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Plasma amino-terminal propeptide of procollagen type III is associated with subclinical left ventricular systolic dysfunction in aortic stenosis

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ABSTRACT

Objective: The aim of the study was to investigate the association of plasma amino-terminal propeptide of procollagen type III (PIIINP) with subclinical left ventricular (LV) systolic dysfunction in patients with aortic stenosis (AS) and normal LV ejection fraction.
Methods: The study was performed in 57 AS patients with normal LV ejection fraction and in 30 control subjects with normal aortic valve and normal LV ejection fraction. Tissue Doppler and speckle tracking image were performed to assess LV diastolic and systolic function. Plasma PIIINP level was measured by specific radioimmunoassay.
Results: In AS patients, LV systolic longitudinal strain was significantly reduced (-17.1 ± 2.1 vs. -18.8 ± 1.4%, $P<0.001$) and plasma PIIINP was increased compared with controls (2.5 ± 0.6 vs. 2.1 ± 0.4 μg/l, $P<0.001$). A significant correlation was found between LV systolic longitudinal strain and PIIINP ($r=-0.67$, $P<0.001$). In patients with abnormal LV diastolic function, LV systolic longitudinal strain was reduced compared with patients with normal LV diastolic function (-16.3 ± 1.5 vs. -18.8 ± 2.1%, $P<0.001$) and plasma PIIINP was increased (2.8 ± 0.5 vs. 2.0 ± 0.3 μg/l, $P<0.001$). A stepwise multivariate regression analysis revealed that LV systolic longitudinal strain and diastolic blood pressure were independent predictors of plasma PIIINP (multiple $r=0.71$, $P<0.001$).
Conclusions: Plasma PIIINP is associated with subclinical LV systolic dysfunction (the impaired LV systolic long axis function) in patients with AS and normal LV ejection fraction. In addition, the impaired LV systolic long axis function and increased plasma PIIINP concentration are most marked in patients with abnormal LV diastolic function.
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1. Introduction

Aortic stenosis (AS) is the most frequent cardiovascular disease after hypertension and coronary artery disease in the elderly and is one of the most commonly encountered valvular pathologies requiring surgery in developed countries [1]. The left ventricle (LV) gradually hypertrophies in response to pressure overload caused by long-standing AS, resulting in various degrees of LV dysfunction.

The process of LV hypertrophic remodeling involves both cardiomyocyte hypertrophy and abnormalities of the extracellular network (myocardial fibrosis) [2], which may be maladaptive rather than beneficial for maintaining normal LV function in the setting of AS [3]. Heymans and colleagues [2] demonstrated that myocardial fibrosis in patients with AS is most prominent in the subendocardial area and is associated with diastolic dysfunction. However, the subendocardial fibres which are arranged longitudinally also contribute to LV long axis systolic contraction [4]. In patients with severe AS and normal LV ejection fraction, LV long axis systolic function is globally abnormal showing reduced amplitude of motion, velocities, and strain [5]. Therefore, myocardial fibrosis which includes interstitial and perivascular fibrosis is likely to affect the subendocardial function. The impact of myocardial fibrosis on LV systolic long axis function however, has not been fully elucidated in patients with AS.

The amino-terminal propeptide of type III procollagen (PIIINP) is a marker of type III collagen synthesis, which is cleaved off stoichiometrically during conversion from type III procollagen to type III collagen and liberated to serum [6]. Elevated serum PIIINP is believed to reflect enhanced collagen turnover, including synthesis and deposition as well as alteration in degradation and elimination [7]. This study aimed to investigate the association of plasma PIIINP with LV systolic long axis function in patients with AS and normal LV ejection fraction.

2. Methods

2.1. Study population

This study included a total of 57 consecutive patients (33 males) with AS who were referred to our cardiovascular centre for evaluation and treatment. Their mean age was 65.3 ± 8.2 years, and the age range was 42–81 years. The control group was composed of 30 subjects (18 males, mean age 66.1 ± 7.4 years) with normal aortic valve and normal LV ejection fraction. Subjects with poor echo windows, LV wall motion abnormalities, significant aortic or mitral regurgitation, mitral stenosis, liver disease,

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renal disease, skeletal disease or pulmonary obstructive disease were excluded. Clinical examination, conventional echocardiography, tissue Doppler and speckle tracking imaging were performed in all subjects. Plasma PIIINP level was measured by specific radioimmunoassay. AS was defined as a peak aortic jet velocity ≥2.5 m/s [8].

