Int J Clin Exp Med 2016;9(9):18133-18141
www.ijcem.com /ISSN:1940-5901/IJCEM0025936

Original Article

Serum vaspin: a reliable independent predictor for major adverse cardiac events

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Received February 13, 2016; Accepted August 13, 2016; Epub September 15, 2016; Published September 30, 2016

Abstract: Aim: This study aimed to determine the prognostic value of baseline serum vaspin for major adverse cardiac events (MACE) in a cohort of patients with known or suspected coronary artery disease (CAD) referred for coronary angiography. Methods: Serum vaspin was measured in 191 subjects (CAD patients: n=88; controls: n=103) who were followed up in following 2 years for MACE including unstable angina pectoris (UAP), non-fatal myocardial infarction, revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting, ischemic stroke, death and rehospitalization. Results: The serum vaspin was significantly lower (0.25±0.393 ng/mL vs. 0.96±1.901 ng/mL, P=0.037) in MACE group than in non-MACE group. Multivariate Cox regression analysis showed that MACE was negatively correlated with vaspin (B=-0.408, RR=0.665, P=0.039), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and positivelywith systolic blood pressure (SBP). Analysis with receiver operating characteristic curves confirmed that serum vaspin could predict MACE (area under the curve =0.768, P<0.001). The incidence of MACE was significantly reduced inhigh-vaspin group (cut-off value: 0.283 ng/mL) as compared to low-vaspin group (45 [46.88%] vs. 4 [4.44%], P<0.01). In addition, subjects inhigh-vaspin group were more likely to have bettercardiac function (LVEF-drop: 3.37±6.144 in low-vaspin group vs -3.30±11.636 in high-vaspin group, P<0.05). Kaplan-Meier survival analysis showed a significantly reduced MACE-free survival rate in subjects with high serum vaspin. Conclusion: Lower baseline serum vaspin is independently associated with an increased risk for MACE in 2 years in a cohort of CAD patients with different severity, and Non-CAD subjects.

Keywords: Adipokine, vaspin, adiponectin, coronary artery disease, major adverse cardiac events, prognosis

Introduction

Adipose tissues may secrete a number of adipokines that are closely related to the development of obesity-related diseases, such as diabetes mellitus (DM), dyslipidaemia, hypertension and atherosclerotic vascular disease [1]. Many adipokines have been found to contribute to insulin resistance, metabolic disturbances and atherosclerosis, and may influence the prognosis of these diseases [2, 3].

Vaspin, a visceral adipose tissue-derived serine protease inhibitor, is an adipokine with insulin-sensitizing activityand was first identified in the visceral adipose tissues of genetically obese rats [4-6]. It represents a compensatory mechanism stimulated by the obesity, severe insulin resistance, and type 2 DM (T2DM) [6, 7]. Studies from our group and other groups have shown that low serum vaspin is associated with coronary artery disease (CAD) and unstable angina pectoris (UAP) [8-10], as well as ischemic events in patients with carotid stenosis [11] and coronary artery stenosis [12]. Moreover, our results have demonstrated that low serum vaspin correlates with the severity of CADdetermined according to number of affected coronary vessels, suggesting that vaspin may serve as abiomarker of CAD [9]. In addition, there is evidence showing that low serum vaspin is also associated with microvascular complications, including neuropathy, retinopathy and nephropathy in diabetes mellitus (DM) patients [13, 14]. *In vitro* studies have demonstrated that vaspin exerts anti-imflammatory [6, 15, 16] and anti-apoptoticeffects [17]. It has been found that vaspin may inhibit the proliferation, chemokinesis and reactive oxygen species (ROS) production of vascular smooth mus-

cle cells [18, 19]. Taken together, available findings suggest that vaspin plays important roles in the development of CAD and may serve as abiomarker for CAD.

However, to date, no studies have been conducted to examine the prognostic value of baseline serum vaspin in patients with known or suspected CAD. Therefore, based on the population in our pervious study, this study was undertaken to determine the prognostic significance of serum vaspin in subjects with CAD.

