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ORIGINAL RESEARCH ARTICLE

Echocardiographic diastolic function evolution in patients with an anterior Q-wave myocardial infarction: insights from the REVE-2 study

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Abstract

Aims Myocardial fibrosis plays a key role in the development of adverse left ventricular remodelling after myocardial infarction (MI). This study aimed to determine whether the circulating levels of BNP, collagen peptides, and galectin-3 are associated with diastolic function evolution (both deterioration and improvement) at 1 year after an anterior MI.

Methods and results The REVE-2 is a prospective multicentre study including 246 patients with a first anterior Q-wave MI. Echocardiographic assessment was performed at hospital discharge and ±1 year after MI. BNP, galectin-3, and collagen peptides were measured ±1 month after MI. Left ventricular diastolic dysfunction (DD) was defined according to the presence of at least two criteria of echocardiographic parameters: septal $e' < 8$ cm/s, lateral $e' < 10$ cm/s, and left atrial volume ≥ 34 mL/m^2. At baseline, 87 (35.4%) patients had normal diastolic function and 159 (64.6%) patients had DD. Follow-up of 61 patients among the 87 patients with normal diastolic function at baseline showed that 22 patients (36%) developed DD at 1 year post-MI. The circulating levels of amino-terminal propeptide of type III procollagen > 6 mg/L [odds ratio (OR) = 5.29; 95% confidence interval (CI) = 1.05–26.66; $P = 0.044$], galectin-3 > 13 μg/L (OR = 5.99; 95% CI = 1.18–30.45; $P = 0.031$), and BNP > 82 ng/L (OR = 10.25; 95% CI = 2.36–44.50; $P = 0.002$) quantified at 1 month post-MI were independently associated with 1 year DD. Follow-up of the 137 patients with DD at baseline among the 159 patients showed that 36 patients (26%) had a normalized diastolic function at 1 year post-MI. Patients with a BNP > 82 ng/L were less likely to improve diastolic function (OR = 0.06; 95% CI = 0.01–0.28; $P = 0.0003$).

Conclusions The present study suggests that circulating levels of amino-terminal propeptide of type III procollagen, galectin-3, and BNP may be independently associated with new-onset DD in post-MI patients.

Keywords Myocardial infarction; Diastolic dysfunction; Cardiac remodelling; Galectin-3; Collagen peptides

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Introduction

Cardiac remodelling after a myocardial infarction (MI) is an important prognostic and treatment response indicator.[1] Declines in post-MI events have been observed in patients with heart failure and reduced ejection fraction but not for those with heart failure and preserved ejection fraction (HF-PEF),[2] suggesting that new diagnostic strategies and early identification of patients prone to develop HF-PEF are required. In HF-PEF patients, diastolic dysfunction (DD) has been described as a marker of impaired cardiac remodelling and has also been associated with HF-PEF onset and adverse prognosis.[3,4]

Myocardial fibrosis has been identified as one of the major pathways leading to adverse remodelling and DD after acute MI.[5–8] In subjects undergoing cardiac resonance

imaging (excluding those referred for severe valvulopathy, congenital heart disease, pericarditis, or pericardial disease), those with normal diastolic function exhibited no or minimal fibrosis. In contrast, the majority of patients with abnormal diastolic function indices exhibited substantial fibrosis regardless of underlying cause.[7] We previously reported that a ratio ≤ 1 of amino-terminal propeptide of type III procollagen to type 1 collagen telopeptide (PIIINP/ICTP) at 1 month was associated with a >20% increase in left ventricular (LV) end-diastolic volume at 1 year after a Q-wave anterior MI.[9] However, an increase in LV end-diastolic volume may be misleading in the setting of preserved left ventricular ejection fraction (LVEF). Indeed, in this context, the 'fibrosis burden' may actually lead to a reduction in LV end-diastolic volume and potentially increase the LVEF in the setting of a stable stroke volume.[10,8] In a model of age-associated adverse cardiac remodelling, the LV end-diastolic volume was shown to markedly decrease with age, despite altered strain patterns reflecting both systolic dysfunction and DD,[11] suggesting that DD is a better reflection of adverse remodelling compared with an increase in LV end-diastolic volume in the setting of a preserved ejection fraction (LVEF may actually increase in this context).[10–12] Despite the lack of definitive consensus for the definition of DD,[13] the echocardiographic parameters used to assess DD (such as septal e′, lateral e′, and left atrial volume) have been shown to be associated with natriuretic peptides and long-term outcomes.[14] Biomarkers such as brain natriuretic peptide (BNP) and galectin-3 (Gal-3) have also been studied in the acute MI setting and have been associated with adverse remodelling and prognosis.[6,15]

The aim of the present study was to assess whether BNP, Gal-3, PIIINP, ICTP, and PIIINP/ICTP ratio measured at 1 month after an anterior Q-wave MI may be associated with LV remodelling at 1 year as assessed by the evolution in LV diastolic function.

Methods

Study population

The design and entry criteria of the REVE-2 study have been previously published.[9,16] In short, the REVE-2 was a prospective multicentre observational study designed to analyse the association of circulating biomarkers with LV remodelling in patients with a first anterior wall Q-wave MI.[16] Patients were enrolled from February 2006 to September 2008. Main inclusion criteria were hospitalization within 24 h after symptom onset and a pre-discharge echocardiogram showing at least three akinetic LV segments in the infarct zone. Exclusion criteria were inadequate quality of the echocardiographic image, life-limiting non-cardiac disease, significant valvular disease, or a prior Q-wave MI.

The Institutional Ethics Committee (Centre Hospitalier Universitaire de Lille) approved the study, and written informed consent was obtained from all patients.

No ClinicalTrials.gov number was assigned to this study since it was initiated in 2006.

