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ORIGINAL ARTICLE

The Relationship between Galectin-3 and Different Patterns of Ventricular Geometry Remodelling in Aortic Valve Stenosis

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Background This study was conducted to assess expression of Galectin-3 (Gal-3) in patients with different types of left ventricle (LV) hypertrophy geometry, and the relationship between Gal-3 expression and LV remodelling in patients with aortic valve stenosis (AS).

Methods Galectin-3 expression was measured in the plasma and myocardia of AS patients who underwent an aortic valve replacement procedure.

Results The study enrolled 77 consecutive patients with severe AS. Fifty-five (71.43%) of the enrolled patients had concentric hypertrophy (CH group), and had the highest degree of fibrosis (27.10 ± 5.25%; p < 0.001) and expression of Gal-3 in both plasma (19.11 ± 2.06 ng/mL) and myocardial tissue (3.01 ± 0.79). There was a strong positive correlation between the levels of fibrosis and Gal-3 expression in both plasma (r = 0.584, $p < 0.001$) and myocardium (r = 0.522, $p < 0.001$). Relative wall thickness (RWT) was strongly correlated with Gal-3 expression in both myocardium (r = 0.594, $p < 0.001$) and plasma (r = 0.323, $p = 0.005$). Additionally, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were positively correlated with both fibrosis (r = 0.313, $p = 0.036$) and LV mass index (r = 0.559, $p < 0.001$).

Conclusions Concentric hypertrophy geometry was the most common type of myocardium remodelling, and AS patients with CH geometry showed the highest levels of Gal-3 expression. Galectin-3 levels were positively correlated with fibrosis and RWT, both of which are crucial indicators of geometric remodelling. Galectin-3 and NT-proBNP levels may be valuable prognostic predictors in AS patients with myocardial remodelling.

Keywords Aortic stenosis • Myocardial hypertrophy • Galectin-3 • Myocardial remodelling • Fibrosis

Background

Aortic stenosis (AS) accompanied by chronic pressure overload is a known precursor of left ventricular (LV) hypertrophy and remodelling. Moreover, cardiac remodelling involving cardiomyocyte hypertrophy, cardiac fibrosis, and inflammation is associated with a worsened clinical course of heart failure (HF). Four different LV geometric configurations have been identified based on their degree of associated LV hypertrophy and relative wall thickness (RWT) [1]. The pattern of LV geometry, various haemodynamic features, and the clinical outcomes associated with AS can vary based on the stage of the AS process. In addition to increased pressure overload, cardiac interstitial fibrosis has

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also been implicated in the pathogenesis of AS LV remodelling [2]. Furthermore, the stage of fibrosis may contribute to the clinical presentation of heart failure in AS, [3] and significantly impact the prognosis of AS patients having undergone aortic valve replacement (AVR) [2,4]. Thus, the phase of LV remodelling and the degree of fibrosis may both play critical roles in determining which diagnostic and prognostic applications can be used to predict the appropriate timing for AVR.

Although some common biomarkers such as collagen, fibronectin, and matrix metalloproteinase [5] are known to be associated with cardiac remodelling, these markers are often elevated as a result of the remodelling process, and do not substantively contribute to the remodelling process itself. As a result, there remains a need to identify some reliable biomarkers which can stratify the risk for cardiac remodelling and predict its progression. Galectin-3 is a highly expressed 30 kD MW galactoside-binding lectin secreted by macrophages, and a potent mitogen for fibroblasts in vitro [6]. Galectin-3 may be seen as a ''culprit'' biomarker as it is found to augment fibrosis and modulate immune response in myofibroblast accumulation and activation, as well as in remodelling development [7,8]. Sharma et al. [9] first reported that Gal-3 expression was increased in AS patients with a depressed ejection fraction; and since that time, numerous clinical studies have shown Gal-3 to be significantly upregulated in the hypertrophied and fibrous hearts of AS patients, as well as the plasma of patients with acute and chronic HF [10,11]. Therefore, such a biomarker related to cardiac remodelling might be valuable for use in risk stratification of AS patients.