Methods

Study population

All study participants, definitions and collection ofbaseline characteristics in this study were identical to those in our previous study [9]. Briefly, a total of 88 patients with angiographically documented CAD (stable angina pectoris [SAP]: n=47; unstable angina pectoris [UAP]: n=41) and 103 healthy subjects as controls were included in this study. The CAD patients were recruited from the Department of Cardiology, Shanghai Tenth People's Hospital (China) and had >50% stenosis in at least 1 coronary arteryas shown by catheterization. Exclusion criteria were as follows: acute myocardial infarction (troponin-T≥0.10 ng/mL), heart failure (left ventricular ejection fraction [LVEF] <30%), cardiomyopathy, acute infection, acute state of a chronic infection or inflammatory disease, severe liver or renal disease, neoplasm and hematologic disorders. Controlsmatched in age and gender had no history of angina or other heart diseases, a normal resting ECG, and normal ECG in exercise stress test.

Detection of serum vaspin and other biochemical markers

The fasting blood wascollected from all the subjects before coronary angiography and processed for the detection of vaspin and other biomarkers. Vaspin (Adipogen, Seoul, South Korea) and adiponectin (R&D Systems, Minneapolis, MN, USA) were measured with commercially available ELISA kits according to the manufacturers' instructions. Other biochemical parameters were measured by colorimetric enzymatic assay systems (Roche MODULAR P-800, Switzerland), including white blood cell count, high sensitive C-reactive protein (hsCRP), fastingplasma glucose (FPG), 2-hour post-load serum glucose, glycosylated hemoglobin, total cholesterol (TC), triglyceride (TG), high-density lipoproteincholesterol (HDL-C), low-density lipoproteincholesterol (LDL-C), total apoprotein A, glutamic-pyruvic transaminase, glutamic oxalacetic transaminase, creatinine (Cr) and uric acid (UA).

Q-PCR quantitative polymerase chain reaction (Q-PCR)

Total RNA was extracted from peripheral blood mononuclear cells by using an RNeasy Plant Mini kit (Qiagen, Hilden, Germany), reverse transcription of RNA into cDNA was done with PrimeScriptRT reagent Kit (Takara Biotechnology, Tokyo, Japan). Real-time PCR was performed to detect the mRNA expression of XXXX with SYBR Premix Ex Taq (Takara Biotechnology, Tokyo, Japan).

Follow-up and endpoints

The primary endpoint was the presence of major adverse cardiac events (MACE) within 24 months in the entire cohort of 191 patients, including UAP, non-fatal myocardial infarction (MI), revascularization by either PCI or coronary artery bypass grafting, ischemic stroke and cardiac death.

The secondary endpoints weretotal rehospitalization and rehospitalization due to the cardiac diseases such as cardiogenic heart failure, arrhythmia and stable angina pectoris (SAP).

Followup was conducted via a combination of telephone, reviewing of the medical records andclinic visits. All subjects were advised to contact our out-patient clinic whenever they experienced cardiac symptoms. Five subjects were lost to follow up, and others' occurrences of MACE were recorded. UAP was defined by a chest pain with the troponin T between 0.004 ng/mL and 0.1 ng/mL. Non-fatal MI during follow-up (i.e. as a clinical outcome) was defined by a history of chest pain with an associated elevation of either troponin I >1.0 ng/mL or troponin T >0.1 ng/mL. Coronary revascularization was defined by a history of either PCI or coronary artery bypass grafting. Ischemic stroke was defined as the presence of a new neurological deficit lasting for at least 24 h with definite evidence of a cerebrovascular accident as shown by either magnetic resonance imaging or computed tomography. Arrhythmia in the