Echocardiographic assessment

Serial echocardiographic studies were performed at hospital discharge (Days 3 to 7) and 12 months after initial MI. A standard echocardiographic imaging protocol was used, with apical four-chamber and two-chamber views; two-dimensional echocardiograms of the LV short axis were recorded from the left parasternal region at three levels: the mitral valve, the mid-papillary muscle, and the apex. All echocardiograms were analysed at the Lille Core Echo Laboratory (Lille, France), as previously described.[17] Diastolic dysfunction was defined according to the 2009 recommendations of the American Society of Echocardiography and the Committee of the European Association of Echocardiography.[18] Patients with at least two of the following parameters, namely, (i) septal $e' < 8$ cm/s, (ii) lateral $e' < 10$ cm/s, and (iii) left atrial volume index (LAVi) ≥ 34 mL/m^2, were considered to have DD, that is, the primary outcome of the present post hoc study.

Biomarkers

All biomarkers were measured in plasma and serum samples obtained at 1 month after MI, as previously described.[9] Plasma and serum were collected in glass tubes and processed within 2 h. Samples were stored at −80°C. Samples underwent no more than two freeze/thaw cycles before analysis in a core laboratory (Lille, France, for BNP and Nancy, France, for collagen peptides and Gal-3). Brain natriuretic peptide was measured with a fully automated two-site sandwich immunoassay on an Advia Centaur analyser (Siemens Diagnostic, Zurich, Switzerland). The lowest measurable concentration with this assay with a ≤20% coefficient of variation is 2.5 ng/L. Radioimmunoassay kits (Orion Diagnostica, Espoo, Finland) were used for determination of serum collagen peptide concentrations: amino-terminal propeptide of type I procollagen (reference range: 22 to 87 and 19 to 83 mg/L in men and women, respectively), PIIINP (reference range: 2.3 to 6.4 mg/L), and ICTP (reference range: 3.2 to 3.5 mg/L). The inter-assay variations were <9.8%.[19] Determination of Gal-3 was assessed using enzyme-linked immunosorbent assay kits (BGM Galectin-3 assay; BG Medicine, Inc., Waltham, MA, USA). The minimum sensitivity was 0.96 μg/L. Normal serum ranges were provided by the assay manufacturer, on the basis of apparently healthy

volunteers. The 90th, 95th, and 97.5th percentiles of the normal reference interval were 17.6, 20.3, and 22.1 μg/L, respectively. Intra-assay and inter-assay variations were <8% and 10%, respectively.[20] Estimated glomerular filtration rate (eGFR) was computed using the four-variable Modification of Diet in Renal Disease study formula.[21]

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and median (percentile$_{25–75}$). Categorical variables are expressed as absolute numbers and proportions (%).

Factors associated with DD were first identified using univariable followed by multivariable stepwise backward conditional logistic regression. The covariates inserted in the models were identified among patient characteristics listed in *Table 1* with a *P*-value < 0.1. Efforts were made to respect the 'rule of thumb' of one variable for each 10 events.[22] Linearity was assessed by plotting the β-estimates vs. mean according to quintiles of the studied variable and by using restricted cubic splines. Variables were then categorized in order to obtain log-linearity corresponding to median for PIIINP, ICTP, PIIINP/ICTP, BNP, and Gal-3. Logistic regression data are presented as odds ratios (ORs) and respective 95% confidence intervals (CIs).

Table 1 Patient characteristics according to diastolic function at 1 year post-myocardial infarction in the subgroup of patients with normal diastolic function at baseline (n = 61)

	Diastolic dysfunction n = 22		Normal diastolic function n = 39		
	Mean ± SD/n (%)	Median (Q1–Q3)	Mean ± SD/n (%)	Median (Q1–Q3)	*P*-value
Baseline characteristics					
Age	55 ± 14	53 (45–68)	48 ± 13	46 (38–56)	0.043
Male	17 (77%)		32 (82%)		0.74
BMI (kg/m^2)	26.6 ± 4.3	26.3 (24.3–28.6)	27.0 ± 4.5	26.8 (24.2–29.7)	0.74
Hypertension	10 (45%)		8 (21%)		0.04
Diabetes mellitus	4 (18%)		4 (10%)		0.44
Dyslipidaemia	5 (23%)		14 (36%)		0.29
Current smoker	12 (55%)		27 (69%)		0.25
eGFR (mL/min/1.73 m^2)	81 ± 19	78 (68–88)	91 ± 24	92 (75–105)	0.079
Myocardial infarction					
Killip class 2–4	8 (36%)		10 (26%)		0.38
CPK peak (UI/L)	3352 ± 2084	2900 (2013–4593)	2757 ± 1810	2237 (1272–4200)	0.31
Multivessel disease	11 (52%)		11 (29%)		0.075
PCI during hospitalization	21 (95%)		33 (85%)		0.40
Baseline haemodynamics					
Heart rate (bpm)	74 ± 16	70 (60–86)	66 ± 12	65 (59–74)	0.15
Systolic BP (mmHg)	110.7 ± 17.9	110 (100–120)	107.8 ± 11.7	110 (100–111)	0.79
Diastolic BP (mmHg)	66.0 ± 12.2	63.5 (60–70)	59.1 ± 8.4	60 (54–65)	0.013
LVEF (%)	50.50 ± 10.28	49 (40–61)	52.28 ± 7.13	54 (47–58)	0.45
LVEF ≤45%	8 (36%)		8 (21%)		0.18
Septal e′ (cm/s)	6.47 ± 2.12	6.30 (4.9–8.7)	8.53 ± 1.70	8.60 (8.00–9.10)	0.012
Lateral e′ (cm/s)	9.71 ± 3.08	10.50 (6.5–12.0)	10.67 ± 2.15	10.00 (9.7–12.0)	0.54
LAVi	19.95 ± 4.89	21.16 (16.43–22.26)	19.11 ± 4.56	18.79 (15.69–21.02)	0.38
Biomarkers at 1 month					
BNP (ng/L)	194 ± 139	185 (63–321)	60 ± 53	43 (27–66)	0.0002
Galectin-3 (μg/L)	19.9 ± 10.6	18.3 (12.7–22.2)	11.0 ± 8.4	8.3 (3.9–15.8)	0.002
PINP (mg/L)	38.4 ± 10.6	38.4 (32.0–45.1)	42.0 ± 17.8	40.5 (33.1–47.6)	0.52
PIIINP (mg/L)	6.9 ± 3.1	6.5 (4.3–8.1)	5.3 ± 1.8	5.4 (3.6–6.3)	0.059
ICTP (mg/L)	5.7 ± 3.3	5.3 (3.6–6.5)	5.0 ± 2.6	4.4 (4.0–5.4)	0.28
PIIINP/ICTP ratio	1.59 ± 1.59	1.25 (0.86–1.61)	1.15 ± 0.49	1.05 (0.80–1.39)	0.34
Medication at discharge					
Aspirin	22 (100%)		38 (97%)		1.00
Anti-platelet agents	22 (100%)		38 (97%)		1.00
Beta-blockers	21 (95%)		38 (97%)		1.00
ACE-inhibitors	22 (100%)		39 (100%)		—
Mineralocorticoid receptor antagonist	6 (27%)		11 (28%)		0.94
Diuretics	5 (23%)		3 (8%)		0.12
Statins	22 (100%)		35 (90%)		0.29

