Decreased levels of soluble receptor for advanced glycation end-products in aortic valve calcification patients

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ABSTRACT. The soluble receptor for advanced glycation end-products (sRAGE) shows a close relationship with atherosclerosis. The goal of this study was to compare the levels of sRAGE in patients with and without aortic valve calcification and to investigate the relationship between them. After transthoracic echocardiographic examination, 120 male patients with aortic valve calcification and 120 age-matched male controls without aortic valve calcification were included in our study. sRAGE levels were compared between groups. The prevalence of diabetes mellitus and coronary artery disease were significantly higher in the aortic valve calcification group than in the control group (63.3 versus 45%, $P = 0.01$, and 65 versus 51.7%, $P < 0.01$, respectively). The levels of sRAGE were lower in the aortic valve calcification group than in the control group (203.8 ± 34.6 versus 324.7 ± 41.6 pg/mL,

P < 0.01). In multivariate analysis, age, coronary artery disease, and sRAGE levels were independent predictors of aortic valve calcification. Our study demonstrates that sRAGE, which was proven to be a potential marker of atherosclerosis, might have a role in the development of aortic valve calcification.

Key words: Aortic valve calcification; Atherosclerosis; Soluble receptor for advanced glycation end-products

INTRODUCTION

Aortic valve (AV) calcification (AVC) is a common clinical concern; it carries high morbidity and mortality, is present in nearly 30% of adults over 65 years, and is increasing rapidly due to the aging of the population (Bonow et al., 2008). AVC has traditionally been considered as a degenerative disorder, involving passive deposition of calcium on AV leaflets. Recently, studies have demonstrated that AVC instead has many features characteristic of an active pathobiological process akin to atherosclerosis, including chronic inflammation, endothelial dysfunction, lipoprotein deposition, and extracellular matrix remodeling (Latsios et al., 2012). Despite these considerable advances, there is no evidence to suggest that a pharmacologic therapy could impede the development of the disease, and treatment strategies for symptomatic AVC only include careful monitoring and judicious timing of AV replacement, even though not every candidate is fit for surgery. An attractive prospect in management of these patients is the use of robust biomarkers that could potentially assess the severity, prognosis, and response to therapy of the disease (Vahanian et al., 2007).

The interaction between the receptor for advanced glycation end-products (RAGE) and its ligands is intimately involved in the pathobiology of atherosclerosis. The associations among RAGE, inflammation, and arterial calcification have been well documented (Lin et al., 2009; Cecil and Terkeltaub, 2011). Soluble RAGE (sRAGE), which is comprised of a spliced variant of RAGE and a shed form derived from the cell-surface RAGE, circulates in human plasma. sRAGE only retains the extracellular domains of RAGE but is still able to bind ligands and antagonize RAGE signaling (Vazzana et al., 2009). High plasma levels of sRAGE have been reported to be associated with a lower incidence of coronary artery disease (CAD) in non-diabetic men (Falcone et al., 2005). Recently, it has been found that the levels of sRAGE were significantly lower in AV stenosis patients scheduled for surgical AV replacement than in the controls without AV stenosis; in multivariable logistic regression analysis after adjustment for potential confounders, the sRAGE levels were significantly and independently associated with the risk of AV stenosis (Basta et al., 2010). Having been scheduled for surgical AV replacement means those patients who had obtained the highest level of AV stenosis severity and calcification, so these results might not transpose to mild AVC patients. However, there are few data available investigating the relationship between plasma sRAGE levels and common AVC. As previous studies have pointed out that the male gender is one of the risk factors for calcific AV stenosis (Latsios et al., 2012), we designed this cross-sectional study to compare the levels of sRAGE in male patients with AVC with age-matched male controls without AVC.

MATERIAL AND METHODS

Subjects

Participants were recruited from patients admitted to the geriatric department of our hospital. Consecutive male patients (N = 120) in whom a diagnosis of AVC was made by transthoracic echocardiography (AVC group) and 120 consecutive age-matched male patients without AVC (control group) were included in our study. Participants were excluded if they had any of the following: Marfan syndrome, congenital heart disease or congenital valvular disease (e.g., bicuspid aortic valve), serum creatinine values of 1.5 mg/dL or greater, rheumatic heart disease, heart failure, prior aortic valve surgery, endocarditis, active malignancy, chronic liver failure, coagulation diseases, calcium regulation disorders, or chronic or acute inflammatory states (sepsis, autoimmune diseases, and inflammatory bowel diseases). The study was approved by the local Ethics Committee and written informed consent was obtained from all patients.