Table 1. Baseline characteristics of patients with and without MACE

Parameters	Non-CAD (n=97)	CAD (n=86)	*P* Value
Age, yr	65.86	64.6	0.484
Male, n (%)	50.3	46.1	0.005*
BMI, kg/m^2	24.22	24.99	0.274
Smoking, n (%)	13.19	17.26	0.213
Diabetes, n (%)	71.13	77.33	0.257
Hypertension, n (%)	17.85	1.07	0.314
LVEF, %	66.61	63.81	0.039*
LVEDD, mm	48.43	48.77	0.687
Total cholesterol, mmol/L	4.70	4.44	0.169
Triglycerides, mmol/L	1.58	1.74	0.474
HDL-C, mmol/L	1.13	1.12	0.936
LDL-C, mmol/L	2.72	2.50	0.134
Apo-A, mmol/L	1.29	1.25	0.184
hsCRP, mg/L	7.88	10.35	0.119
BUN, mmol/L	5.78	5.83	0.868
sCr, mg/L	64.55	75.77	0.114
Uric acid, mg/L	335.49	354.23	0.262
Vaspin, ng/ml	1.09	0.53	0.032*
Vaspin mRNA	2.85	3.94	0.722
Adiponectin, μg/ml	11892.70	10809.59	0.34

Notes: Continuous variables are expressed as mean ± SD and categorical variables as frequencies. CAD: coronary artery disease; n: number of patients; BMI: body mass index; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LDL-C: low-density lipoprotein cholesterol; HDLC: high-density lipoprotein cholesterol; Apo-A: total apoprotein A; BUN: blood urine nitrogen; sCr: serum creatinine concentrations; WBC: white blood cells count; hsCRP: high sensitivity CRP. *P<0.05.

secondary endpoint was defined as an emergence or exacerbation of arrhythmia since recruitment. Stable angina was defined as chest pain sustaining for 30 min without an elevation of cardiac makers. Cardiac heart failure was defined as an event of hospitalization or requirement of pharmacotherapy for the cardiac symptoms such as tachypnea, oliguria, edema and other after exclusion of definite history of structural heart disease, hypertensive heart disease, endocrine heart disease and pulmonary heart disease. The subjects were also excluded from the study if metastatic malignancy, sepsis, liver failure, or pulmonary embolism was present during follow up period.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variablesas frequencies. Normal distribution was tested with the Kolmogorov-Smirnov test. Comparisons between groups were made using unpaired t test, analysis of variance (ANOVA) ornon-parametric Mann-Whitney U test when appropriate. Chi-square test or Fisher exact test was employed for the analysis of non-parametric data. The correlations among vaspin, adiponectin and other continuous variables were evaluated by Spearman's rank correlation analysis in which distribution was tested for normality using Shapiro-Wilk W test, and parameters with abnormal distribution were logarithmically transformed before analyses. Multivariate Cox regression analysis was performed to determine the independent predictors of MACE. Survival curves were generated with the Kaplan-Meier method, and the survival among groups was compared using the log-rank test. Receiver operating characteristic (ROC) curve was used to evaluate the role of vaspin, vaspin mRNA and adiponectin in differentiating the occurrence of MACE. A value of 2-sided P≤0.05 was considered statistically significant. All the statistical analyses were done with SPSS version 16.0 for Windows (SPSS Inc, Chicago, Illinois, USA).

Results

Patients' characteristics

Baseline characteristics between CAD patients and non-CAD subjects had been reported in our previous study [9]. A total of 191 patients were enrolled into this study, of who 97.4% received two-year follow up. 49 MACEs occurred in 41 patients, including UAP (n=35; 18.9%), revascularization (n=4; 2.2%), cardiovascular death (n=3; 1.6%) and ischemic stroke (n=12; 6.5%), and none suffered a non-fatal MI. The baseline characteristics of all patients are shown in **Table 1**. There were no marked differences in the age, gender, BMI, lipid profile (except for Apo-a) and renal function between MACE group and non-MACE group. There were more diabetic mellitus patients and smaller LVEDD in MACE group than in non-MACE group (P<0.05), and more smoking, drinking and hypertension patients in MACE group thoughno significant difference was not observed between them.

