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Impact of low-grade albuminuria on left ventricular diastolic dysfunction

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ABSTRACT

Background: Albuminuria is an established risk factor for mortality and cardiovascular events in high-risk populations. However, few studies have evaluated the relationship between normoalbuminuria and left ventricular (LV) diastolic function. The present study evaluated the impact of the low-grade albuminuria on LV diastolic function in patients with coronary artery disease (CAD).

Methods: A cross-sectional study was conducted in 202 chronic CAD patients with normal urinary albumin levels. Subjects were divided into 3 tertiles according to sex-specific urinary albumin-to-creatinine concentration ratio (UACR) cut-off points. Subjects in the upper tertile were classified as having low-grade albuminuria. To evaluate the LV function, all subjects underwent echocardiography. LV diastolic dysfunction was defined as $E/e' > 15$ or $8 < E/e' < 15$, with an $E/A < 0.5$, a deceleration time > 280 ms, and a LV mass index > 122 g/m^2 for women or >149 g/m^2 for men.

Results: Among the 202 patients, 76 patients (37.6%) had LV diastolic dysfunction. The prevalence of LV diastolic dysfunction in the upper tertile was significantly greater than that in the middle and lower tertiles (49.3%, 32.3% and 29.2%, respectively; p for trend = 0.029). Adjusting for confounding factors, the presence of low-grade albuminuria independently associated with LV diastolic dysfunction (odds ratio 2.22, 95% confidence interval: 1.05–4.71, p = 0.037).

Conclusions: A high UACR level that is still below the current microalbuminuria threshold is significantly associated with an increased prevalence of LV diastolic dysfunction in CAD patients. Our data suggest that low-grade albuminuria in high-risk populations may provide greater cardiovascular risk stratification.

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1. Introduction

Presence of albuminuria is strongly associated with increased risk of cardiovascular morbidity and mortality in the general population [1], as well as in high-risk populations, which include patients with diabetes and hypertension [2,3]. Recently, low-grade albuminuria (below currently defined cutoff point) was also revealed to be associated with adverse cardiovascular events and could be a predictive factor of hypertension and metabolic syndrome in general populations [4–6].

The high prevalence of patients with heart failure with a preserved ejection fraction (HFpEF) has highlighted the important role of left ventricular (LV) diastolic dysfunction in the development of heart failure (HF) [7,8]. In addition, diastolic dysfunction is associated with poor prognosis, particularly in patients with advanced HF and a reduced ejection fraction [9]. Several studies have reported that higher urinary albumin excretion is associated with higher cardiovascular mortality in patients with HF [10,11].

However, few studies have evaluated the relationship between albuminuria below currently defined cutoff points (normoalbuminuria) and the LV diastolic function in high-risk populations. Therefore, the aim of this study was to evaluate the impact of low-grade albuminuria on LV diastolic dysfunction in patients with CAD.

2. Methods

2.1. Study design

This observational study included a total of 202 chronic CAD patients who were treated with percutaneous coronary intervention at Nagoya University Hospital between September 2012 and April 2014. Chronic

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CAD was defined as stable angina pectoris. We excluded patients with albuminuria (macro- and micro-), those with a history of myocardial infarction, those with congestive heart failure, those with moderate to severe valvular heart disease, and those with LV systolic dysfunction (defined as an LV ejection fraction less than 50%).

This study was approved by the research and ethics committees, and was conducted in accordance with the ethical principles stated by the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients before any procedures were conducted.

2.2. Laboratory analysis

Blood samples were obtained from all patients after a 12-hour overnight fast. Urinary albumin excretion was expressed using an albumin-to-creatinine concentration ratio (ACR), evaluated in a random morning urine specimen. Immunoturbidometry (TIA-ALBG, Serotec, Chitose, Japan) was used to determine urinary albumin concentration, and a modified Jaffe method was used to measure urinary creatinine concentration. Albuminuria was defined as a urinary ACR (UACR) ≥ 30 μg/mg; microalbuminuria was defined as UACR in the 30–300 μg/mg range and macroalbuminuria, as a UACR ≥ 300 μg/mg. Normoalbuminuria was defined as a UACR < 30 μg/mg [12]. Moreover, patients with normoalbuminuria were grouped into tertiles on the basis of sex-specific UACR distribution. Males with a UACR < 4 μg/mg, 4 μg/mg ≤ UACR <9 μg/mg, or 9 μg/mg ≤ UACR <30 μg/mg were grouped into tertiles 1, 2 and 3 respectively. Females with a UACR < 3 μg/mg, 3 μg/mg ≤ UACR <10 μg/mg, or 10 μg/mg ≤ UACR <30 μg/mg were grouped into tertiles 1, 2 and 3 respectively. Subjects in the highest UACR tertile were defined as having low-grade albuminuria.

2.3. Echocardiography

Standard M-mode and 2-dimensional echocardiography, Doppler blood flow, and tissue Doppler imaging measurements were performed in concordance with the American Society of Echocardiography guidelines [13], using the Vivid 7 system (GE Healthcare, Milwaukee, WI, USA). LV end-diastolic volume and end-systolic volume were measured using Simpson's biplane method to calculate LV ejection fraction. Mitral inflow velocities were recorded using pulsed-wave Doppler echocardiography in the apical 4-chamber view. The early (E) and late (A) transmitral diastolic velocities and deceleration time were measured at the leaflet tips. The ratio of E wave to the early diastolic mitral annular velocity (E/e′) was determined using color-coded tissue Doppler imaging with the sample volume positioned in the septal mitral annulus. LV diastolic dysfunction was defined in line with the findings from a previous report [14]. Briefly, electrocardiographic evidence of atrial fibrillation or an E/e′ > 15 or 8 < E/e′ < 15, with an E/A < 0.5, a deceleration time > 280 ms, and an LV mass index > 122 g/m^2 for women or >149 g/m^2 for men defined LV diastolic dysfunction.