All study subjects were in sinus rhythm and with a normal LV ejection fraction (>55%) evaluated by echocardiography. Written informed consents were obtained from all patients and this study protocol was approved by the medical ethics committee of the hospital.

2.2. Conventional echocardiography

Standard M-mode, 2D, color Doppler, pulsed-wave and continuous-wave Doppler were performed using a Philips iE33 ultrasound imaging system with a S5-1 (5 to 1 MHz) phased-array transducer. All echocardiographic examinations were used according to the American Society of Echocardiography's (ASE) Guidelines and Standards [9,10]. Images were stored digitally and analysed with no knowledge of the clinical data. All measurements were averaged over 3 cardiac cycles.

LV end-diastolic and end-systolic dimensions, septal and posterior wall thicknesses were measured directly from 2D images or using 2D-targeted M-mode [9]. The LV mass was calculated by the ASE-recommended formula [9]. The LV mass index (LVMI) was calculated with correction for body surface area. The LV ejection fraction was calculated using the biplane method of disks (modified Simpson's rule) in the apical 4-chamber and 2-chamber views. The left ventricular outflow tract diameter (LVOT) was measured at the level of the aortic annulus in the parasternal long axis view. The peak LVOT velocity was obtained using pulsed-wave Doppler in the apical 5-chamber view. The peak aortic valve velocity was obtained using continuous-wave Doppler. The peak instantaneous gradient across aortic valve was derived using the modified Bernoulli equation, and the indexed aortic valve area was calculated based on the continuity-equation [10]. The peak early diastolic mitral inflow velocity (E) was measured using pulsed-wave Doppler in the apical 4-chamber view.

2.3. Tissue Doppler and speckle tracking imaging

Tissue Doppler imaging (frame rate range 90–150 frames/s) was obtained in the apical 4-chamber view during end expiration. A 1.5 mm pulsed Doppler sample volume was placed sequentially at the lateral and medial mitral annulus. The peak early diastolic mitral annular velocity (Ea) was obtained as the average of two values which were measured at the medial and lateral annulus. The ratio of E to Ea (E/Ea) was calculated.

Speckle tracking images were obtained at a frame rate of 60–80 frames/s in the apical 4-chamber view during end expiration. Three consecutive cardiac cycles with best image quality and without any artifacts were acquired and transferred to a QLAB workstation for off-line analysis. Analysis was conducted using QLAB Quantification software. The regions of interest were defined manually by marking the endocardial border and adjusting the region to include the whole LV wall thickness. The software then automatically detected the frame-to-frame motion of the natural ultrasound reflecting markers (speckles). The LV septum and lateral wall were divided into basal, middle and apical segments respectively. The LV systolic longitudinal strain was calculated as the average of six values which were obtained at the individual segments.

2.4. Diastolic LV function

Patients with AS were divided into two groups on the basis of the mitral E/Ea ratio: the normal and abnormal LV diastolic function groups. The normal LV diastolic function is defined as a mitral E/Ea ratio <8, whereas a mitral E/Ea ratio ≥8 was considered to indicate abnormal LV diastolic function [11].

2.5. Determination of plasma PIIINP

Serum samples to determine concentration of plasma PIIINP were taken at the time of the clinical studies and stored at −40 °C for up to 6 months. Plasma PIIINP was analysed by radioimmunoassays (Orion Diagnostica, Oununsalo, Finland). The inter-assay and intra-assay variations for determining PIIINP were 6% and 3%, respectively.

