

Association of Serum Soluble Receptor for Advanced Glycation End Products (sRAGE), S100A12, and VCAM-1 Levels with Further Post-Coronary Angiogram Endothelial Injury in Elderly and Younger Patients

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Abstract

Objective: Coronary Angiography (CAG) refers to an aggressive process that is likely to lead to endothelial injury and possibly drive further interpretation of the cause for patients within current atherosclerotic illnesses. Therefore, this study aims to test certain correlations among concentration of sRAGE, VCAM-1, as well as S100A12 pre- and post-coronary angiography alongside likelihood of endothelial injury among various patients in different ages including the younger and the geriatric groups, thereby offering a full connection upon CAG impacts of patients having atherosclerosis. **Method:** In this study, the whole patients chosen had been grouped into two major groups on the basis of ages: the younger patient aged less than 65 years old (Group 1), and the elderly patient aged over 65 years old (Group 2). Soluble RAGE (sRAGE), VCAM-1 and S100A12 degrees in blood sampling gathered followed by measurements of CAG session for evaluating the inflammatory responses and likelihood of endothelial injury caused via CAG. All data was analyzed using SPSS version 21.0. **Findings:** Significant enhancement among concentration of serum VCAM-1 ($P = 0.007$) in younger patients and sRAGE ($P = 0.019$) in elderly patients had been observed, but that of serum S100A12 was still unaltered. **Conclusions:** Enhanced concentration of sRAGE and VCAM-1 post-CAG of patients having CAD are able to be related to follow-up endothelial injury, thus contributing to different pathway in exacerbating endothelial injury among younger and elderly patients.

Keywords

Coronary Angiography, Typical sRAGE, VCAM-1, S100A12

1. Introduction

In China, Coronary Angiographies (CAG) has been commonly performed to investigate the severity of Coronary Artery Diseases (CAD). Although CAG has been a standardized medical operation, it is a typical invasive process. Soft plastic catheters applied in CAG are most likely to interfere normal endothelial injuries, or lead to follow-up atherosclerotic plaque information. Endothelial injury causes inflammatory reactions, which leads to inflammatory markers like sRAGE, S100A12, as well as VCAM-1.

RAGE (Receptor for Advanced Glycation End Products) belongs to the immunoglobulin super family and is expressed upon appearance of endothelial, lymphocytes as well as smooth muscle cells [1]. Full-length, N-truncated as well as C-truncated soluble RAGEs are typical RAGEs [2] [3] [4]. Interaction between full-length RAGE and AGEs causes enhanced expression of adhesion molecules, covering soluble vascular cell adhesion molecule-1 (sVCAM-1) together with cytokine tumor necrosis factor- α (TNF- α) [5] [6]. Conversely, activation of nuclear factor-kappa results in enhanced expression of pro-inflammatory genes [5] [7]; Circulating isoforms RAGE covering sRAGE is laminated from cell appearance via matrix metalloproteinases as well as endogenous secretory RAGE (esRAGE) [3] [4].

S100A12 refers to an inflammatory ligand of RAGE, which belongs to the S100 protein family. S100A12 adjusts inflammation and immune reaction [8]. Ligature of it within RAGE upon the endothelium, mononuclear phagocytes as well as lymphocytes drives cellular activation within emergence of primary pro-inflammatory mediators like: interleukin (IL)-1, tumor necrosis factor (TNF) and so on.

VCAM-1 is able to boost generation of leukocytes to endothelial cells, meanwhile accelerating migration of leukocytes along the endothelial appearance [8] [9]. Importantly, ascertaining concentration of VCAM-1 among arterial tissues, and elucidating correlation between arterial VCAM-1 expression and unstable endothelial homeostasis, can cause atherosclerosis' interpretation of the cause [10].