2.4. Definitions

Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg and/or current antihypertensive medication use. Diabetes mellitus was defined as the use of any antihyperglycemic medication, a current diagnosis of diabetes or a fasting plasma glucose concentration > 126 mg/dL and/or a glycosylated hemoglobin concentration ≥ 6.5% (National Glycohemoglobin Standardization Program). Dyslipidemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein (HDL) cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL, and/or administration of lipid-lowering therapy. Smoking habit was defined as a current habit or discontinued cigarette use ≤ 6 months before PCI. The estimated glomerular filtration rate (eGFR) was calculated according to a new equation developed in Japan: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine − 1.094 × age − 0.287 × 0.739 (in females) [15].

2.5. Statistical analysis

Continuous variables were expressed as means ± standard deviations or median (interquartile range) if they were non-normally distributed. Categorical variables were expressed as percentages. The Student's *t*-test was used to statistically analyze normally distributed data (continuous variables), and the chi-squared test or Fisher's exact test was used to statistically analyze categorical data. To identify independent predictors of LV diastolic dysfunction, multivariate logistic regression analysis was performed for traditional cardiovascular risk factors. A 2-sided p-value < 0.05 was considered to indicate statistical significance. SPSS version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical analyses.

3. Results

Among the 202 patients, 76 patients in the study population (37.6%) had LV diastolic dysfunction. Patient characteristics and echocardiographic findings are listed in Table 1 and Table 2, respectively. There were significant differences in age, number of males, eGFR levels, UACR, and in the prevalence of hypertension and diabetes between the 2 groups. The prevalence of beta-blocker use and diuretic use tended to be higher in patients with LV diastolic dysfunction compared to those without.

The prevalence of LV diastolic dysfunction in tertile 3 (low-grade albuminuria) was higher than the prevalence observed in tertile 2 and tertile 1 (49.3%, 32.3% and 29.2%, respectively; p for trend = 0.029, Fig. 1). Table 3 shows the results of multivariate logistic analysis that investigated the relationship between LV diastolic dysfunction and age, sex, body mass index, hypertension, diabetes mellitus, UACR and eGFR levels in all subjects. Low-grade albuminuria independently associated with LV diastolic dysfunction after adjustment for these confounding factors (odds ratio 2.22, 95% confidence interval: 1.05–4.71,

Table 1
Baseline patient characteristics.

Variables	LV diastolic dysfunction		p-Value
	Yes ($N = 76$)	No ($N = 126$)	
Demographics			
Male, n (%)	49 (64.5)	99 (78.6)	0.033
Age, years	71.4 ± 8.5	67.5 ± 10.3	0.006
BMI, kg/m^2	23.3 ± 3.9	23.9 ± 3.7	0.24
Hypertension, n (%)	60 (78.9)	84 (66.7)	0.077
Diabetes, n (%)	36 (47.4)	36 (28.6)	0.010
Dyslipidemia, n (%)	57 (75.0)	99 (78.6)	0.61
Current smoker, n (%)	16 (21.1)	27 (21.4)	0.98
Systolic blood pressure (mm Hg)	127.1 ± 17.7	125.8 ± 17.0	0.61
Diastolic blood pressure (mm Hg)	72.2 ± 11.3	73.1 ± 10.0	0.54
Laboratory data			
Hemoglobin (g/dL)	12.9 ± 1.8	13.3 ± 1.8	0.16
LDL-C (mg/dL)	98.1 ± 31.5	97.8 ± 30.1	0.94
HDL-C (mg/dL)	45.7 ± 12.4	45.7 ± 11.3	0.97
Triglycerides (mg/dL)	110 (74–150)	122 (83–167)	0.13
Fasting glucose (mg/dL)	121.0 ± 35.8	111.7 ± 31.1	0.056
Hemoglobin A1C (%)	6.5 ± 0.9	6.2 ± 0.9	0.017
eGFR (mL/min/1.73 m^2)	64.8 ± 17.1	71.6 ± 17.5	0.008
UACR (mg/gCr)	10.7 ± 7.3	7.5 ± 5.9	0.001
BNP (pg/dL)	36 (18–103)	19 (10–62)	0.015
Medications			
ACE-I or ARB, n (%)	48 (63.2)	74 (58.7)	0.56
Ca channel blocker, n (%)	31 (40.8)	50 (39.7)	0.88
Beta-blocker, n (%)	27 (35.5)	26 (20.6)	0.022
Diuretics, n (%)	12 (15.8)	14 (11.1)	0.39

Data are presented as means ± SD, or as medians (interquartile ranges), or as number (percentages).
LV, left ventricular; BMI, body mass index; LDL-C, low-density lipoprotein-cholesterol. HDL-C, high-density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate. UACR, urinary albumin to creatinine ratio; BNP, brain natrium peptide.
ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotension receptor blocker.

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