Clinical data

All patients' demographic parameters were recorded, including: systemic hypertension (blood pressure ≥140/90 mmHg or ongoing antihypertensive medication); CAD (>50% luminal diameter narrowing of ≥1 coronary artery by angiography) (Scanlon et al., 1999); history of coronary revascularization; abnormal myocardial perfusion scan or dobutamine stress echocardiogram; regional left ventricular akinesia and/or dyskinesia on echocardiogram or pathologic Q-waves on 12-lead electrocardiogram; diabetes mellitus (fasting serum glucose level >126 mg/dL or ongoing diabetes medication) (Alberti and Zimmet, 1998); hypercholesterolemia (fasting serum total cholesterol level >200 mg/dL or ongoing lipid-lowering therapy) (Bhatnagar et al., 2008); stroke history (symptoms or signs of stroke, and the corresponding injured location was confirmed by magnetic resonance imaging or computerized tomography of the brain) (Donnan et al., 2008); or past or present tobacco use.

Echocardiographic examination

Complete two-dimensional transthoracic and Doppler color flow measurements were performed in all participants using a Vivid 7 System GE with a 4-MHz transducer (GE Healthcare, Little Chalfont, UK). The echocardiographic diagnosis of AVC was made by two-dimensional and M-mode transthoracic echocardiography, following the American Society of Echocardiography criteria (American College of Cardiology Foundation Appropriate Use Criteria Task Force et al., 2012). Left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), left atrial volume index (LAVI), peak early (E) and late diastolic (A) transmitral filling flow velocities, E/A ratio, and deceleration time (DT) of the E wave were measured. AVC was defined as bright dense echoes of ≥1 mm in size on one or more cusps without restricted motion, the area of AV ≥3 cm^2, and the transaortic velocity <2.5 m/s (Boon et al., 1997). When limitation of AV opening was diagnosed, Doppler evaluation was mandatory to quantitate the stenosis. The gradient of pressure between the left ventricle and the aorta was measured, using the Bernouilli law, by measuring the maximum velocity across the AV with continuous Doppler. AV stenosis was qualitatively classified into three categories, according to jet velocity,

mean gradient, the area of AV, indexed AV area, and velocity ratio: mild (jet velocity 2.6-2.9 m/s, mean gradient <30 mmHg, AV area >1.5 cm², indexed AV area >0.85 cm²/m², and velocity ratio >0.5); moderate (jet velocity 3-4 m/s, mean gradient 20-40 mmHg, AV area 1-1.5 cm², indexed AV area 0.6-0.85 cm²/m², and velocity ratio 0.25-0.5); and severe (jet velocity >4 m/s, mean gradient >40 mmHg, AV area <1 cm², indexed AV area <0.6 cm²/m², and velocity ratio <0.25) (Baumgartner et al., 2009). Two experienced echocardiologists who were unaware of the patients' clinical data performed all echocardiographic evaluations. A patient was chosen for the study only when the two echocardiologists were in agreement about the absence or presence of AVC. Subjects were excluded if there was disagreement between the two echocardiologists.

Laboratory measurements

A 3-mL peripheral venous blood sample was obtained from all participants after echocardiography for the measurement of sRAGE. Blood samples were drawn in tubes containing heparin and were immediately centrifuged. Creatinine, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) were determined by standard laboratory methods. The estimated glomerular filtration rate was calculated. Plasma sRAGE levels were determined using a double-sandwich enzyme-linked immunosorbent assay kit (96T/Kit, Yifeng Ltd., Shanghai, China) according to manufacturer instructions. Intra-assay and inter-assay coefficients of variation values were 4 and 10%, respectively. The lower limit of detection of sRAGE was 25 pg/mL.