ACE, angiotensin-converting enzyme; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; ICTP, type 1 collagen telopeptide; LVEF, left ventricular ejection fraction; LAVi, left atrial volume indexed to body surface area; PCI, percutaneous coronary intervention; PINP, amino-terminal propeptide of type I procollagen; PIIINP, amino-terminal propeptide of type III procollagen; SD, standard deviation.

All analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC, USA). The two-tailed significance level was set at $P < 0.05$.

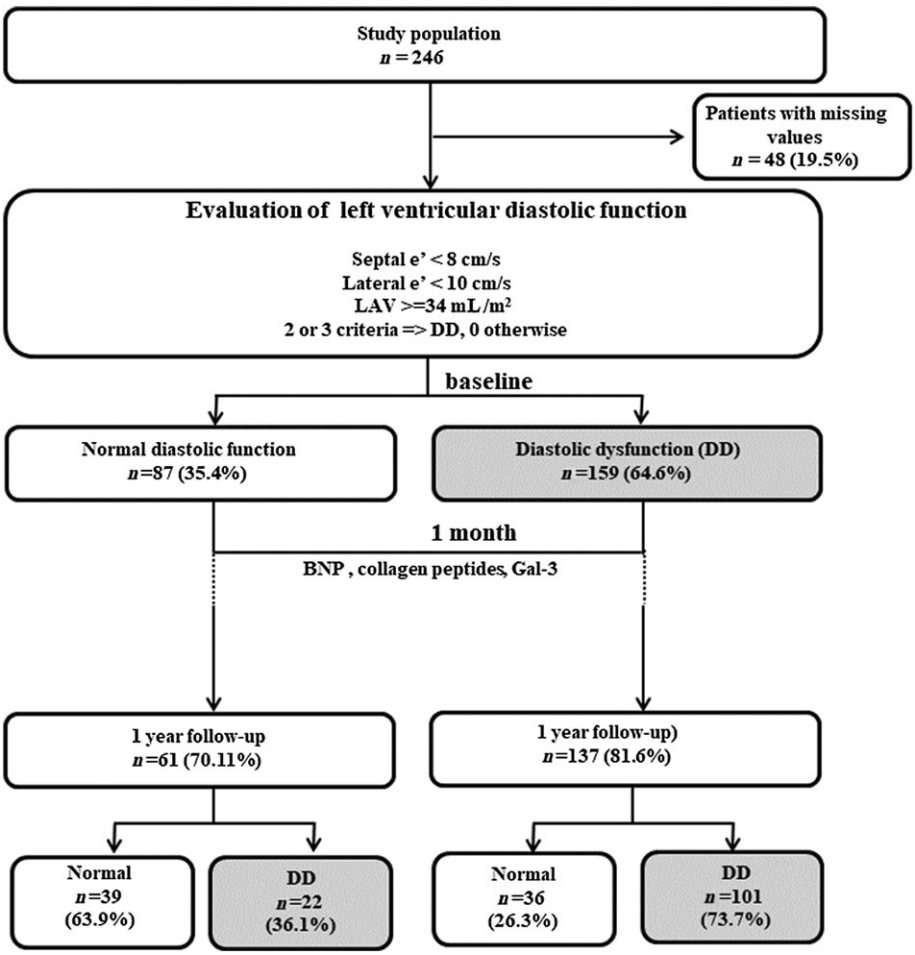
Results

Patient characteristics

A total of 246 patients were included in the REVE-2 study, and 198 patients (80.5%) were analysed for a follow-up of diastolic function at 1 year post-MI. Among the 198 patients, 87 patients (35.4%) had a normal diastolic function at baseline (septal e′ median = 8.5 [Q1–Q3 = 7.0–9.10], lateral e′ = 10.0 [9.2–12.0], and left atrial volume = 19.4 [16.7–22.5]) and 159 patients (64.6%) had DD (septal e′ = 5.7 [4.7–6.6], lateral e′ = 7.0 [5.6–8.3], and left atrial volume = 19.8 [16.0–24.4]). The two subgroups of patients (normal diastolic function vs. DD) were analysed for evolution of LV diastolic function 1 year post-MI as described in the flow chart (*Figure 1*). A total of 26 patients (29.8%) with normal diastolic function and 22 patients (20.1%) in the DD subgroup were not analysed because of missing data (n = 42) or low quality (n = 6) for the parameters required to evaluate DD.

