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Association of serum soluble receptor for advanced glycation end products (sRAGE), S100A12, and VCAM-1 levels with further post-coronary angiogram endothelial injury in patients with Coronary Artery Disease (CAD) and stenosed coronary vessels

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Abstract:

Objective: *More than a million Cardiac Angiographies (CAG) are performed annually in China to assess coronary occlusion. CAG as*

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an invasive procedure may result in endothelial injury and potentially cause further pathogenesis in patient with existing atherosclerotic diseases. In this study, we examine the associations of the expression level of sRAGE, VCAM-1, and S100A12 pre- and post-coronary angiography with possibility of endothelial injury in different groups of patients with varying degree of arterial occlusion; hence, providing a more comprehensive link on CAG effects on patients with atherosclerosis.

Methods and results: *All patients selected were divided into three main groups based on their angiograph results: patient with at least one coronary artery with (Group 1) more than 50% occlusion, (Group 2) less than 50% occlusion, and (Group 3) patients with no coronary artery occlusion. Soluble RAGE (sRAGE), VCAM-1 and S100A12 levels in blood samples collected after CAG session were measured to assess the inflammatory responses and possibility of endothelial injury induced by CAG. Significant increase in expression level of serum sRAGE (P=0.018) and VCAM-1 (P=0.018) were observed while, expression level of serum S100A12 remained unchanged. Increase expression of sRAGE and VCAM-1 were highest in group 1, follow by group 2 then group 3.*

Conclusions: *Increased expression level of sRAGE and VCAM-1 post-CAG in patients with CAD and stenosed coronary vessels can be associated with further endothelial injury and therefore contribute to pathogenesis of present atherosclerotic disease.*

Key words: serum soluble receptor for advanced glycation end products (sRAGE); S100A12, VCAM-1 levels; post-coronary angiogram endothelial injury; patients with Coronary Artery Disease (CAD) and stenosed coronary vessels

INTRODUCTION

Diagnostic Cardiac Catheterizations or Coronary Angiographies (CAG) are performed frequently in China in order to detect severity of Coronary Artery Diseases (CAD). Despite that CAG

is a standard medical operation, it is an invasive procedure; Soft plastic catheters or contrast dye used in CAG may interfere nomal endothelial function or injure other coronary blood vessels or cause further formation of atherosclerotic plaque. Endothelial injury induces inflammatory responses, that results in the rise of inflammatory markers such as: sRAGE, S100A12, and VCAM-1.

The first biomarker, RAGE (Receptor for Advanced Glycation End Products) is a member of the immunoglobulin superfamily and is expressed on the surface of endothelial cells, mononuclear phagocytes, lymphocytes and smooth muscle cells[1,2]. There are three forms of RAGEs [2,3,4,5]– full-length, N-truncated and C-truncated soluble RAGEs (sRAGE). The interaction of full-length RAGE with AGEs leads to increased expression of adhesion molecules, including soluble vascular cell adhesion molecule-1 (sVCAM-1) and the cytokine tumor necrosis factor-alpha (TNF-α) [2, 6, 7]; activation of nuclear factor-kappa B [6], which in turn leads to increased expression of proinflammatory genes for adhesion molecules and cytokines [2]; and generation of oxygen radicals [8,9]. Circulating isoforms of RAGE include soluble RAGE (sRAGE) that has been cleaved from cell surface by matrix metalloproteinases and endogenous secretory RAGE (esRAGE) [2,4]. The second biomarker, S100A12 is an inflammatory ligand of RAGE and is a member of the S100 protein family. It regulates inflammation and immune response [10]. Its ligation with RAGE on the endothelium, mononuclear phagocytes and lymphocytes triggers cellular activation with the generation of key pro-inflammatory mediators such as: interleukin (IL)-1 and tumour necrosis factor (TNF). The last biomarker, VCAM-1 can promote the adhesion of leukocytes to endothelial cells and accelerate the migration of the leukocytes along the endothelial surface [11]. It is of great importance to investigate the

expression levels of VCAM-1 in arterial tissues, and to elucidate the association between arterial VCAM-1 expression and unstable endothelial haemostasis leading to the pathogenesis of atherosclerosis.

