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Echocardiographic Diastolic Function Evolution in Patients with an Anterior Q-wave Myocardial Infarction: Insights from the REVE-2 Study

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Abstract

Background: Myocardial fibrosis plays a key role in the development of adverse left ventricular remodeling 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: The REVE-2 is a prospective multicenter 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 2 criteria of echocardiographic parameters: septal $e' < 8$ cm/s, lateral $e' < 10$ cm/s and left atrial volume ≥ 34 mL/m².

Results: At baseline 87 (35.4%) patients had normal diastolic function and 159 (64.6%) patients had diastolic dysfunction. 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 PIIINP > 6 mg/l (Odds Ratio, OR=5.29; 95%CI=1.05-26.66; $p=0.044$), Galectin-3 > 13 μ g/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 PIIINP, Galectin-3 and BNP may be independently associated with new-onset DD in post-MI patients.

Key-words: Myocardial infarction; diastolic dysfunction; cardiac remodeling; Galectin-3; collagen peptides.

Introduction

Cardiac remodeling after a myocardial infarction (MI) is an important prognostic and treatment response indicator¹. Declines in post-MI events have been observed in patients with heart failure and reduced ejection fraction (HF-REF) 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 remodeling 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 remodeling and diastolic dysfunction after acute MI⁵⁻⁸. 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 cause⁷. 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 LV end-diastolic volume at 1-year after a Q-wave anterior MI⁹. However, an increase in LV end-diastolic volume may be misleading in the setting of preserved 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 remodeling, the LV end-diastolic volume was shown to markedly decrease with age, despite altered strain patterns reflecting both systolic and diastolic dysfunction¹¹, suggesting that DD is a better reflection of adverse remodeling compared to an increase in LV end-diastolic volume in the setting of a preserved EF (LVEF may actually increase in this context)¹⁰⁻¹². Despite the lack of definitive consensus for the definition of DD¹³, 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 outcomes¹⁴. 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 remodeling 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 remodeling 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 multicenter observational study designed to analyze the association of circulating biomarkers with LV remodeling in patients with a first anterior wall Q-wave

MI¹⁶. Patients were enrolled from February 2006 to September 2008. Main inclusion criteria were hospitalization within 24h after symptom onset and a pre-discharge echocardiogram showing at least 3 akinetic LV segments in the infarct zone. Exclusion criteria were inadequate quality of the echocardiographic image, life-limiting noncardiac 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 clinical trials.gov number was assigned to this study since it was initiated in 2006.

Echocardiographic assessment

Serial echocardiographic studies were performed at hospital discharge (day 3 to 7) and 12 months after initial MI. A standard echocardiographic imaging protocol was used, with apical 4- and 2-chamber views; 2D echocardiograms of the LV short axis were recorded from the left parasternal region at 3 levels: the mitral valve, the mid papillary muscle and the apex. All echocardiograms were analyzed at the Lille Core Echo Laboratory (Lille, France), as previously described¹⁷. Diastolic dysfunction was defined according to the 2009 recommendations of the American Society of Echocardiography and the Committee of the European Association of Echocardiography¹⁸. Patients with at least 2 of the following parameters, namely 1) septal $e' < 8$ cm/s; 2) lateral $e' < 10$ cm/s; and 3) left atrial volume index (LAVi) ≥ 34 ml/m², were considered to have DD, i.e. the primary outcome of the present post-hoc study.

Biomarkers

All biomarkers were measured in plasma and serum samples obtained at 1 month after myocardial infarction, as previously described⁹. Plasma and serum were collected in glass tubes and processed within 2 hours. Samples were stored at -80°C. Samples underwent no more than 2 freeze/thaw cycles before analysis in a core laboratory (Lille, France for brain natriuretic peptide (BNP) and Nancy, France for collagen peptides and Galectin-3). BNP was measured with a fully automated 2-site sandwich immunoassay on an Advia Centaur analyzer (Siemens Diagnostic, Zurich, Switzerland). The lowest measurable concentration with this assay with a $\leq 20\%$ coefficient of variation is 2.5 ng/l. Radioimmunoassay kits (Orion Diagnostica, Espoo, Finland) were used for determination of serum collagen peptide concentrations: PINP (aminoterminal propeptide of type I procollagen; reference range: 22 to 87 and 19 to 83 mg/l in men and women, respectively); PIIINP (aminoterminal propeptide of type III procollagen; reference range: 2.3 to 6.4 mg/l); and ICTP (type I collagen telopeptide; 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 immuno-sorbent assay (ELISA) kits (BGM Galectin-3 assay; BG Medicine, Inc., Waltham, MA, USA). The minimum sensitivity was 0.96 μ g/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 μ g/l, respectively. Intra- and interassay variations were $< 8\%$ and 10% ²⁰. Estimated glomerular

filtration rate (eGFR) was computed using the 4-variable MDRD (Modification of Diet in Renal Disease) Study formula²¹.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation (SD) and median (percentile₂₅₋₇₅). 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 1 variable for each 10 events²². 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 Galectin-3. Logistic regression data are presented as odds ratios (OR) and respective 95% confidence intervals (95%CI).

