International Journal of Cardiology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Galectin-3 is associated with left ventricular reverse remodeling and outcome after percutaneous mitral valve repair

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ARTICLE INFO

Article history:
Received 23 November 2017
Received in revised form 26 February 2018
Accepted 5 April 2018
Available online xxxx

Keywords:
Percutaneous mitral valve repair
Reverse remodeling
Biomarker
Outcome
Galectin-3

ABSTRACT

Background: Plasma Galectin-3 is a marker of myocardial inflammation and fibrosis, was associated with left ventricular (LV) reverse remodeling after conventional surgical mitral valve repair (MVR) and predicted clinical events in patients undergoing transcatheter aortic valve replacement (TAVR). We aimed to evaluate the association between pre-interventional Galectin-3 levels and (1) reverse LV remodeling and (2) major adverse cardiovascular events (MACE) in patients undergoing percutaneous MVR.
Methods: Forty-four consecutive patients (median age 79 years, LV ejection fraction 39.5 ± 11.4%, 91% in NYHA functional class ≥III) with symptomatic moderate to severe mitral regurgitation undergoing percutaneous MVR were prospectively included. Plasma Galectin-3 levels were measured before the procedure. Echocardiographic and clinical assessment was performed at baseline and after 3 months. LV reverse remodeling was prospectively defined as a ≥10% increase in global longitudinal strain. MACE included death, myocardial infarction, heart failure related rehospitalization and stroke and was assessed after a mean follow-up time of 2 years.
Results: 72.7% of the patients showed LV reverse remodeling. Pre-interventional Galectin-3 < 10 ng/ml was an independent predictor of LV reverse remodeling (OR 10.3, 95% CI 1.2–83.9, $p = 0.036$). 25 patients (56.8%) experienced a MACE. Patients with Galectin-3 levels ≥ 10 ng/ml had significantly more MACE than patients with Galectin-3 levels < 10 ng/ml (100% vs. 45.5%, $p = 0.003$). Diabetes independently predicted MACE (HR 3.1, 95% CI 1.0–9.4, $p = 0.049$); Galectin-3 ≥ 10 ng/ml was of borderline significance (HR 2.2, 95% CI 0.9–5.4, $p = 0.088$).
Conclusions: Pre-interventional plasma Galectin-3 levels are associated with LV reverse remodeling and with clinical outcome after percutaneous MVR.

1. Introduction

Percutaneous mitral valve repair (MVR) using the MitraClip system has been associated with improvement of clinical status and quality of life, but also with left ventricular (LV) reverse remodeling [1–4]. The occurrence of LV reverse remodeling has important prognostic implications, which is predominantly proven in patients undergoing conventional surgical MVR [5].

Recently, plasma Galectin-3 has emerged as a novel biomarker in heart failure. Galectin-3 plays a major role in the development of myocardial fibrosis [6–8]. Elevated levels of Galectin-3 are associated with the release of different mediators, for example transforming growth factor (TGF)-β1. This leads to macrophage migration and fibroblast proliferation within the myocardium and to deposition of collagen, which was associated with a worsening of LV function in animal models [8]. In addition, Galectin-3 is an important mediator during inflammation [9].

In patients with mitral regurgitation (MR) undergoing surgical MVR, higher pre-operative plasma levels of Galectin-3 were associated with the absence of LV reverse remodeling [10]. In patients with aortic stenosis undergoing transcatheter aortic valve replacement (TAVR) an association of Galectin-3 with clinical outcome was proven [11]. Patients with higher levels of Galectin-3 suffered from more complications within 30 days after TAVR and experienced a higher rate of cardiac events. Additionally, elevated levels of Galectin-3 have been associated with mortality in patients with acutely decompensated and chronic heart failure [12,13]. Galectin-3 levels have also been positively correlated with the severity of heart failure as elevated plasma levels were detected at the time of mechanical circulatory support and in non-survivors when compared to patients successfully bridged to heart transplantation [6].

However, the prognostic impact of plasma Galectin-3 has not been assessed in patients with MR undergoing percutaneous MVR so far.

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https://doi.org/10.1016/j.ijcard.2018.04.025
0167-5273/

Therefore, we aimed to evaluate the association between pre-interventional plasma Galectin-3 levels and (1) reverse remodeling of the LV and (2) major adverse cardiovascular events (MACE) in patients with symptomatic moderate to severe MR undergoing percutaneous MVR with the MitraClip system.