Table 2. Multivariable Cox proportional hazard analysis of MACE

Risk factors	*B*	*OR*	*95% CI*	*P value*
Previous-CAD	2.542	12.706	0.716-225.554	0.083
Male	1.329	0.265	0.020-3.478	0.312
Smoking	2.903	0.055	0.008-0.394	0.055
Drinking	1.592	0.203	0.012-3.458	0.271
Lesion-vessels	0.788	2.200	1.181-4.097	0.013*
BMI	0.287	1.332	1.014-1.751	0.040*
Vaspin	-0.21	1.979	0.437-2.193	0.045*
Adiponectin	-0.096	0.908	0.783-1.054	0.204

Notes: B: regression coefficient; OR: odds ratio; CI: confidence interval. *P<0.05.

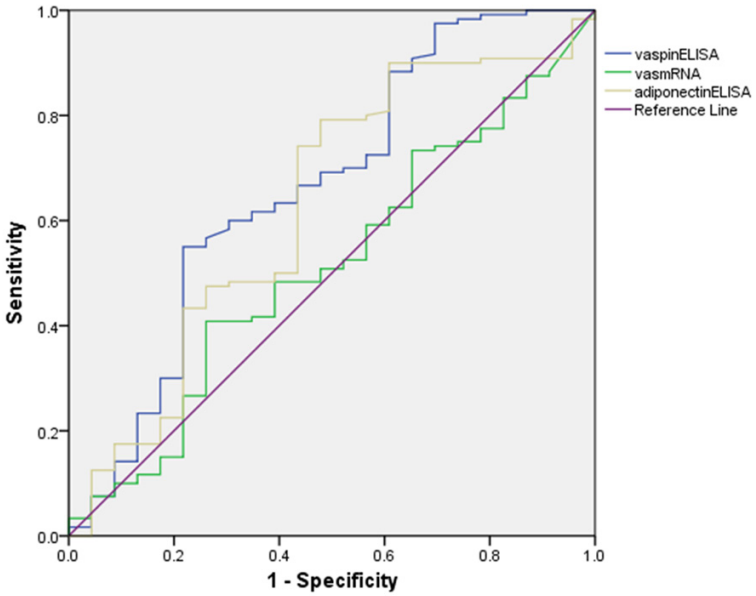

Figure 1. ROC curves. ROC curves indicated that serum vaspincould differentiate the occurrence of MACE. Vaspin (blue): AUC=0.768, P<0.01; vaspin mRNA (green): AUC=0.61, P=0.143; adiponectin (yellow): AUC=0.501, P=0.986.

hsCRP and heart function were comparable between MACE group and non-MACE group, which may be predominantly explained by the history of CAD. Significantly lower serum vaspin (0.25±0.393 ng/mL vs. 0.96±1.901 ng/mL, P=0.037) was found in MACE group than in non-MACE group (**Table 1**).

Relationship of serum vaspin with MACEs

Spearman correlation analysis was used to evaluate the correlation of parameters with MACE. Results showed that MACE was significantly correlated with vaspin (r=-0.422, P<0.01), LVEDD-enlarge percentage (r=0.512, P=0.025) and smoking (r=0.353, P=0.024), but not with others parameters (data not shown). In order to investigate the association of vaspin with future cardiovascular events, multivariate Cox regression analysis was performed after adjusting for classical risk factors. As shown in **Table 2**, the serum vaspinwas anegatively independent predictor of MACE (B: -0.21, OR: 1.979, *P* value: 0.045). Other valuable risk factors are lesion-vessels (B: 0.788, OR: 2.200, *P* value: 0.013) and BMI (B: 0.287, OR: 1.332, *P* value: 0.040), which means more number of lesion-vessels and larger BMI predict worseprognosis. According to the ROC curves (**Figure 1**), vaspin could significantly differentiate the occurrence of MACE (vaspin: area under the curve (AUC) =0.768, P<0.01. Details are showed in **Table 3**. It suggests that vaspin is able to predict MACE in subjects.

Baseline characteristics according to different serum vaspin levels

As the baseline serum vaspin could predict the occurrence of MACE, the cut-off value of vaspin concentration (0.283 ng/ml) was calcualated for the prediction of MACE with the largestsum of sensibility and specificity. All the subjects were divided into two subgroups according the cut-off value: low-vaspin group and high-vaspin group. As shown in **Table 4**, age, smoking, hypertension, serum glucose, and lipid profile (except for TC) were similar between low-vaspin group and high-vaspin group. However, there were more males, CAD patients and a worse cardiac function in low-vaspin group, and the adiponectin concentration was significantly higher in high-vaspin group than in low-vaspin group.