Among the 61 patients without DD at baseline, 22 (36%) developed DD at 1 year post-MI and 39 (64%) remained without DD. Compared with patients without DD at 1 year, those with 'new-onset' DD were older (55 ± 14 vs. 48 ± 13 years; P = 0.043), had higher diastolic blood pressure (66.0 ± 12.2 vs. 59.1 ± 8.4 mmHg; P = 0.013), had hypertension history (45% vs. 21%; P = 0.04), and exhibited higher BNP (median = 185 [percentile$_{25–75}$ = 63–321] vs. 43 [27–66] ng/L; P = 0.0002) and Gal-3 (18.3 [12.7–22.2] vs. 8.3 [3.9–15.8] μg/L; P = 0.002) concentrations at 1 month post-MI. Left ventricular ejection fraction was similar between the two groups (51% ± 10% vs. 52% ± 7%; P = 0.45) (*Table 1*). Among the 137 patients with

Figure 1 Study flow chart. BNP, brain natriuretic peptide; Gal-3, galectin-3; LAV, left atrial volume.



DD at baseline, 36 (26%) normalized diastolic function at 1 year post-MI and 101 (74%) remained with DD. Compared with patients that remained with DD at 1 year, those who improved their diastolic function were younger (53 ± 11 vs. 62 ± 12 years; $P = 0.0002$) and had higher eGFR (88 ± 21 vs. 78 ± 19 mL/min/1.73 m^2; $P = 0.011$) (Supporting Information, *Table S1*).

Association of the studied biomarkers with diastolic function evolution at 1 year

In patients without DD at baseline, circulating levels of PIIINP > 6 mg/L, Gal-3 > 13 μg/L, and BNP > 82 ng/L were associated with the development of DD at 1 year post-MI. These associations remained significant after adjusting for eGFR and hypertension: adjusted OR (95% CI) = 5.29 (1.05–26.66) for PIIINP; 5.99 (1.18–30.45) for Gal-3; and 10.25 (2.36–44.50) for BNP (*Table 2*). Patients with BNP > 82 ng/L were less likely to normalize diastolic function at 1 year post-MI: adjusted OR (95% CI) = 0.06 (0.01–0.28) (Supporting Information, *Table S2*). The studied biomarkers were poorly correlated and did not present significant collinearity in the multivariable models (Supporting Information, *Table S3*). There were no significant medication changes at 1 year that could potentially be associated with biomarker changes (Supporting Information, *Table S4*).

Correlation between the studied biomarkers and diastolic function parameters

Certain echocardiographic parameters of diastolic function were correlated with circulating biomarkers. In the global REVE-2 population, BNP was significantly correlated with lateral e′, septal e′, and left atrial volume (the higher the BNP level, the lower/worse the lateral e′ and septal e′, and the higher the left atrial volume); PIIINP was correlated with septal e′ (the higher the PIIINP level, the lower/worse the septal e′); and Gal-3 was correlated with lateral e′ and septal e′ (the higher the Gal-3 level, the lower/worse the lateral e′ and septal e′) (*Figure 2*).

Discussion

The present study shows that circulating levels of PIIINP, Gal-3, and BNP measured at 1 month post-MI may be associated with the development of DD 1 year after MI in patients with normal diastolic function at baseline. On the other hand, patients with DD and higher BNP levels are less likely to recover normal diastolic function, but PIIINP and Gal-3 were not associated with DD normalization. These results may help in identifying a subset of patients more prone to develop adverse LV remodelling and DD in whom tailored anti-remodelling and preventive strategies could be tested.

The present findings confirm that myocardial fibrosis turnover is critical after a first anterior wall MI, playing a key role in adverse remodelling and DD development.

In the post-MI setting, time-dependent damage to both myocytes and extracellular matrix occurs in the infarct zone. This acute damage is followed by gradual repair with fibrosis. The non-infarct zone exhibits reactive hypertrophy, interstitial fibrosis, and increased collagen, potentially leading to cardiac dysfunction.[23,24] Myocardial fibrosis may represent a major pathway leading to adverse remodelling, cardiac dysfunction, and worse prognosis.[25,26] Thus, identifying patients more prone to adverse remodelling and DD may help clinicians in tailoring treatments with anti-adverse remodelling properties.[6,27,28] Whether this strategy improves outcomes in patients without systolic dysfunction or symptomatic heart failure is yet to be determined.[27,28]