Statistical analysis

Statistical analyses were performed with the use of the SPSS software, version 15.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are reported as means ± standard deviation (SD) and categorical variables are reported as percentages. Differences between study groups were assessed with the use of two-sided Fisher exact tests and chi-square tests for categorical variables and Student t-tests for continuous variables. The parameters in three AV stenosis subgroups were compared by one-way analysis of variance. Multivariate binary logistic regression analysis was performed to determine which clinical variables would independently predict the development of AVC. AVC was entered into the model as a dependent variable. Results are reported as odds ratios (ORs) and 95% confidence intervals (95%CIs). Multiple linear regression analysis was used to examine the effect of clinical variables on sRAGE levels. sRAGE level was entered into the model as a dependent variable. Results are reported as β coefficients and 95%CI. All P values were two-tailed, and values <0.05 were considered to be statistically significant.

RESULTS

The clinical data of 120 male patients with AVC and 120 age-matched male patients without AVC are summarized in Table 1. There were no statistically significant differences between AVC and control groups in the prevalence of hypertension, hypercholesterolemia, or cigarette smoking (P > 0.05). In regard to echocardiographic parameters, there were no significant differences in LVEF, LVMI, LAVI, E/A, or DT between the two groups. In the AVC group, there were 43 patients with AV stenosis (29 mild, 11 moderate, and 3 severe). CAD,

diabetes mellitus, and previous stroke history were more frequent in the AVC group than in the control group (P < 0.05). The plasma sRAGE level in the AVC group was significantly lower than that of the control group (P < 0.01).

Table 1. Clinical characteristics, echocardiographic parameters, and lab measurements of study participants.

Variable	AVC group	Control group	P value
Age (years)	64.8 ± 5.2	65.1 ± 4.6	0.23
Hypertension [N (%)]	64 (53.3%)	68 (56.7%)	0.45
Coronary artery disease [N (%)]	78 (65%)	62 (51.7%)	<0.01
Diabetes mellitus [N (%)]	76 (63.3%)	54 (45%)	0.01
Hypercholesterolemia [N (%)]	49 (40.8%)	46 (38.3%)	0.57
Stroke history [N (%)]	42 (35%)	34 (28.3%)	0.03
BMI (kg/m^2)	24.7 ± 3.1	25.0 ± 3.2	0.34
Cigarette smoking [N (%)]	49 (40.8%)	51 (42.5%)	0.28
Antihypertension treatment [N (%)]	61(50.8%)	65 (54.2%)	0.37
Antidiabetics [N (%)]	73 (63.3%)	52 (43.3%)	0.02
Lipid-lowering treatment [N (%)]	38 (31.7%)	35 (29.2%)	0.58
Antithrombotic treatment [N (%)]	93 (77.5%)	84 (70.0%)	0.09
LVEF (%)	58.4 ± 7.1	60.3 ± 8.5	0.27
LVMI (g/m^2)	103.6 ± 12.9	105.2 ± 11.7	0.16
LAVI (mL/m^2)	26.8 ± 4.0	27.1 ± 3.6	0.61
E/A	0.89 ± 0.17	0.93 ± 0.22	0.14
DT (ms)	226.3 ± 19.2	217.4 ± 20.4	0.08
eGFR [mL·min^{-1}·(1.73 m^2)$^{-1}$]	75.3 ± 12.1	77.8 ± 10.6	0.42
Total cholesterol (mg/dL)	201.3 ± 33.7	194.8 ± 36.9	0.15
LDL cholesterol (mg/dL)	126.4 ± 27.6	121.0 ± 30.3	0.62
sRAGE (pg/mL)	203.8 ± 34.6	324.7 ± 41.6	<0.01

AVC = aortic valve (AV) calcification; BMI = body mass index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LAVI = left atrial volume index; E/A = peak early and late diastolic transmitral filling flow velocities ratio; DT = deceleration time of the E wave; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; sRAGE = soluble receptor for advanced glycation end-products. The error ranges are reported as standard deviation.

Multivariate logistic regression analysis identified age (OR = 1.17, P = 0.02), CAD (OR = 0.49, P = 0.02), and sRAGE (OR = 0.53, P = 0.04) as independent variables significantly associated with AVC (Table 2). The adjusted R^2 value was 0.39 for this model.

Table 2. Logistic regression analysis for AVC.