Prognostic significance of baseline serum vaspin

Themain endpoints and second endpoints in two vaspin subgroups are shown in **Table 5**.

Table 3. Receiver operator characteristic curve (ROC) analysis of vaspin, vaspin mRNA, adiponectin for predicting MACE

MACE	AUC	Cut-off point	Sensitivity	Specificity	95% CI	*P* value
Vaspin	0.768	0.283	54.8%	76.2%	0.289-0.642	0.007*
Vaspin mRNA	0.610	0.586	41.7%	60.5%	0.332-0.668	0.430
Adiponectin	0.501	7.596	32.9%	46.7%	0.116-4.290	0.986

Notes: AUC: area under the curve; 95% CI: confidence interval. *P<0.05.

Table 4. Baseline characteristics of subjects in high and low serum vaspin subgroups

Parameters	Low-vaspin	High-vaspin	*P* value
Age, yr	65.64	64.56	0.543
Male, n (%)	67%	53%	0.091*
BMI, kg/m^2	25.11	24.35	0.268
SBP, mmHg	145.75	141.87	0.328
DBP, mmHg	81.91	80.24	0.451
Smoking, n (%)	27%	19%	0.246
Drinking, n (%)	8%	4%	0.358
Diabetes, n (%)	24%	27%	0.667
Hypertension, n (%)	65%	64%	0.846
LVEF, %	63.30	66.20	0.053*
LVEDD, mm	48.80	48.47	0.686
Total cholesterol, mmol/L	4.37	4.72	0.062*
Triglycerides, mmol/L	1.71	1.65	0.701
HDL-C, mmol/L	1.08	1.16	0.164
LDL-C, mmol/L	2.54	2.64	0.527
Apo-A, mmol/L	1.26	1.28	0.477
Apo-B, mmol/L	1.00	0.99	0.934
hsCRP, mg/L	9.10	9.22	0.938
HbALC, %	6.25	6.38	0.720
FBG, mmol/L	5.86	5.65	0.532
P2BG, mmol/L	8.24	8.80	0.554
BUN, mmol/L	5.87	5.82	0.859
Creatinine, mg/L	83.36	80.45	0.447
Uric acid, mg/L	354.04	341.34	0.448

Notes: CAG: coronary angiogram; n: number of patients; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; Apo-A: total apoprotein A; Apo-B: total apoprotein B; FBG: fasting blood glucose; P2BG: 2-hour post-meal blood glucose; BUN: blood urine nitrogen; hsCRP: high sensitivity CRP. *P<0.05.

The incidence of MACE, UAP and stroke was significantly reduced in the high-vaspin group when compared withlow-vaspin group. Moreover, the mortality and revascularization rate were also markedly reduced inhigh-vaspin group as compared to low-vaspin group. As to the second endpoint, there were more patients with rehospitalization, especially due to angina pectorisin low-vaspin group, but the proportion of patients with rehospitalization due to cardiac events or arrhythmia was comparable between two groups (**Table 5**). In addition, patients in the high-vaspin group were more likely to have an improved cardiac function, and the LVEF reduced in low-vaspin group and raised in high-vaspin group.

Similarly, in respect of CAD patients, patients in high-vaspin group had a significantly lower incidence of MACE and rehospitalization as compared to low-vaspin group; they also had an improved cardiac function though significant difference was not observed. In non-CAD subjects, subjects in high-vaspin group had a significantly lower incidence of MACE and improved cardiac function, but a higher rehospitalization rate as compared to low-vaspin group (**Table 5**).

To determine the relationship between MACE free survival and serum vaspin, Kaplan-Meier survival analysis was performed. Results showed a significantly reduced MACE-free survival rate in subjects of low-vaspin group. When CAD or non-CAD subjects analyzed independently, a significantly reduced MACE-free survival rate was still found in those of low-vaspin group (**Figure 2**).