2.6. Statistical analysis

Continuous data were expressed as mean ± standard deviation and categorical data were presented as numbers or percentage. Continuous variables were tested by Student's t tests for unpaired data once normality was shown; otherwise, a non-parametric test (Mann–Whitney test) was used. Categorical variables were analysed by χ^2 test or Fisher's exact test when necessary. Comparisons among 3 groups were obtained for continuous variables with one-way analysis of variance (ANOVA). Relations between two variables were assessed using Pearson's and Spearman's correlation coefficient, depending on whether variables were normally distributed. Predictors of plasma PIIINP were assessed using stepwise multivariate regression analysis with a forward entry stepping algorithm; variables with a P value of ≤0.05 on univariate analysis were entered in the model. Significance was accepted at the level P<0.05. All statistical analyses were conducted using the Minitab (Release 15) statistic software package (Minitab Inc, USA).

3. Results

3.1. Baseline characteristics

The baseline characteristics of AS patients and control subjects are shown in Table 1. There were no significant differences between AS patients and control subjects with respect to age, gender, systolic and diastolic blood pressure, body mass index, the presence of concomitant coronary artery disease, hypertension or diabetes mellitus. Heart rate was lower in AS patients compared with control subjects (63.5 ± 8.5 vs. 70.0 ± 8.4 beats/min, P = 0.001).

3.2. LV structure, systolic and diastolic function, and the severity of AS

Table 2 presents all echocardiographic measurements in AS patients and control subjects. In patients with AS, as expected, LV septal and posterior wall thicknesses, LV end-diastolic dimension, LVMI, E/Ea, peak transaortic velocity and peak pressure gradient were significantly increased (all P<0.01); indexed aortic valve area was significantly reduced (P<0.001). Furthermore, LV systolic longitudinal strain was significantly reduced in AS group compared with control group (−17.1 ± 2.1 vs. −18.8 ± 1.4%, P<0.01). However, LV end-systolic dimension and ejection fraction did not differ between AS patients and controls (both P>0.05).

The main echocardiographic measurements in AS patients with normal or abnormal LV diastolic function are listed in Table 3. There were no significant differences between the normal and abnormal LV diastolic function groups with respect to LV ejection fraction, peak pressure gradient and indexed aortic valve area (all P>0.05). However, LV dimensions and LVMI were significantly increased in the abnormal LV diastolic function group compared with the normal LV diastolic function group (all P<0.01). In addition, LV systolic longitudinal strain was significantly reduced in the abnormal LV diastolic function group (−16.3 ± 1.5 vs. −18.8 ± 2.1%, P<0.001, Fig. 1).

3.3. Collagen marker

Plasma PIIINP was significantly increased in the AS group as a whole compared with control subjects (2.5 ± 0.6 vs. 2.1 ± 0.4 μg/l, p<0.001, Table 2). Analysis of the AS group showed that patients with evidence of diastolic dysfunction had significantly higher plasma concentrations of PIIINP (2.8 ± 0.5 vs. 2.0 ± 0.3 μg/l, p<0.001, Fig. 2) than patients with normal LV diastolic function.

Table 1
Baseline characteristics.

Variable	Control group	AS group	p value
n	30	57	
Age (years)	66.1 ± 7.4	65.3 ± 8.2	0.656
Male gender (n, %)	18 (60)	33 (58)	0.780
NYHA class (n, %)			
II	–	20 (35)	–
III	–	5 (9)	–
IV	–	2 (4)	–
Syncope (n, %)	–	10 (18)	–
Angina (n, %)	–	17 (30)	–
Systolic blood pressure (mm Hg)	133.1 ± 21.9	139.4 ± 23.3	0.226
Diastolic blood pressure (mm Hg)	74.5 ± 11.4	75.6 ± 11.1	0.684
Heart rate (beats/min)	70.0 ± 8.4	63.5 ± 8.5	0.001
Body mass index (kg/m^2)	25.7 ± 2.7	26.4 ± 4.3	0.431
Coronary artery disease (n, %)	7 (23)	16 (28)	0.634
Hypertension (n, %)	11 (37)	31 (54)	0.116
Diabetes mellitus (n, %)	4 (13)	12 (21)	0.377

Values are means ± SD. AS, aortic stenosis; NYHA, New York Heart Association.

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