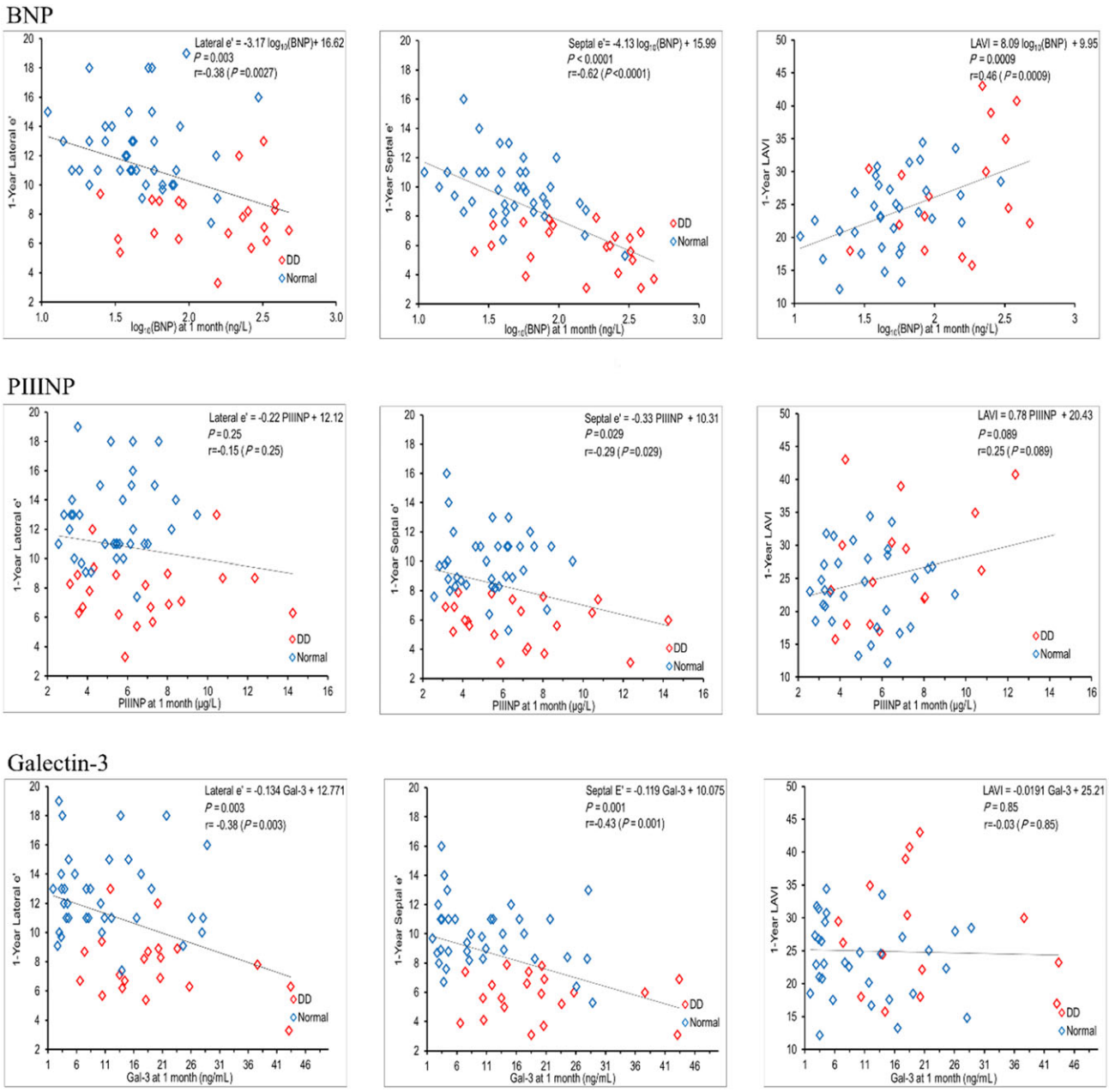
Natriuretic peptides, such as BNP, are produced by cardiomyocytes and may be increased by cardiac and atrial stretch, and also by other factors, such as renal impairment or atrial fibrillation.[29] Brain natriuretic peptide was positively associated with DD onset and negatively associated with DD improvement at 1 year. Additionally, higher BNP was associated

Table 2 Association of the studied biomarkers with diastolic dysfunction at 1 year post-myocardial infarction in the subgroup of patients with normal diastolic function at baseline ($n = 61$)

	Univariable model		Backward selected model[a]	
Biomarker	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
PIIINP > 6 mg/L	3.85 (1.20–12.31)	0.023	5.29 (1.05–26.66)	0.044
ICTP > 5 mg/L	3.30 (1.05–10.33)	0.040	NS	NS
PIIINP/ICTP ratio < 1	0.94 (0.32–2.78)	0.91	NS	NS
Galectin-3 > 13 μg/L	6.07 (1.82–20.20)	0.003	5.99 (1.18–30.45)	0.031
BNP > 82 ng/mL	13.33 (3.68–48.29)	0.0001	10.25 (2.36–44.50)	0.002

Thresholds were defined according to method combining the shape of the restricted cubic spline and percentiles corresponding to Q3 or median: ST-2 (Q3), PIIINP, ICTP, PIIINP/ICTP, BNP, and galectin-3 (median).
See *Table 1* for abbreviations.
[a]Model including estimated glomerular filtration rate and history of hypertension.

Figure 2 Correlation between the studied biomarkers and diastolic function parameters. BNP, brain natriuretic peptide; Gal-3, galectin-3; LAVi, left atrial volume index; PIIINP, amino-terminal propeptide of type III procollagen.



with lower lateral e′, septal e′, and increased left atrial volume, suggesting that both diastolic impairment and congestion may lead to BNP augmentation, as previously reported.[30,31]

Serum PIIINP has been found to be correlated with myocardial collagen type III in HF patients of ischaemic aetiology and idiopathic dilated cardiomyopathy.[32,33] Furthermore, higher PIIINP has been associated with insulin resistance and adverse lipid profile in obese patients without overt cardiovascular diseases[34] and associated with DD in patients with abdominal obesity.[35] In the present study, higher PIIINP was associated with a lower septal e′ supporting the association of this biomarker with DD as reported in other populations.[35,36] Higher PIIINP also trended to be associated with increased left atrial volume but showed no association with lateral e′ in the present study. Collagen scar formation after acute MI causing LV systolic dysfunction can also be quantified by serum PIIINP concentrations.[37] In patients with dilated cardiomyopathy, the reduction in myocardial collagen as a result of spironolactone

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treatment is also accompanied by a significant reduction in PIIINP serum levels.[32] In post-MI patients with systolic dysfunction (findings from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study: EPHESUS),[26] eplerenone treatment also consistently reduced PIIINP levels. In 134 patients with acute anterior ST-elevation myocardial infarction, a strategy of early aldosterone blockade with intravenous potassium canrenoate (the active metabolite of spironolactone) improved LVEF and reduced LV end-diastolic volume in comparison with controls. In the present study, cardiac aldosterone extraction was suppressed, and plasma PIIINP levels were also significantly reduced in the aldosterone antagonist group.[38] In a subanalysis of the REMINDER trial that included patients with ST-elevation myocardial infarction without heart failure or systolic dysfunction, eplerenone was also found to reduce serum PIIINP levels when the latter were above the median of 3.9 ng/mL[6].