Variable	Odds ratio	95%CI	P value
Age	1.17	1.09-1.26	0.02
Hypertension	0.74	0.42-1.33	0.18
Coronary artery disease	0.49	0.27-0.88	0.02
Diabetes mellitus	0.86	0.41-1.57	0.34
Hypercholesterolemia	0.61	0.36-1.14	0.58
BMI	0.82	0.67-1.03	0.09
Cigarette smoking	1.04	0.59-2.27	0.67
eGFR	0.85	0.34-3.68	0.13
sRAGE	0.53	0.28-0.94	0.04

AVC = aortic valve calcification; CI = confidence interval; BMI = body mass index; eGFR = estimated glomerular filtration rate; sRAGE = soluble receptor for advanced glycation end-products.

Significant differences in plasma sRAGE concentrations were found between patients with AVC and those without AVC. Patients with CAD had lower sRAGE levels than those with CAD in the control group. There were also statistically significant differences in sRAGE levels in both the CAD and diabetes mellitus subgroups (Table 3).

Table 3. sRAGE levels in the AVC and Control groups.					
	AVC (+)		AVC (-)		
	N	sRAGE (pg/mL)	N	sRAGE (pg/mL)	P value
All patients	120	203.8 ± 34.6	120	324.7 ± 41.6	<0.01
Coronary artery disease (+)	78	182.4 ± 40.1	62	297.3 ± 34.0	<0.01
Coronary artery disease (-)	42	229.5 ± 32.6	58	351.4 ± 37.8	<0.01
Diabetes mellitus (+)	73	177.5 ± 30.9	54	261.7 ± 32.1	<0.01
Diabetes mellitus (-)	47	246.3 ± 28.2	66	347.8 ± 39.2	<0.01

sRAGE = soluble receptor for advanced glycation end-products; AVC (+) = patients with aortic valve calcification; AVC (-) = patients without aortic valve calcification; Coronary artery disease (+) = patients with coronary artery disease; Coronary artery disease (-) = patients without coronary artery disease; Diabetes mellitus (+) = patients with diabetes mellitus; Diabetes mellitus (-) = patients without diabetes mellitus. The error ranges are reported as standard deviation.

In the patients with AV stenosis, plasma sRAGE levels in the severe stenosis subgroup were lower than in the moderate or mild stenosis subgroups ($156.3 ± 21.5$, $187.1 ± 29.8$, $209.2 ± 24.0$ pg/mL, respectively, $P < 0.05$), but there was no significant difference between the mild and moderate AV stenosis subgroups ($P > 0.05$).

In multiple linear regression analysis, CAD ($\beta = -0.21$, $P < 0.01$) and hypercholesterolemia ($\beta = -0.17$, $P < 0.01$) were independently associated with the levels of sRAGE (Table 4). The adjusted R^2 value was 0.27 for this model.

Table 4. Multiple linear regression analysis with sRAGE level as the dependent variable.			
Variable	β	95%CI	P value
Age	-0.24	-0.830.39	0.08
Hypertension	0.19	-0.2-1.7	0.21
Coronary artery disease	-0.21	-0.05-0.06	<0.01
Diabetes mellitus	-0.18	-0.43-0.25	0.27
Hypercholesterolemia	-0.17	-0.38-0.02	<0.01
BMI	0.05	-0.01-0.24	0.46
Cigarette smoking	-0.02	-0.06-0.11	0.37
eGFR	0.26	0.11-0.45	0.53

sRAGE = soluble receptor for advanced glycation end-products; BMI = body mass index; eGFR = estimated glomerular filtration rate; CI = confidence interval.

DISCUSSION

In this study, we demonstrated that patients with AVC had lower levels of sRAGE than control subjects, and the value in the severe AV stenosis subgroup was even lower than that of the moderate or mild AV stenosis subgroups. Furthermore, in multivariate analysis, age, CAD, and sRAGE levels were independent predictors of AVC.