It is important to monitor these inflamatory markers as these markers signify how CAG procedure could potentially aggravate pathogenesis of atherosclerosis. Hence, this study tries to affirm the aforementioned risk through monitoring three biomarkers (sRAGE, S100A12, and VCAM-1) and comparing each serum levels before and after CAG. The subsequent clinical association between expression levels of the mentioned biomarker serums with possibility of resultant endothelial injury in the different groups of patients may establish better basis for further medical assessment.

RESEARCH METHODOLOGY

Sample Size

The study included seventy-nine consecutive patients who underwent elective coronary angiography [53 males and 26 females, aged 46-81years (62.7, 8.4 years)]. The study classified the sample size into three main groups; Group 1 consisted of 30 CAG patients who had CAD with at least one stenosed coronary artery with more than 50% occlusion, Group 2 comprised 28 CAG patients with at least one stenosed coronary artery with less than 50% occlusion, Group 3 consisted of 21 CAG patients with no occluded coronary artery.

The population sampled in this study are CAG patients of Jiangsu Province Hospital (Jiangsu, China) and the data was collected between July 2015 to January 2016. Indications for elective angiography included patients with both stable and unstable angina, patients with present CAD, patients with nonspecific chest pain, preoperative evaluation of patients with

valvular heart disease. Inclusion criteria for the study population was based on"ACC/AHA Guidelines for Coronary Angiography" Subsequently, patients with several conditions are excluded from the sampling. The conditions were as follow: any type of malignancies, liver and/or kidney dysfunction, thyroid disease, acute coronary syndrome, acute or chronic inflammatory disease, autoimmune, cardiomyopathy, acute cerebrovascular and peripheral vascular diseases, peripheral artery disease. Following the admission in this study, detailed medical record for each patient (that includes family history, past, and present illnesses) was compiled and routine physical examinations and laboratory tests were carried out in order to establish clinical diagnosis. Prior written and informed consent was obtained from all patients and the study was approved by the Ethics Review Board of the Jiangsu Province Hospital.

All patients were subjected through Cardiac Ultrasound Measurements. Both systolic and diastolic blood pressure of each patient was measured with a mercury sphygmomanometer after a minimum of 10-min rest in the sitting position. Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.The study also took note of cardiovascular risk factors such as smoking habits, hypertension and diabetes mellitus. Out of the 79 patients selected, 36 patients were smokers, 40 had hypertension and 15 had diabetes mellitus.

Coronary Angiography

Coronary angiography (CAG) was performed through radial approach using standard angiographic technique. Prior to the angiography, all patients were given Heparin 2000 IU IVP. Angiogram collected was performed from 4 standard projections for each right and left coronary artery. The degree of stenosis determined in projection that showed the most severe

narrowing. All cineangiograms were peer reviewed by three experienced interventional cardiologists, whom all are made unknown to the research methodology.

Blood sample collection

There were three blood sample collections: in the morning prior to the operation, before and after the angiography session. The first blood collection extracted 7ml of venous blood in the morning before the operation and after a 12-hour overnight fast and is mainly for baseline blood profile analysis. These samples were drawn from the antecubital vein. Samples were drawn and tested in accordance with standard hospital procedure in Jiangsu Province Hospital.

The second and third blood collection were blood extraction before and after angiography session, collected through a guiding sheath, and were mainly for measuring serum level of sRAGE, VCAM-1, and S100A12. Blood samples of each patient were centrifuged at 3000 rpm for 10 min at $4^{o}C$ and stored at – $59^{o}C$ in order to separate serums from cells. Levels of serum sRAGE, VCAM-1, and S100A12 were determined by an enzyme-linked immunosorbent assay kit method. (Nanjing SenBeiJia Biological Technology Co., Ltd.)

Statistical analysis

All data is presented as mean ± standard deviation and was analyzed with SPSS 13.0 (SPSS, Inc., Chicago, IL, USA) with T-Test and under normal distribution. Comparison of baseline characteristics between groups is done through one way ANOVAs. Both tests use two-tailed $P<0.05$ as a significant indicator of a statistical difference.

RESULTS

Measurement of baseline characteristics in all patients.

There were no significant differences in age, gender, BMI, blood pressure, Ejection Fraction, and used medication among the 3 groups of patients. Nevertheless, it is observed that there is a significant difference in the number of aspirin (p=0.001) and statin (p=0.003) users among the 3 groups. Group 1 has the highest number of aspirin and statin users, followed by group 2 and 3 respectively (refer to Table 1). These results also denote that major cardiovascular risk factors, such as smoking (P=0.182), hypertension (P=0.178) and diabetes mellitus (P=0.141), are not associated with the expression levels of sRAGE, VCAM-1, and S100A121 in all 3 groups patients before and after CAG.