Galectin-3 is a ubiquitous beta-galactoside-binding animal lectin present in the tissue micro-environment (e.g. fibroblasts, macrophages, myocytes, and renal cells) and may be extracellular, cytoplasmic, or nuclear. These properties make great flexibility on Gal-3 as a modulator of numerous biological systems including inflammation and collagen deposition by fibroblasts that is likely up-regulated by the renin–angiotensin–aldosterone system,[39–42] although its direct correlation with the extent of cardiac fibrosis was found to be lacking in human heart failure of hypertensive origin in one study.[43] Nonetheless, experimental models suggest that blocking Gal-3 pathways may attenuate cardiac fibrosis, vascular remodelling, LV dysfunction, and heart failure onset.[44,45] In this study, higher Gal-3 levels were associated with lower lateral e′ and septal e′, suggesting that Gal-3 may also be related to DD independently of increased congestion.[46,47]

Reduced systemic concentrations of ICTP may reflect reduced collagen type I fibre degradation by MMP-1 given that high lysyl oxidase-mediated cross-linking increases the resistance of the fibre to MMP-1 proteolysis.[48] In the present study, ICTP was not associated with 1 year DD.

Altogether, in patients with non-complicated MI (≈70% of patients with Killip class <2, mean creatine phosphokinase peak ≈3000 UI/L, and mean LV ejection fraction ≈50%), higher BNP, PIIINP, and Gal-3 were associated herein with the development of DD at 1 year post-MI. These biomarkers were correlated with DD echocardiographic parameters. The above findings may help to tailor therapeutic decisions (such as mineralocorticoid receptor antagonist introduction in a dedicated trial) and in the early identification of patients more prone to develop DD.

Study limitations

Several limitations should be acknowledged in the present study. First, this is a secondary non-pre-specified analysis of an observational study; hence, causality cannot be ascertained. Second, few patients (n = 22) developed 'new-onset' DD; hence, the models developed herein lack accuracy and precision. Moreover, the adjustment on more than two variables (one for each 10 'outcome events') may be questionable as proposed by some authorities; hence, we could not adjust on full models considering, for example, age, gender, diabetes, and echocardiographic parameters because it provided largely inaccurate results.[22] These findings should thus be regarded as hypothesis generating and should be confirmed in other cohorts. Third, while echocardiographic assessment of DD remains a matter of debate, the definition used for this analysis has nonetheless been shown to be reproducible and easily assessable.[13] Fourth, the biomarkers herein were measured at 1 month post-MI, as already reported[9,16]; hence, they do not reflect the acute event kinetics but may better reflect cardiac remodelling in the short-term post-MI phase. Fifth, the echocardiographic and biomarker assessment was not performed simultaneously; hence, the correlation between the biomarker levels and echocardiographic parameters is suboptimal. Sixth, this study aimed to show associations with DD status and not to subclassify patients with DD in grades (1, 2, or 3) for which purpose of the present sample is largely underpowered (DD n = 22). Seventh, it should be noted that the studied biomarkers were associated with different DD parameters: BNP with lower lateral e′, septal e′, and increased LAVi; PIIINP with a lower septal e′ only; and Gal-3 with lower lateral e′ and septal e′, but not LAVi. These findings should be interpreted with caution, because neither cardiac MRI nor echocardiographic strain is available to identify cardiac regions with potentially different fibrosis patterns. Furthermore, the outcome of interest was the onset of DD for which all these biomarkers were independently associated. Eighth, this study did not incorporate magnetic resonance imaging, which could have provided a better assessment of myocardial 'fibrosis'. Finally, the low event rate (≈4%) does not allow ascertaining hard outcome associations.

Conclusions

The present study suggests that PIIINP, Gal-3, and BNP may be independently associated with new-onset DD in post-anterior MI patients. Moreover, patients with higher baseline BNP may be less likely to recover normal diastolic function, but PIIINP and Gal-3 were not associated with DD recovery.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient characteristics according to diastolic function at 1-year post-myocardial infarction in the subgroup with diastolic dysfunction at baseline (*n*=137).
Table S2. Association of the studied biomarkers and normal diastolic function at 1-year post-myocardial infarction in the subgroup of patients with diastolic dysfunction at baseline (*n*=137).
Table S3. Biomarker correlation table.
Table S4. Medication at 1-year.