Discussion

Previous studies have reported that low serum vaspin is associated with CAD and UAP [8-10], and vaspin may serve as a novel biomarker of CAD and UAP [9]. The present study for the first-time demonstrated that vaspin was an inde-

Table 5. The difference of first and second end-points between low and high baseline vaspin subgroups

Parameters	Low-vaspin	High-vaspin	*P* value
Last-LVEF, %	61.42	62.45	0.823
Last-LVEDD, mm	49.95	49.45	0.800
LVEF-drop, %	3.17	-3.29	0.055*
MACE-occurrence, n (%)	28.77	8.3	0.007*
Percentage of rehospitalization, n (%)	68.49	68.01	0.959
Percentage of cadiac-rehospitalization, n (%)	45.21	41.67	0.484
Percentage of arrhythmic-rehospitalization, n (%)	16.44	12.5	0.473
Percentage of anginal-rehospitalization, n (%)	42.47	29.17	0.484
Death, n (%)	2.74	0	0.000*
Revascularization, n (%)	2.74	1.39	0.571
Uric acid, n (%)	13.70	1.39	0.266
Stroke, n (%)	9.59	1.39	0.02*

Notes: Categorical variables are presented as frequencies. Last-LVEF and last-LVEDD were recorded in follow-up period. The change in LVEF was defined as the ratio of difference between LVEF at baseline and LVEF in follow-up period divided by the LVEF at baseline. MACE-occurrence was the amount of the events. CAG: coronary angiogram; n: number of patients; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; *P<0.05.

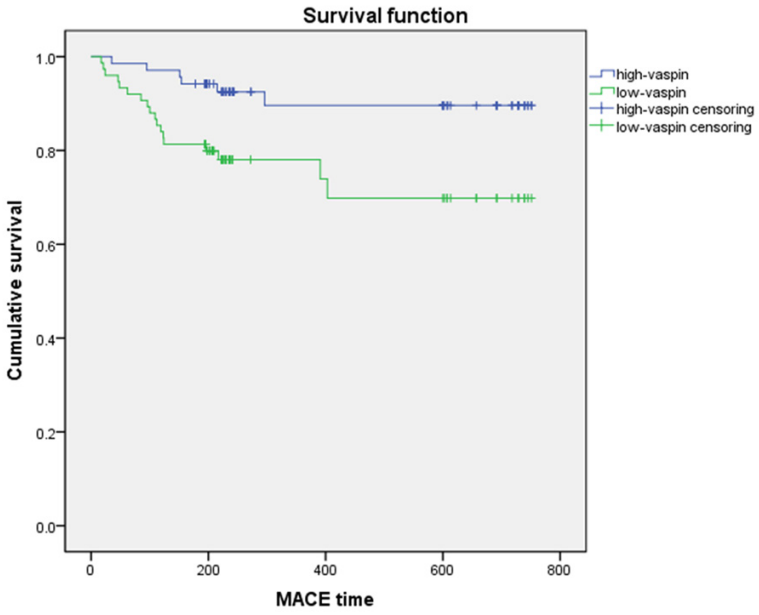

Figure 2. Kaplan-Meier analysis of MACE-free survival in high and low vaspin subgroups.

pendent predictor ofMACE in a cohort of 186 subjects with or without CAD. In addition, patients with higher serum vaspin (cut value at 0.283 ng/mL) had a reduced risk for future cardiovascular events and improved LV systolic function, suggesting an important cardioprotective role of vaspin.

Substantial experimental findings support that vaspin plays a protective role in the development of atherosclerosis [8-10, 18-20]. Our results demonstrated that low serum vaspinwas an independent predictor of MACE, which also proves the protective role of vaspin in CAD. There was also a significant association of MACE with diabetes mellitus, blood pressure, cardiac function and lipid profile, and clinical evidence demonstrated that the serum vaspin correlated with these factors [21, 22]. Our results also demonstrated a positive correlation betweenserum vaspin and adiponectin which is independently predictive of the subsequent risk for death and MI [2, 23], indirectly proving a close relationship between vaspin andMACE. In addition, vaspin is related to the metabolism regulation by controlling glucose uptake, lipolysis and overall food intake as shown in rodents and humans [24]. Moreover, vaspin may inhibit proteases that are able to degrade insulin or anti-orexigenic factors [25]. Thus, vaspin may influence the association of these factors with MACE.