2. Material and methods

2.1. Study population

Consecutive patients with symptomatic moderate to severe MR undergoing percutaneous MVR at the Heart Center of the University Hospital of Tuebingen, Germany, were prospectively included in this single-center observational study. Baseline parameters including age, gender, renal insufficiency (GFR < 60 ml/min/1.73m^2), NYHA functional class, 6 min walk test (6MWT), heart failure medication, and comorbidities were registered. The logistic EuroSCORE (logEuroSCORE) and STS Score (morbidity/mortality) were calculated as described previously. The study was approved by the local Ethics Committee of the University of Tuebingen (Project-No.097/2011B02) and all patients gave written informed consent before baseline investigations were performed.

2.2. Echocardiography

Two-dimensional transthoracic echocardiography was performed one or two days before percutaneous MVR and at 3 months follow-up using a Philips IE 33 ultrasound system. Severity and classification of MR (functional vs. degenerative) was assessed using a multiparameteric approach [14]. Left ventricular ejection fraction (LVEF) was calculated by the biplane Simpson's method. Left ventricular enddiastolic and endsystolic diameters (LVEDD and LVESD) were measured by M-mode echocardiography. Size of the left atrium (LA) was measured in parasternal long axis in M-mode. The systolic pulmonary artery pressure (PAP_{sys}) was estimated by adding right ventricular pressure (maximum velocity of the regurgitant jet over the tricuspid valve) and estimated central venous pressure (CVP; according to the diameter and inspiratory collapse of the inferior vena cava). Global longitudinal strain (GLS) was measured by speckle tracking strain analysis using the QLAB Advanced Quantification Software (version 8.0, Philips, Best, The Netherlands). GLS was assessed from apical 4-chamber, 2-chamber, long axis and short axis views as described before [15]. LV reverse remodeling was prospectively defined as a ≥10% increase in GLS [15].

2.3. Hemodynamic parameters

The following parameters were invasively assessed by left and right heart catheterization prior to and immediately after percutaneous MVR by the use of standard techniques: cardiac output (CO), pulmonary capillary wedge pressure (PCWP), mean PAP, CVP and arterial blood pressure (ABP).

2.4. Laboratory measurements

Plasma Galectin-3 levels were measured before the procedure by a commercially available ELISA kit (R&D Systems, DGAL30, Lot 211144). The minimum detectable dose of Galectin-3 ranged from 0,003–0,085 ng/ml. Nt-pro BNP was measured by the Siemens ADVIA centaur immunoassay system.

2.5. Follow-up

Peri-interventional complications were defined as intrahospital death, myocardial infarction, re-do of percutaneous MVR due to failure of initial repair, urgent or emergent cardiovascular surgery for adverse events, major stroke, renal failure, deep wound infection, ventilation > 48 h, gastrointestinal complication requiring surgery, new onset of persistent atrial fibrillation (AF), septicemia or transfusion of ≥2 units of blood. Three months after percutaneous MVR, all patients presented at our heart failure clinics for reassessment of NYHA functional class, 6MWT and performance of transthoracic echocardiography. After a mean follow-up time of 2 years, all patients were contacted by phone for the assessment of MACE. MACE included death, myocardial infarction, rehospitalization due to heart failure and non-fatal stroke.

2.6. Sample size calculation

Based on prior results of protein analysis via the ELISA-kit for Galectin-3 used in this study, mean levels of Galectin-3 were assumed to be 8 ± 2 ng/ml for patients with reverse LV remodeling (group 1) and 10 ± 2 ng/ml for patients without reverse LV remodeling (group 2). Using the method of Dhand et al. [16] and assuming a pooled standard deviation of 2 units, the study would require a sample size of 16 for each group (i.e. a total sample size of 32), to achieve a power of 80% and a two-sided level of significance of 5%, for detecting a true difference in means between the test and the reference group of −2 (i.e. 8–10) units.