References

1. St John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moye LA, Dagenais GR, Lamas GA, Klein M, Sussex B, Goldman S, Menapace FM, Parker JO, Lewis S, Sestier F, Gordon DF, McEwan P, Bernstein V, Braunwald E, Save Investigators, Brigham and Woman's Hospital, Harvard Medical School, Boston. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. *Circulation* 1994; **89**: 68–75.
2. Gerber Y, Weston SA, Berardi C, McNallan SM, Jiang R, Redfield MM, Roger VL. Contemporary trends in heart failure with reduced and preserved ejection fraction after myocardial infarction: a community study. *Am J Epidemiol* 2013; **178**: 1272–1280.
3. Moller JE, Pellikka PA, Hillis GS, Oh JK. Prognostic importance of diastolic function and filling pressure in patients with acute myocardial infarction. *Circulation* 2006; **114**: 438–444.
4. Yoon HJ, Kim KH, Kim JY, Cho JY, Yoon NS, Park HW, Hong YJ, Kim JH, Ahn Y, Jeong MH, Cho JG, Park JC. Impaired diastolic recovery after acute myocardial infarction as a predictor of adverse events. *J Cardiovasc Ultrasound* 2015; **23**: 150–157.
5. Jugdutt BI. Ventricular remodeling after infarction and the extracellular collagen matrix: when is enough enough? *Circulation* 2003; **108**: 1395–1403.
6. Ferreira JP, Duarte K, Montalescot G, Pitt B, de Sa EL, Hamm CW, Flather M, Verheugt F, Shi H, Turgonyi E, Orri M, Rossignol P, Vincent J, Zannad F. Effect of eplerenone on extracellular cardiac matrix biomarkers in patients with acute ST-elevation myocardial infarction without heart failure: insights from the randomized double-blind REMINDER Study. *Clin Res Cardiol* 2017; **107**: 49–59.
7. Moreo A, Ambrosio G, De Chiara B, Pu M, Tran T, Mauri F, Raman SV. Influence of myocardial fibrosis on left ventricular diastolic function: noninvasive assessment by cardiac magnetic resonance and echo. *Circ Cardiovasc Imaging* 2009; **2**: 437–443.
8. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation* 2015; **131**: 550–559.
9. Eschalier R, Fertin M, Fay R, Bauters C, Zannad F, Pinet F, Rossignol P. Extracellular matrix turnover biomarkers predict long-term left ventricular remodeling after myocardial infarction: insights from the REVE-2 study. *Circ Heart Fail* 2013; **6**: 1199–1205.
10. Lam CS. What is normal in HFNEF?: The case for HFpEF. *JACC Heart Fail* 2014; **2**: 541–543.
11. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging* 2009; **2**: 191–198.
12. Anversa P, Palackal T, Sonnenblick EH, Olivetti G, Meggs LG, Capasso JM. Myocyte cell loss and myocyte cellular hyperplasia in the hypertrophied aging rat heart. *Circ Res* 1990; **67**: 871–885.
13. Huttin O, Fraser AG, Coiro S, Bozec E, Selton-Suty C, Lamiral Z, Frikha Z, Rossignol P, Zannad F, Girerd N. Impact of changes in consensus diagnostic recommendations on the echocardiographic prevalence of diastolic dysfunction. *J Am Coll Cardiol* 2017; **69**: 3119–3121.
14. Shah AM, Claggett B, Kitzman D, Biering-Sorensen T, Jensen JS, Cheng S, Matsushita K, Konety S, Folsom AR, Mosley TH, Wright JD, Heiss G, Solomon SD. Contemporary assessment of left ventricular diastolic function in older adults: the atherosclerosis risk in communities study. *Circulation* 2017; **135**: 426–439.
15. Hashmi S, Al-Salam S. Galectin-3 is expressed in the myocardium very early post-myocardial infarction. *Cardiovasc Pathol* 2015; **24**: 213–223.
16. Fertin M, Hennache B, Hamon M, Ennezat PV, Biausque F, Elkohen M, Nugue O, Tricot O, Lamblin N, Pinet F,