Table 1 - Baseline characteristics in the three different groups of the patients

	group 1 (*n*=30)	group 2 (*n*=28)	group 3 (*n*=21)	*P* value
Age (years)	65 ± 9.2	63.3 ± 6.9	58.5 ± 7.6	0.478
Male/female	23/7	20/8	10/11	0.078
BMI (kg/m2)	25 ± 2.2	25.2 ± 3.6	24.2 ± 2.8	0.471
Hypertension (%)	19 (63.3)	13 (46.4)	8 (38.0)	0.178
Diabetes mellistus (%)	9 (30)	3 (10.7)	3 (14.2)	0.141
Smoking (%)	15 (50)	15 (53.5)	6 (28.5)	0.182
EF (%)	62.9 ± 4.2	59.6 ± 10.8	56.9 ± 9.2	0.163
Aspirin use (%)	**25 (83.3)**	**12 (42.8)**	**8 (38.0)**	**0.001**
Beta-blockers' use (%)	14 (46.6)	12 (42.8)	4 (19.0)	0.109
ACEI use (%)	4 (13.3)	7 (25)	2 (9.5)	0.296
CCB use (%)	11 (36.6)	10 (35.7)	4 (19.0)	0.349
Statins use (%)	**25 (83.3)**	**13 (46.4)**	**2 (9.5)**	**0.003**
Nitrate use (%)	21 (70)	15 (53.7)	9 (42.8)	0.141
SBP (mmHg)	131.0 ± 18.2	128.2 ±16.9	11.7 ± 18.2	0.572
DBP (mmHg)	78.6 ± 10.1	73.3 ± 13.7	67.2 ± 10.1	0.103

Measurement of blood profile levels in all patients.

Preoperative blood profiles of all sample population are presented in Table2. Among the three groups, it is observed

that there is no significant difference in all serum levels: TC (P=0.869), HDL-C (P=0.358), LDL-C (P=0.108), TG (P= 0.391), Hb (P=0.988), FPG (P=0.608), and UA (P= 0.839). Blood coagulation profiles (platelet (P=0.084), D-D (P=0.083) and Fib (P=0.163) among the three groups do not have significant difference either.

Table 2 - Blood profile and lipid levels in patients

	group 1 (*n*=23)	group 2 (*n*=11)	group 3 (*n*=8)	*P* value
Hb (g/l)	138.3 ± 13.0	136.6 ± 18.0	138.0 ± 78.4	0.988
Platelet (10^9/L)	194.7 ± 68.8	227.1 ± 81.0	163.7 ± 85.6	0.084
D-D (μg/mL)	0.66± 0.69	0.37 ± 0.31	0.96 ± 1.69	0.083
Fib (mmol/l)	2.65± 1.57	2.9 ± 1.35	2.5 ± 0.62	0.163
TC (mmol/l)	4.5 ± 0.82	4.5 ± 0.90	3.6 ± 0.79	0.869
HDL- C (mmol/l)	1.4 ± 1.80	1.1 ± 0.26	1.0 ± 0.26	0.358
LDL- C (mmol/l)	2.9 ± 0.63	2.6 ± 0.83	2.3 ± 0.63	0.108
TG (mmol/l)	1.9 ± 0.74	1.9 ± 1.89	1.5 ± 0.78	0.391
FPG (mmol/l)	5.7 ±1.47	5.5 ± 1.61	5.3 ± 1.48	0.608
UA (mmol/l)	346.4 ± 84.7	361.8 ± 120.9	345.4 ±106.9	0.839

Results are presented as the mean ± standard deviation. Hb, hemoglobin; D-D, D-dimer; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; FGP, fasting plasma glucose; UA, uric acid.

Expression levels of sRAGE, VCAM-1, and S100A12 in arterial blood before and after coronary angiography.

To investigate the expression levels of sRAGE, VCAM-1, and S100A12 in arterial blood before and after coronary angiography, immunohistochemistry was performed.