2.7. Statistical methods

Continuous variables are expressed as median with interquartile ranges (IQR) and compared using a Mann-Whitney *U* test. Categorical data is presented as proportions and analyzed by a chi-square test. To compare parameters at baseline and follow-up, Wilcoxon signed-rank test for two related samples was used. We calculated a receiver operating characteristic (ROC) curve to evaluate the predictive power of Galectin-3 and of the multivariable model including both Galectin-3 and renal function for reverse LV remodeling by the area under the curve (AUC). Endpoint analyses are displayed using a Kaplan-Meier curve. The association of risk factors with reverse LV remodeling was tested by univariate and multivariate binary logistic regression analyses. Cox regression analyses were performed to evaluate the association of risk factors with MACE. Risk factors with a *p*-value < 0.1 in univariate analysis were included in multivariable analysis. Comparisons were considered statistically significant if two-sided *p* value was < 0.05. Statistical analyses were performed using SPSS software version 22 (SPSS Inc.).

3. Results

3.1. Baseline characteristics

In total, 44 patients with symptomatic moderate to severe MR undergoing percutaneous MVR were prospectively included. Median age of the patients was 79 (73–82) years, 36.4% were females. 54.5% suffered from functional MR. 75% had coronary artery disease, 38.6% were diabetics, 77.3% were in AF at study entry. 20.5% of the patients had an implantable cardioverter defibrillator (ICD), 13.6% had received cardiac resynchronization therapy (CRT). Median LVEF was 40% (30–50%). Median logEuroSCORE was 15.7% (10.4–30.5%). Median plasma levels of Galectin-3 were 8.29 ng/ml (6.0–9.7 ng/ml) and median Nt-proBNP levels was 2922 pg/ml (1023–4869 pg/ml). Patients were treated with the following heart failure medication: 88.6% were on betablockers, 95.5% on ACE inhibitors or ARBs, 52.3% were on MRAs, 22.7% on digitalis, 93.2% received diuretics, and 2.3% ivabradine. The baseline characteristics of the patient population are summarized in the left column of Table 1.

3.2. Change of hemodynamic, clinical and echocardiographic parameters from baseline to follow-up

Immediately after Clip deposition, CO increased from 4.2 (3.2–4.7) l/min to 4.9 (3.9–5.6) l/min ($p < 0.0001$) while MAP remained unchanged (72 (63–76) mm Hg to 70 (65–72) mm Hg, $p = 0.646$). PCWP, mean PAP and CVP significantly decreased (from 17 (10–23.5) mm Hg to 12 (8.5–15.0) mm Hg, $p < 0.0001$; from 28 (23.5–33.5) mm Hg to 25 (20.8–30.0) mm Hg, $p < 0.0001$ and from 13 (9.5–16.5) to 11 (7.0–13.0) mm Hg, $p = 0.015$, respectively).

After 3 months (mean follow-up time of 106 ± 62 days), there was a significant improvement in NYHA functional class from a mean of 3.0 ± 0.4 to 2.1 ± 0.8 ($p < 0.0001$) and in 6 MWT (from 265 (120–360) m to 320 (240–400) m, $p = 0.005$). On echocardiography, a significant reduction of MR from 3.1 ± 0.3 to 1.2 ± 0.5 ($p < 0.0001$), LA diameter (from 51 (46–59) mm to 50 (46–54) mm, $p = 0.048$), reduction of diameter of mitral annulus (from 43 (41–46) mm to 40 (39–45) mm, $p = 0.001$) and PAP_{sys} (from 53 (45–60) mm Hg to 43 (39–54) mm Hg, $p < 0.0001$) was observed over time. In addition, LVEF and GLS significantly improved (from 39.5 ± 11.4% to 40.9 ± 11.3%, $p = 0.023$ and from −12 (−15 to −10) to −15 (−18 to −11), $p < 0.0001$, respectively).

3.3. Comparison of patients with left ventricular reverse remodeling vs. patients without reverse remodeling

Patients were divided into two subgroups based on the presence of LV reverse remodeling (prospectively defined as a ≥10% increase in GLS) [15,17–19] at 3 months follow-up. LV reverse remodeling was observed in 32 patients (72.7%). The middle and right column of Table 1 presents the baseline characteristics of patients with and without LV reverse remodeling. Patients with LV reverse remodeling had a lower prevalence of renal insufficiency at baseline (43.8% vs. 83.3% in patients without LV reverse remodeling, $p = 0.019$) and were significantly more often treated with digitalis (31.1% vs. 0%, $p = 0.028$). In addition, patients showing LV reverse remodeling had significantly lower pre-

Please cite this article as: C.S. Zuern, et al., Galectin-3 is associated with left ventricular reverse remodeling and outcome after percutaneous mitral valve repair, Int J Cardiol (2018), https://doi.org/10.1016/j.ijcard.2018.04.025