Bauters C. Usefulness of serial assessment of B-type natriuretic peptide, troponin I, and C-reactive protein to predict left ventricular remodeling after acute myocardial infarction (from the REVE-2 study). *Am J Cardiol* 2010; **106**: 1410–1416.
17. Beygui F, Collet JP, Benoliel JJ, Vignolles N, Dumaine R, Barthelemy O, Montalescot G. High plasma aldosterone levels on admission are associated with death in patients presenting with acute ST-elevation myocardial infarction. *Circulation* 2006; **114**: 2604–2610.
18. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009; **22**: 107–133.
19. Lax A, Sanchez-Mas J, Asensio-Lopez MC, Fernandez-Del Palacio MJ, Caballero L, Garrido IP, Pastor-Perez FJ, Januzzi JL, Pascual-Figal DA. Mineralocorticoid receptor antagonists modulate galectin-3 and interleukin-33/ST2 signaling in left ventricular systolic dysfunction after acute myocardial infarction. *JACC Heart Fail* 2015; **3**: 50–58.
20. Savoye C, Equine O, Tricot O, Nugue O, Segrestin B, Sautiere K, Elkohen M, Pretorian EM, Taghipour K, Philias A, Aumegeat V, Decoulx E, Ennezat PV, Bauters C. Left ventricular remodeling after anterior wall acute myocardial infarction in modern clinical practice (from the REmodelage VEntriculaire [REVE] study group). *Am J Cardiol* 2006; **98**: 1144–1149.
21. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease study group. *Ann Intern Med*, United States 1999; **130**: 461–470.
22. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007; **165**: 710–718.
23. Weisman HF, Bush DE, Mannisi JA, Bulkley BH. Global cardiac remodeling after acute myocardial infarction: a study in the rat model. *J Am Coll Cardiol* 1985; **5**: 1355–1362.
24. Manhenke C, Orn S, Squire I, Radauceanu A, Alla F, Zannad F, Dickstein K. The prognostic value of circulating markers of collagen turnover after acute myocardial infarction. *Int J Cardiol* 2011; **150**: 277–282.
25. Manhenke C, Ueland T, Jugdutt BI, Godang K, Aukrust P, Dickstein K, Orn S. The relationship between markers of extracellular cardiac matrix turnover: infarct healing and left ventricular remodelling following primary PCI in patients with first-time STEMI. *Eur Heart J* 2014; **35**: 395–402.
26. Iraqi W, Rossignol P, Angioi M, Fay R, Nuee J, Ketelslegers JM, Vincent J, Pitt B, Zannad F. Extracellular cardiac matrix biomarkers in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study. *Circulation* 2009; **119**: 2471–2479.
27. Montalescot G, Pitt B, Lopez de Sa E, Hamm CW, Flather M, Verheugt F, Shi H, Turgonyi E, Orri M, Vincent J, Zannad F. Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the randomized double-blind REMINDER study. *Eur Heart J* 2014; **35**: 2295–2302.
28. Beygui F, Cayla G, Roule V, Roubille F, Delarche N, Silvain J, Van Belle E, Belle L, Galinier M, Motreff P, Cornillet L, Collet JP, Furber A, Goldstein P, Ecollan P, Legallois D, Lebon A, Rousseau H, Machecourt J, Zannad F, Vicaut E, Montalescot G. Early aldosterone blockade in acute myocardial infarction: the ALBATROSS randomized clinical trial. *J Am Coll Cardiol* 2016; **67**: 1917–1927.
29. Clerico A, Zucchelli GC, Pilo A, Emdin M. Clinical relevance of biological variation of B-type natriuretic peptide. *Clin Chem*, United States 2005; **51**: 925–926.
30. Tekten T, Yenisey C, Ceyhan C, Onbasili AO, Discigil G, Kaya M, Unal S. Correlation between N-terminal pro B-natriuretic peptide and ultrasonic backscatter: implications for diastolic dysfunction in hypertension. *Echocardiography* 2007; **24**: 837–842.
31. Morita E, Yasue H, Yoshimura M, Ogawa H, Jougasaki M, Matsumura T, Mukoyama M, Nakao K. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. *Circulation* 1993; **88**: 82–91.
32. Izawa H, Murohara T, Nagata K, Isobe S, Asano H, Amano T, Ichihara S, Kato T, Ohshima S, Murase Y, Iino S, Obata K, Noda A, Okumura K, Yokota M. Mineralocorticoid receptor antagonism ameliorates left ventricular diastolic dysfunction and myocardial fibrosis in mildly symptomatic patients with idiopathic dilated cardiomyopathy: a pilot study. *Circulation* 2005; **112**: 2940–2945.
33. Klappacher G, Franzen P, Haab D, Mehrabi M, Binder M, Plesch K, Pacher R, Grimm M, Pribill I, Eichler HG et al. Measuring extracellular matrix turnover in the serum of patients with idiopathic or ischemic dilated cardiomyopathy and impact on diagnosis and prognosis. *Am J Cardiol* 1995; **75**: 913–918.
34. Quilliot D, Alla F, Bohme P, Bruntz JF, Hammadi M, Dousset B, Ziegler O, Zannad F. Myocardial collagen turnover in normotensive obese patients: relation to insulin resistance. *Int J Obes (Lond)* 2005; **29**: 1321–1328.
35. Eschalier R, Rossignol P, Kearney-Schwartz A, Adamopoulos C, Karatzidou K, Fay R, Mandry D, Marie PY, Zannad F. Features of cardiac remodeling, associated with blood pressure and fibrosis biomarkers, are frequent in subjects with abdominal obesity. *Hypertension* 2014; **63**: 740–746.
36. Vautrin E, Pepin JL, Faure P, Barone-Rochette G, Tamisier R, Ormezzano O, Gauchez AS, Levy P, Baguet JP. Procollagen type III amino terminal peptide (PIIIP) is associated with left ventricular diastolic dysfunction in obstructive sleep apnoea. *Int J Cardiol* 2011; **151**: 387–388.
37. Uusimaa P, Risteli J, Niemela M, Lumme J, Ikaheimo M, Jounela A, Peuhkurinen K. Collagen scar formation after acute myocardial infarction: relationships to infarct size, left ventricular function, and coronary artery patency. *Circulation* 1997; **96**: 2565–2572.
38. Hayashi M, Tsutamoto T, Wada A, Tsutsui T, Ishii C, Ohno K, Fujii M, Taniguchi A, Hamatani T, Nozato Y, Kataoka K, Morigami N, Ohnishi M, Kinoshita M, Horie M. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. *Circulation* 2003; **107**: 2559–2565.
39. Lin YH, Chou CH, Wu XM, Chang YY, Hung CS, Chen YH, Tzeng YL, Wu VC, Ho YL, Hsieh FJ, Wu KD. Aldosterone induced galectin-3 secretion *in vitro* and *in vivo*: from cells to humans. *PLoS One* 2014; **9**: e95254.
40. Azibani F, Benard L, Schlossarek S, Merval R, Tournoux F, Fazal L, Polidano E, Launay JM, Carrier L, Chatziantoniou C, Samuel JL, Delcayre C. Aldosterone inhibits antifibrotic factors in mouse hypertensive heart. *Hypertension* 2012; **59**: 1179–1187.
41. Martinez-Martinez E, Ibarrola J, Fernandez-Celis A, Calvier L, Leroy C, Cachofeiro V, Rossignol P, Lopez-Andres N. Galectin-3 pharmacological inhibition attenuates early renal damage in spontaneously hypertensive rats. *J Hypertens* 2018; **36**: 368–376.
42. Henderson NC, Sethi T. The regulation of inflammation by galectin-3. *Immunol Rev* 2009; **230**: 160–171.
43. Lopez B, Gonzalez A, Querejeta R, Zubillaga E, Larman M, Diez J. Galectin-3 and histological, molecular and biochemical aspects of myocardial fibrosis in heart failure of hypertensive origin. *Eur J Heart Fail* 2015; **17**: 385–392.
44. Yu L, Ruifrok WP, Meissner M, Bos EM, van Goor H, Sanjabi B, van der Harst P, Pitt B, Goldstein IJ, Koerts JA, van Veldhuisen DJ, Bank RA, van Gilst WH,

Sillje HH, de Boer RA. Genetic and pharmacological inhibition of galectin-3 prevents cardiac remodeling by interfering with myocardial fibrogenesis. *Circ Heart Fail* 2013; **6**: 107–117.
45. Ibarrola J, Martinez-Martinez E, Sadaba JR, Arrieta V, Garcia-Pena A, Alvarez V, Fernandez-Celis A, Gainza A, Rossignol P, Cachofeiro Ramos V, Lopez-Andres N. Beneficial effects of galectin-3 blockade in vascular and aortic valve alterations in an experimental pressure overload model. *Int J Mol Sci* 2017; **18**: E1664.
46. Edelmann F, Holzendorf V, Wachter R, Nolte K, Schmidt AG, Kraigher-Krainer E, Duvinage A, Unkelbach I, Dungen HD, Tschope C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Stough WG, Pieske BM. Galectin-3 in patients with heart failure with preserved ejection fraction: results from the Aldo-DHF trial. *Eur J Heart Fail* 2015; **17**: 214–223.
47. Martinez-Martinez E, Lopez-Andres N, Jurado-Lopez R, Rousseau E, Bartolome MV, Fernandez-Celis A, Rossignol P, Islas F, Antequera A, Prieto S, Luaces M, Cachofeiro V. Galectin-3 participates in cardiovascular remodeling associated with obesity. *Hypertension* 2015; **66**: 961–969.
48. Robins SP. Biochemistry and functional significance of collagen cross-linking. *Biochem Soc Trans* 2007; **35**: 849–852.