However, the changes in ventricular geometry which occur in response to LV pressure overload in AS patients have not been fully discussed, and the relationship between ventricular geometry and Gal-3 levels in AS patients has not been established. Thus, we conducted this study to identify the levels of Gal-3 in AS patients with different LV geometric patterns, and investigate the relationship between Gal-3 expression and left ventricular geometry in AS patients.

Methods

All patients provided their written informed consent to undergo a myocardial biopsy performed intra-operatively during AVR, and for the specimens to be used for experimental purposes. The study protocol was reviewed and approved by the local institutional Medical Ethics Committee.

Study Population

This study enrolled 77 patients (49 males and 28 females; mean age, 48.88 y $\pm$ 13.96 y) with isolated severe AS; defined as a mean gradient $\geq$ 40 mmHg as determined by the continuity equation, the results of a transthoracic echocardiogram (TTE) or the patient displaying symptoms of heart failure [12]. The enrolled patients had been referred for AVR surgery in the Cardiovascular Department of the 2nd Xiangya Hospital of Central South University between July 2012 and January 2014. Patients were excluded from the study if they had more than mild aortic regurgitation, had previously undergone concomitant coronary artery bypass surgery or some other type of valve surgical procedure, had undergone a redo surgery, or had infectious endocarditis, hypertension, or a malignant tumour.

Echocardiography

The LV dimensions for each subject were measured in the parasternal long axis view according to guidelines published by the American Society of Echocardiography [13]. Measurements of the interventricular septum (IVS) and left ventricular posterior wall (LVPW) were made during the diastolic period, and left ventricular dimensions were determined during both the diastolic and systolic phase (LVDd or LVDs). Measurements of peak aortic jet velocity, mean aortic gradient pressure, and derived variables such as ejection fraction (EF) were also obtained.

Left Ventricular Geometry

The following equations were used to obtain measurements for additional parameters from echocardiographic data: Left ventricular mass (LVM) (g) = $0.8 \times \{1.04[(\mathrm{LVDd} \times \mathrm{PWTd} \times \mathrm{SWTd})^3 - (\mathrm{LVDd})^3]\} + 0.6$ g; where PWTd and SWTd are the posterior wall thickness and septal wall thickness at end diastole in centimetres, respectively [13]. Body surface area (BSA) = $[0.006 \times \mathrm{Height\ (cm)} + 0.0128 \times \mathrm{Weight\ (kg)} - 0.1529$; Left ventricular mass index [LVMI ($\mathrm{g/m^2}$)] = LVM/BSA. A LVMI > 125 $\mathrm{g/m^2}$ in male patients or > 120 $\mathrm{g/m^2}$ in female patients was defined as LV hypertrophy (LVH) [14]. Relative wall thickness (RWT) = (IVS + LVPW)/LVDd. A RWT $\geq$ 0.42 was used to define increased RWT in both men and women [13]. Patterns of LV geometry were divided into four groups: Patients with an increased LVMI and a RWT ratio $\geq$ 0.42 were considered to have concentric hypertrophy (CH group). If this ratio was < 0.42, the hypertrophy was considered to be eccentric (EH group). Patients with a normal LVMI and a RWT ratio $\geq$ 0.42 were considered to have concentric remodelling (CR group). Patients with a normal LVMI and RWT ratio < 0.42 were considered to have normal geometry (N group).

Sample Collection

Blood samples were collected after an overnight fast and immediately centrifuged at 3000 rpm for 15 min at 4 °C. The samples were then stored at -70 °C until being assayed. Cardiac biopsies were obtained from AS patients undergoing AVR and snap-frozen in liquid nitrogen until being assayed for Gal-3 expression.

Galectin-3 Measurements

Plasma concentrations of Gal-3 were assessed using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA). All ELISA assays were calibrated according to the manufacturer's instructions. Protein isolation and western blotting were performed as follows: Primary antibodies against Gal-3 (Abcam, Cambridge, MA, USA) were diluted 1/1000 in Tris-buffered saline containing Tween-20