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 analyzed 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 LAV =19.4 [16.7-22.5]) and 159 patients (64.6%) had diastolic dysfunction (DD) (Septal e' =5.7 [4.7-6.6], Lateral e' =7.0 [5.6-8.3] and LAV =19.8 [16.0-24.4]). The two subgroups of patients (normal diastolic function vs. DD) were analyzed for evolution of LV diastolic function 1-year post-MI as described in the flowchart (**Figure 1**). A total of 26 patients (29.8%) with normal diastolic function and 22 patients (20.1%) in the DD subgroup were not analyzed due to missing data (n=42) or low quality (n=6) for the parameters required to evaluate diastolic dysfunction.

Among the 61 patients without DD at baseline, 22 (36%) developed DD at 1-year post-MI, and 39 (64%) remained without DD. Compared to patients without DD at 1-year, those with “new-onset” DD were older (55 \pm 14 vs. 48 \pm 13 years; $p=0.043$), had higher diastolic blood pressure (66.0 \pm 12.2 vs. 59.1 \pm 8.4 mmHg; $p=0.013$), hypertension history (45% vs. 21%; $p=0.04$), and exhibited higher BNP (median =185 [percentile₂₅₋₇₅ =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] μ g/l, $p=0.002$) concentrations at 1month post-MI. LVEF was similar between the two groups (51% \pm 10% vs. 52% \pm 7%, $p=0.45$). **Table 1**. Among the 137 patients with DD at baseline, 36 (26%) normalized diastolic function at 1-year post-MI, and 101 (74%) remained with DD. Compared to patients that remained with DD at 1-year, those who improved their diastolic function were younger (53 \pm 11 vs. 62 \pm 12 years; $p=0.0002$) and had higher eGFR (88 \pm 21 vs.

78±19 ml/min/.73m²; p=0.011). **Supplemental Table 1.**

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). **Supplemental Table 2.** The studied biomarkers were poorly correlated and did not present significant collinearity in the multivariable models. **Supplemental Table 3.** There were no significant medication changes at 1-year that could potentially be associated with biomarker changes. **Supplemental Table 4.**

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', 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 remodeling and DD in whom tailored anti-remodeling 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 remodeling and DD development.

In the post-MI setting, time-dependent damage to both myocytes and extracellular matrix (ECM) 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 remodeling, cardiac dysfunction and worse prognosis^{25, 26}. Thus, identifying patients more prone to adverse remodeling and DD may help clinicians in tailoring treatments with anti-adverse remodeling 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 fibrillation²⁹. BNP was positively associated with DD onset and negatively associated with DD improvement at 1-year. Additionally, higher BNP was associated 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 ischemic etiology and idiopathic dilated cardiomyopathy (DCM)^{32,33}. Furthermore, higher PIIINP has been associated with insulin resistance and adverse lipid profile in obese patients without overt cardiovascular diseases³⁴ and associated with DD in patients with abdominal obesity³⁵. 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 concentrations³⁷. In patients with DCM, the reduction in myocardial collagen as a result of spironolactone treatment is also accompanied by a significant reduction in PIIINP serum levels³². 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 STEMI, 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 to controls. In the present study, cardiac aldosterone extraction was suppressed and plasma PIIINP levels were also significantly reduced in the aldosterone antagonist group³⁸. In a subanalysis of the REMINDER trial which included patients with STEMI 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/mL⁶.

Gal-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 upregulated by the renin-angiotensin-aldosterone system (RAAS)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 study⁴³. Nonetheless, experimental models suggest that blocking Gal-3 pathways may attenuate cardiac fibrosis, vascular remodeling, 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 diastolic dysfunction independently of increased congestion^{46,47}.

Reduced systemic concentrations of ICTP may reflect reduced collagen type I fiber degradation by MMP-1 given that high lysyl oxidase-mediated cross-linking increases the resistance of the fiber to MMP-1 proteolysis⁴⁸. In the present study, ICTP was not associated with 1-year DD.

Altogether, in patients with non-complicated MI ($\approx 70\%$ of patients with Killip class < 2 , mean CPK peak ≈ 3000 UI/l, and mean LV ejection fraction $\approx 50\%$) 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 MRA 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-prespecified 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 2 variables (1 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 results²². 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 assessible¹³. 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 remodeling 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 sub-optimal. 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 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; PIIIN 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 are 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 ($\approx 4\%$) does not allow ascertaining hard outcome associations.

Conclusions

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

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Disclosures

None.

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