AVC is a chronic process that ranges from early alterations in leaflet cell biology to calcific lesions on the aortic surface of the valve cusp, resulting in impaired movement of the AV leaflets followed by left ventricular outflow obstruction. With regard to pathophysiology, it has been proven that early lesions of AVC implicate active processes similar to atherosclerosis, such as lipid deposition, macrophage infiltration, and production of osteopontin as well as other proteins (Rajamannan, 2010). Further changes associated with extracellular matrix remodeling and neovascularization ultimately lead to active calcification (Prasad and Bhalodkar, 2004;

Helske et al., 2007). Experimental animal models of AVC (Rajamannan et al., 2005; Drolet et al., 2006) demonstrated that early lesions contained inflammatory cells. These studies not only indicated that the underlying mechanisms of AVC were similar to those of atherosclerotic arterial calcification, but also established the concept of inflammation-dependent development of AVC. In our study, CAD was more prevalent in the AVC group, and CAD was an independent predictor of AVC in multivariate analysis, which supports the theory mentioned above.

As there are some striking similarities between AVC and atherosclerosis, many studies have been designed to explore whether arteriosclerotic or inflammatory biomarkers could play an analogous role in AVC, such as high-sensitive C-reactive protein, B-type natriuretic peptide, and homocysteine. Meanwhile, sRAGE, as a new biomarker in diagnosis and prognosis of chronic inflammatory diseases including atherosclerosis, has emerged (Maillard-Lefebvre et al., 2009). sRAGE corresponds to the extracellular domain of RAGE, and may act as a 'decoy' by binding pro-inflammatory ligands and preventing them from reaching membrane RAGE (Maillard-Lefebvre et al., 2009). The first study to report sRAGE levels in humans focused on the involvement of sRAGE levels in non-diabetic atherosclerosis (Falcone et al., 2005). In a multiple logistic regression analysis, low plasma sRAGE concentration was found to be a risk factor for CAD, independent of hypertension, smoking, and high-density lipoprotein cholesterol levels. In the recent Dallas Heart Study (Lindsey et al., 2009), which included 2571 subjects, lower levels of sRAGE were independently associated with a greater prevalence of coronary artery calcium. In the present study, we found that sRAGE levels were significantly lower in the AVC group than in the control group. Although we also found a difference among the three AV stenosis subgroups, this result was less statistically powerful because of the small size of each subgroup. To our knowledge, this is the first study to report a relationship between sRAGE levels and AVC, which included and was not restricted to AV stenosis. However, our study was a clinical observation and we did not investigate the mechanism by which sRAGE levels decreased in AVC patients. Li et al. (2012) reported that increasing the expression of RAGE induced high levels of pro-inflammatory cytokines and promoted osteoblastic differentiation of cultured porcine AV interstitial cells. Earlier experiments found that RAGE interaction with its ligands was followed by activation of a range of signaling pathways, including nicotinamide adenine dinucleotide phosphate oxidase and reactive oxygen species (Wautier et al., 2001). Although a series of studies has been published assessing the role of RAGE in different animal models of atherosclerosis, the biological importance of the ligand-RAGE axis is not clearly understood in humans.

We did not find a significant relationship between AVC and other traditional risk factors for cardiovascular diseases. Previous studies showed inconsistent results. The Cardio-vascular Health Study (Stewart et al., 1997) concluded that age, gender, height, hypertension, smoking, lipoprotein (a), and LDL-C were independent predictors of degenerative AV disease. Allison et al. (2006) found that age and a history of hypertension were independently associated with AVC, but diabetes mellitus and hyperlipidemia were not. Recently, it was revealed that there are ethnic differences in the degree of AV thickness (Sashida et al., 2010). In our opinion, the differences observed within our study might be explained in part by the patient population and/or statistical power.

There were several limitations to our study, one of which was the cross-sectional design. Although cross-sectional studies can measure association, they are not strong enough to prove causality. It would have been ideal to have obtained serial echocardiograms and sRAGE levels in our study to demonstrate causality. Secondly, our sample size was relatively small

and we included only male subjects. In addition, we defined AVC using echocardiography measurements, which is traditional but might be less precise in the stratification of severity than the newly developed tool, cardiac computed tomography (Mak and Truong, 2012).

Our study demonstrates that sRAGE, which was proven to be a potential marker of atherosclerosis, decreased in patients with AVC. Furthermore, in multivariate analysis, age, CAD, and sRAGE levels were independent predictors of AVC. It would be necessary to carry out long-term prospective and larger studies to confirm whether low sRAGE levels are a contributing factor to the development of AVC.

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