International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Aortic stenosis and aortic regurgitation express different titin isoforms: Differences and relationships with functional and geometric characteristics☆

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ARTICLE INFO

Article history:
Received 11 May 2017
Received in revised form 17 October 2017
Accepted 31 January 2018
Available online xxxx

Keywords:
Aortic valve replacement
Aortic stenosis
Aortic regurgitation
Titin
Left ventricular function

ABSTRACT

Background-Titin represents an important biomechanical sensor which determines compliance and diastolic/systolic function of the left ventricle (LV). To assess the different titin-isoform expression and the relationships with functional and geometric patterns, we analyzed titin-isoform expression and cardiomyocytes contractile function in myocardial biopsy samples of patients undergoing aortic valve replacement (AVR) for aortic stenosis (AS) and for aortic regurgitation (AR).

Method -Specimens, collected from the LV of 35 with AS and 35 with AR undergoing AVR were analyzed for titin-isoform expression and cardiomyocytes force measurement. Ten donor hearts were analyzed as controls for normal values. Results were implemented with preoperative geometry and function assessed by Doppler echocardiography.

Results-Compared to controls, N2BA/N2B titin-isoforms ratio was reduced to 0.24 in AS ($p < 0.001$) but increased to 0.51 in AR ($p < 0.001$). N2BA/N2B titin-isoforms ratio was further reduced in 8 patients with severe (restrictive) diastolic dysfunction (0.17 ± 0.03, $p < 0.001$) but was increased in patients with severe systolic dysfunction (0.58 ± 0.07, $p < 0.001$). As compared to controls, Fpasive was higher in AS (6.7 ± 0.2 vs 4.4 ± 0.4 kN/m^2, $p < 0.001$) but was lower in AR (3.7 ± 0.2 vs 4.4 ± 0.4 kN/m^2, $p < 0.001$). Total force was comparable. Fpassive was significantly higher in AS patients with severe than with moderate LV diastolic dysfunction (7.1 ± 0.5 vs $6.6. \pm 0.6$, $p = 0.004$).

Conclusions-titin-isoform expression differs in AS and AR as adaptive response to different pathophysiologic scenarios. Co-expressing isoforms at varying ratios results in modulation of the passive mechanical behavior of the LV at different degree of dysfunction and allows for compensative adjustment of the diastolic/systolic properties of the myocardium.

1. Introduction

Aortic stenosis (AS) and aortic regurgitation (AR) involve adaptive processes which compensate for pressure or volume overload. These processes are accompanied by structural remodeling substantiated by derangements in the muscular and nonmuscular compartments of the left ventricle (LV). Cardiomyocytes develop distinct structural reshaping of cytoskeletal, modifications in membrane-associated proteins and reassembly of sarcomere components [1–3].

In the last years, several studies emphasized the role of titin within the sarcomeres as the main determinant for the correct alignment of actin and myosin myofilaments and their elastic properties [4,5]. Titin is expressed in two different isoforms, N2B and N2BA, with different molecular and functional characteristics: the N2B isoform is stiffer and less distensible, the longer N2BA isoform is more elastic and compliant [6]. Together with the interstitial elastic and connective components, titin isoform ratio determines not only the rigidity and the diastolic properties of the ventricle, but also the systolic function modulating the Frank-Starling mechanism [7].

☆ All author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2018.01.136
0167-5273/

Table 1
Clinical Profile and Echocardiographic Left Ventricular Morphologic and Functional Characteristics of Patients.

