodeling in patients with relatively preserved LV ejection fraction after acute myocardial infarction, add further weight to the growing body of evidence that suggests that this novel biomarker may play a role in the remodeling process, although, clearly further study is warranted. If a profibrotic role is confirmed in human myocardium after acute myocardial infarction and in chronic heart failure, there is the potential for trials assessing the use of galectin-3 modulating agents in ameliorating outcomes in these costly, highly morbid conditions.

Circulation
Heart Failure

American Heart Association.

Galectin-3 and Cardiac Function in Survivors of Acute Myocardial Infarction
Robin A.P. Weir, Colin J. Petrie, C. Aengus Murphy, Suzanne Clements, Tracey Steedman,
Ashley M. Miller, Iain B. McInnes, Iain B. Squire, Leong L. Ng, Henry J. Dargie and John J.V.
McMurray

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circheartfailure.ahajournals.org/content/6/3/492