As shown in Table 3, before coronary angiography, the average expression level of sRAGE was 87.7 ± 65.1 ng/L, the average expression level of VCAM-1 is 83.1 ± 66.5 μg/L, and the average expression level of S100A12 is 6.5 ± 6.2 μg/L. After coronary angiography, the average expression level of SRAGE is 94.7 ± 60.5 ng/L, the average expression level of VCAM-1 is 91.4 ± 75.3 μg/L, and the average expression level of S100A12 is 6.5 ± 6 μg/L. Significant increase in expression level of serum VCAM-1 (p=0.01829) and sRAGE (p=0.01830) in post CAG

arterial blood is observed. This contrasts with the expression level of serum S100A12 (p=0.45898) in post CAG arterial blood which remains relatively constant.

Table 3 Expression level of S100A12, VCAM-1, sRAGE in the arterial blood before and after CAG.

Serum Protein	Average level before CAG	Average level after CAG	P value
S100A12 ((µg/L)	6.5 ± 6.2	6.5 ± 6	0.45898
VCAM-1 (µg/L)	83.1 ± 66.5	91.4 ± 75.3	**0.01829**
sRAGE (ng/L)	87.7 ± 65.1	94.7 ± 60.5	**0.01830**

Results are presented as the mean ± standard deviation. VCAM-1, vascular cell adhesion molecule-1; sRAGE, soluble receptor of advanced glycation end products.

Student t-test was performed for each group of patients in order to further ascertain the association between the expression level of serums VCAM-1 and sRAGE in arterial blood, and endothelial function in patient referred to coronary angiography. As shown in table 4, there were significant increase in the expression level of serum sRAGE in post CAG arterial blood of group 1(P=0.031) and group 2 (P=0.030**)**. Inversely, expression level of serum sRAGE in post CAG arterial blood of group 3 was slightly lower.

Table 4 - Expression level of sRAGE in the arterial blood before and after CAG in 3 different groups.

GROUP	Average level before CAG	Average level after CAG	P value
Group 1 (CAD patient)	**104.6 ± 61.1**	**113.1 ± 58.5**	**0.03143**
Group 2 (Stenosis patient)	**76.6 ± 56.1**	**87.8 ± 50.0**	**0.03030**
Group 3 (Normal patient)	79.5 ± 78.5	77.8 ± 71.3	0.40185

It was observed that all groups had higher expression level of serum VCAM-1in the post CAG arterial blood. Expression level of serum VCAM-1 in post CAG arterial blood of group 1 was

significantly elevated (p=0.014). Whereas, in group 2 and group 3, expression level of VCAM-1 were higher, but not significant. These results suggested that the expression levels of sRAGE and VCAM-1 in the arterial blood were significantly elevated in patients with atherosclerotic plaque disease compared with those with normal heart condition.

Table 5 - Expression level of VCAM-1 in the arterial blood before and after CAG in 3 different groups.

GROUP	Average level before CAG	Average level after CAG	P value
Group 1 (CAD patient)	**86.3 ± 77.3**	**96.4 ± 78.0**	**0.01447**
Group 2 (Stenosis patient)	84.1 ± 58.6	91.1 ± 65.2	0.20202
Group 3 (Normal patient)	77.2 ± 62.5	84.5 ± 86.2	0.17536

DISCUSSION

In the present study, a significant and independent association of increased expression levels of sRAGE. The expression level of sRAGE were siginificantly higher after CAG in the patient group 1 and group 2. In contrast, expression level of sRAGE in group 3 were lower after CAG, but not significant. This phenomenon may be due to patients with CAD and stenosed coronary vessels may still progressing chronic ischemia. During ischemic condition it will further induce pro-inflammatory response, correlated with production of inflammatory biomarkers. In return, up regulation several inflammatory receptors including RAGE. There are past studies that revealed sRAGE may reflect enhanced activity in the RAGE system since the effects of ligand stimulation mediate sRAGE upregulation [11] and sRAGE is secreted in parallel with RAGE [12, 13].Soluble RAGE (sRAGE) is an isoform of RAGE, which lacks the intracellular domain and thus intracellular signaling

[14]. Instead, sRAGE circulates in the blood and is believed to reflect RAGE and inflammatory activity [15].

Soluble RAGE (sRAGE) is produced in two different pathways, either endogenous secreted as a splice variant, esRAGE [13] or as a cleaved variant. [12, 16, 17]. There is minimal expression of RAGE under normal conditions but it increases significantly during cellular stress [4, 12]. As mentioned before that sRAGE reflect RAGE activity. We found that significant increase of sRAGE after CAG in group 1 and 2 showed higher RAGE activity. Thus, reflecting higher inflammatory activity which is associated with the procedure of CAG itself.