The precise mechanisms responsible for the association between increased serum vaspin and a reduced risk for MACE remain to be determined. The earliest and important mechanism of atherosclerosis and plaque rupture is inflammation [26, 27] and endothelial dysfunction [28]. To date, available findings have shown that vaspin is able to improve insulin resistance [5, 6, 29-31], attenuate inflammation [6] and exert anti-apoptotic effects [17] *in vitro*, suggesting theatheroprotectiveeffect of vaspin. Vaspin may suppress the expression of several pro-inflammatory fac-

tors, including tumor necrosis factor (TNF)-α, leptin, resistin, and adiponectin [6, 15]. In addition to the metabolism regulation, vaspin also contributes to the smooth-muscle cell homeostasis. Phalitakul et al. [16, 19] found a vaspin-mediated reduction in TNF-α-induced p65 phosphorylation, expression of intercellular adhesion molecule-1, and ROS production and inhibition of platelet-derived growth factor-BB-induced vascular smooth muscle cells migration through inhibiting p38/HSP27 signals. It also protects vascular endothelial cells against free fatty acid-induced apoptosis via the phosphatidylinositol 3-kinase (PI3K)/Akt pathway [17]. Recently, our results showed that vaspin was able to reducethe proliferation and chemokinesis of high glucose-induced vascular smooth muscle cells by blocking ROS production and the activation of mitogen-activated protein kinase, PI3K/Akt, insulin receptor signaling and NF-κB signaling pathways [18]. Thus, increased vaspinhas been proposed to inhibit atherothrombosis and prevent cardiovascular events, and to reduce vaspin may compromise the vascular protective effects, leading to atherosclerosis and MACE.

Of note, low vaspinwas found to be an independent predictor of adverse cardiovascular events not only in CAD patients butin non-CAD subjects. In non-CAD group, all subjects were free of diagnosed cardiovascular diseases at the time of blood collection. The lower risk profile in non-CAD subjects was also evident by the lower event rate, small number of participants with diabetes mellitus at baseline and low baseline C-reactive protein (as shown in our previous study [9]). In contrast, In CAD group, patients consisted of a relatively high-risk cohort as manifested not only in the baseline clinical, angiographic, and laboratory findings, butin the high incidence of MACE at 24 months. Therefore, we speculate that, in both high-risk population with either active vascular or myocardial remodeling (such as CAD or ACS patients) and subjects with normal and non-vascular diseases, higher baselinevaspin may in fact be beneficial and predict a decreased cardiovascular risk.

Furthermore, subjects with higher vaspinhad a reduced risk for future MACE with an enhanced left ventricular systolic function. In this study, LVEF was assessed by echocardiography within 7 days and at 24 months after first hospitalization. The change in LVEF was calculated as the difference between ejection fractionat two points. Results showed that patients inhigh-vaspin group were more likely to have an improved cardiac function. Furthermore, results showed that higher baseline vaspin was associated with a reduced rehospitalization, especially due to angina pectoris. Therefore, our findings indicate that vaspin may serve as an important factor in modulating myocardial remodeling under pathologic conditions.

There were still several limitationsin this study. First, the sample size was small in this study. Thus, our findings are required to be confirmed in more prospective studies with large sample size. Second, some medications, such as statin, metformin, angiotensin converting enzyme inhibitor and angiotensin IIreceptor blocker, were used in a fraction of patients, which may influence the serum vaspinand the incidence of MACE. However, the classical risk factors were adjusted and results still showed that vaspin was an independent predictor of future MACE.

In conclusion, our results demonstrate that low baseline serum vaspin is independently associated with an increased risk for MACE (as individual endpoints) within 2-year followup period inCAD patientsand non-CAD subjects.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (No. 30900520; 81070107), and Shanghai Rising-Star Program (No. 10QA1405500).

Disclosure of conflict of interest

None.

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