	Aortic stenosis ($n = 35$)	Aortic regurgitation (n.35)	Controls ($n = 10$)	*p	**p
Age (y)	61.5 ± 8.5	59.8 ± 9.3	38.7 ± 7.1	0.3	<0.001
Female sex	13(37.1%)	14(40%)	3(30%)	0.9	0.9
BMI (units of kg/m^2)	23.6 ± 4.7	25.4 ± 5.1	25.3 ± 3.2	0.2	0.3
Hypertension	14(40%)	17(48.5%)		0.7	
LV diastolic function					
Mild dysfunction		2(6.6%)			
Moderate dysfunction	25(71.4%)	2(6.6%)			
Severe dysfunction	10(28.6)				
LV systolic function					
Normal	35(100%)	8(22.8%)			
Mild dysfunction		14(40%)			
Moderate Dysfunction		8(22.8%)			
Severe dysfunction		5(14.4%)			
LVEDVI (mL/m^2)	68.3 ± 8.2	118.8 ± 28.5			
LVESVI (mL/m^2)	22.4 ± 3.1	54.2 ± 7.2			
LVEF (%)	66.3 ± 5.4	44.7 ± 12.2			
LVMI (g/m^2)	144.3 ± 12.4	210.8 ± 21.5			
RWT (%)	0.48 ± 0.04	0.35 ± 0.04			
LVPWTd (mm)	11 ± 1.8	10 ± 1.7			
IVSTd (mm)	13 ± 0.5	12 ± 0.3			
LAI diameter (mm/cm^2)	29 ± 2.4	25 ± 3.1			
PASP (mm Hg)	61.5 ± 6.6	29.4 ± 7.6			
AVAI (cm^2/m^2)	0.59 ± 0.05	1.8 ± 0.3			
Peak velocity (m/s)	3.9 ± 0.03	2.1 ± 0.6			
Mean pressure drop (mmHg)	42.8 ± 6.2	14.8 ± 2.2			
Peak gradient (mm Hg)	105.5 ± 18.4	13.3 ± 3.1			
Mean gradient (mm Hg)	55.5 ± 7.2	9.3 ± 2.1			
Velocity ratio (m/s)	0.18 ± 0.03	0.9 ± 0.02			
E/A ratio	1.7 ± 0.6	1.6 ± 0.7			
E/E' ratio	13.3 ± 3.2	16.5 ± 2.1			
Deceleration time (m/s)	167.8 ± 23.6	132 ± 18			
S/D ratio	1.8 ± 0.09	0.8 ± 0.03			
Diastolic flow reversal		Prominent olodiastolic			
Pressure half time (m/s)		182 ± 24			
Regurgitant jet/LVOT (width %$^\zeta$)		0.6 ± 0.05			
Vena contracta (width cm$^\zeta$)		0.6 ± 0.04			
Regurgitant volume (mL/beat)		57.1 ± 4.5			
Regurgitant fraction (%)		55.4 ± 5.1			
Effective regurgitant orifice (cm^2)		27.5 ± 3.2			
EFS%	27.8 ± 2.1	18.8 ± 2.2			
MFS%	21.8 ± 2.1	12.8 ± 3.3			

Values are mean ± SD or numbers (percentage). BMI, Body mass index. LV, Left Ventricle. *p, patients with aortic stenosis vs patients with aortic regurgitation. **p, control patients vs diseased patients. LV systolic and diastolic dysfunction were graded according to the ESC or to the EAE/ASE recommendations respectively [21,23]. Hypertension was blood pressure above 140/90 mmHg.
A: peak velocity during atrial systole; AVAI: aortic valve area index; D: diastolic peak velocity; E: early flow velocity; E′: early diastolic velocity; EFS: endocardial fractional shortening; IVSTd: interventricular-septum thickness in diastole; LAI: Left atrium index; LVEDVI: Left ventricular (LV) end diastolic volume index; LVEF: LV ejection fraction; LVESVI: LV end systolic volume index; LVOT: LV outflow tract; LVMI: LV mass index; LVPWTd: LV posterior wall thickness in diastole; MFS: midwall fractional shortening; PASP: pulmonary artery systolic pressure; RWT: relative wall thickness; S: systolic peak velocity.
ζ at a Nyquist limit of 50–60 cm.

Titin has been the subject of a number of studies in animal models [8,9]. However, paucity of data have been published regarding human myocardium hitherto. Even the normal N2BA/N2B isoform ratio in normal human LV has not been definitively assessed [10–12].

Some recent studies described alterations in titin isoform expression in the LV of patient with congestive heart failure secondary to ischemic disease, dilated cardiomyopathy or pressure overload secondary to AS [10,13–15]. Actually, to date, no data are available regarding the titin isoform behavior in patients with AR. Because of insufficient knowledge, the present study compared titin isoform expression and contractile function in the biopsy samples procured from the LV of patients undergoing aortic valve replacement (AVR) for pure AS or pure AR. Specific morphofunctional echocardiographic characteristics were also analyzed for their possible relationship with titin isoforms. A group of normal donor hearts were also analyzed as controls.

2. Materials and method

2.1. Patients

Population consisted of 70 patients equally distributed between AS ($n = 35$) and AR (n = 35) referred for primary isolated surgical AVR and operated on between January 2011 and July 2016. According to ACC/AHA 2006 Guidelines, indications for AVR in patients with AS were: area <1.0 cm2, mean gradient >40 mm Hg, jet velocity >4.0 m/s in symptomatic patients or area <0.6 cm2, mean gradient >60 mm Hg, jet velocity >5.0 m/s in asymptomatic patients. Indications for AVR in patients with AR were: LV dysfunction (ejection fraction ≤0.50) in symptomatic or asymptomatic patient and normal LV systolic function (ejection fraction >0.50) but severe LV dilatation (end-diastolic dimension >75 mm or end-systolic dimension >55 mm) in asymptomatic patients [16].

General exclusion criteria were: severe comorbidities (dialysis, hepatic failure), autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Sjögren's syndrome or psoriatic arthritis) or connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome), acute aortic dissection, congenital defects of the aortic valve (bicuspid valve or sub-valvular stenosis induced by fixed or dynamic components), atrial fibrillation, contemporary mitral and/or tricuspid

Please cite this article as: V. Mannacio, et al., Aortic stenosis and aortic regurgitation express different titin isoforms: Differences and relationships with functional and geome..., Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.01.136