Steiner et al mentioned that, VCAM-1 is one of the markers of vascular endothelial injury and its levels are increased by reflecting VCAM-1 expression in endothelial cells [18]. Some recent studies also have shown that significant elevation in expression level of VCAM-1 can be stimulated by the inflammatory cytokines [19,20]. Since VCAM-1 and RAGE belong to the same immunoglobulin superfamily [5]. Endothelial injury due to CAG procedure can stimulate inflammatory reaction. Combination of inflammatory reaction and AGEs–RAGE interaction stimulates VCAM-1 expression in endothelial cells [21, 22].

Increased expression of the VCAM-1 in the vascular endothelial cells after CAG propagates adhesion and aggregation of leukocytes to vascular wall [23]. VCAM-1 stimulates the migration of adherent leukocytes along the vascular endothelial surface, and stimulate the proliferation of smooth muscle cells; therefore, it is suspected that VCAM-1 may be involved in the further pathogenesis of atherosclerosis due to endothelial injury [21, 24]. Saidi et al [25] mentioned that, in patients with atherosclerosis, damages of endothelial cells have association with elevation of VCAM-1 level. Our

finding corresponds with Saidi et al; The general increase in the expression levels of VCAM-1 (refer to table 5) is associated to the invasive nature of CAG procedure; and the significant increase in expression levels of VCAM-1 in group 1 also indicates that the more severe the artherosclerosis is, the higher the elevation in expression levels of VCAM-1 is. Hence, CAG may instigate further phatogenosis of artherosclerosis in patients with more severe atherosclerotic plague.

The observed increase in sRAGE and VCAM-1 is postulated to be independent of any baseline characteristics, blood coagulation profile, lipid pofiles, and even cardiovascular risk factors as there are no significant difference observed between the three groups except for statin and aspirin use (refer to table 1). The difference in aspirin and statin uses is mainly caused by common medication in treating CAD. Therefore, the significant increase in sRAGE and VCAM-1 in post CAG purely due to CAG itself. Moreover, some studies imply that sRAGE have high affinity for heparin binding [26, 27]. Since all patients are administered with heparin as part of CAG procedure, there is a possibility that expression levels of sRAGE in post CAG-blood samples is lower than reality.

Thus, it is conceivable that significant increase in the expression level of sRAGE and VCAM-1 after CAG is mainly due to CAG procedure itself. CAG procedure was invasive diagnostic technique; there is always a risk that insertion of soft plastic catheters or contrast dye could interfere normal endothelial functions, and initiate inflammatory responses that result in endothelial injury.

There are no siginificant change in the expression level of S100A12 before and after CAG. It might be caused by the binding of pro-inflammatory receptor (RAGE or sRAGE) and s100A12 [10], and therefore reflecting less expression level of S100A12. Another plausible explanation would be due to the

sample population health profile. One study also showed that a serum S100A12 concentration is higher in patients with ACS than patients with stable CAD [28]. Since subjects in this study are mostly patients with CAD, level of S100A12 may not respond as sensitive.

In conclusion, a significant and independent association of increased expression levels of sRAGE and VCAM-1, further strengthen the causation between the endothelial injury and CAG procedure, especially in patients with atherosclerotic disease. Thus, CAG exposed patients with CAD to greater risk of atherosclerosis, which further aggravate existing condition. Therefore, precautionary measures to prevent the aforementioned risk must be performed before CAG and included as part of CAG procedure. There are other non-invasive diagnostic techniques available and preferable for patients with CAD, such as: Cardiac ECT and dual source CT. Nevertheless, furter clinical studies need to be done in order to assess all advantages of applying non-invasive diagnostic techniques instead of CAG.

LIMITATIONS

First, this study employs a cross-sectional sudy with a relatively small sample size. Further multi-center prospective longitudinal studies on larger population are needed in order to reaffirm the observation. Second, the study uses the changes in expression level sRAGE as a direct indicator of RAGE activities. Future studies may need to measure expression of RAGE directly. Third, it would be of a greater significance, if these findings were directly measured by expression of VCAM-1 on arterial tissues instead of the expression level of VCAM-1 in soluble form.

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