To supervise such inflammatory markers is crucial because they imply how CAG process might possibly intensify atherosclerosis' interpretation of the cause [11]. Therefore, purposes of this research are to confirm aforementioned risk by supervising the above biomarkers and contrasting every serum degree prior to and after CAG between elderly and younger patients. Consecutive clinical linkage between different concentrations of the discussed biomarker serums having likelihood of resultant endothelial injury among various patients may possibly build better foundations for follow-up medical appraisal.

2. Patients and Methods

In terms of sample size, the research covered 68 consecutive patients undergoing elective coronary angiography among which 47 were males and 21 were females

aged between 46 to 81 years old. These samples were divided into two groups that Group 1 was made up of 34 younger patients aged less than 65 years old who underwent CAG procedure and having one stenosed coronary artery within over half of occlusion. In the meantime, Group 2 consisted of 34 elderly patients aged more than 65 years old who underwent CAG procedure and having one stenosed coronary artery within over half of occlusion. The target subjects sampled in the research comprise patients of Jiangsu Province Hospital, China. Besides, data was gathered from 07/2015 to 01/2016. Expressions of elective angiography covered patients having stable and unstable angina, having CAD, and having nonspecific chest pain. Inclusion standards for the research subjects were on the basis of "ACC/AHA Directions for Coronary Angiography". Afterwards, patients having certain conditions were ruled out from samples. These conditions included: any malignance, kidney dysfunction, thyroid illness, severe coronary syndrome, autoimmune, as well as peripheral artery diseases. After acknowledgment of the research, comprehensive medical record for every patient has then been collected and combined. Besides, routine physical tests had then been implemented to build clinical diagnosis. Pilot written together with informed consent were gained from the whole patients; subsequently, the research got approval from Ethics Review Board of Jiangsu Province Hospital. The whole patients had been subjected by Cardiac Ultrasound Measurements. The systolic and diastolic blood pressure of every patient had been measured using the commonly applied mercury sphygmomanometer after at least ten minutes rest in sitting position. Body Mass Index (BMI) was estimated to be weight in kilograms classified via square of the height by meters. This research also paid attention to cardiovascular risk elements like smoking habits, high blood pressure as well as diabetes. In the 68 patients chosen, 33 patients were smoking people, 35 suffered from high blood pressure and 14 owned diabetes mellitus.

CAG had been conducted by means of radial method applying standardized angiographic measure. Before the angiography, the whole patients had been provided with Heparin 2000 IU IVP. Angiogram gathered had been conducted from 4 standardized projections for every coronary artery. Stenosis level decided in projection that revealed the determined in projection that showed the top serious shrinking. A total of three proficient interventional heart specialists had reviewed the whole cineangiograms and all of them were made unknown to specific study methods.

When it comes to the blood sample gathering process, two blood sample sets existed, including ones before, during and after operating of angiography session. First of all, blood gathering extracted 7 ml of venous blood during the morning prior to operating and after a half day overnight fast and is majorly for underline blood profile analyses. Such samples had been drawn from antecubital vein and examined complying with standardized hospital process in Jiangsu Province Hospital. The other collection was blood elicitation prior to and after angiography session, gathered by a directing scabbard, and was majorly for measuring serum degree of sRAGE, VCAM-1, as well as S100A12. Every pa-

tient's blood samples was centrifuged in 3000 rpm for ten minutes at 4°C as well as deposited at -59°C for separating serums from cells. Degrees of serum were decided via an enzyme-related immune sorbent assay kit approach.

The statistic results are presented in the form of mean \pm standardized deviation, which was analyzed using SPSS version 21.0. within t-test as well as below common distribution. Confrontation of underline features among groups is conducted by one-way ANOVAs. The two tests take advantage of two-tailed $P < 0.05$ being a significant indicator of statistical discrepancies.

3. Results

Underline attributes of the whole patients are shown in **Table 1**. No significant discrepancies existed regarding in gender ($P = 0.801$), BMI ($P = 0.182$), systolic blood pressure ($P = 0.254$), diastolic blood pressure ($P = 0.193$), ejection fraction ($P = 0.660$), aspirin use ($P = 0.109$), beta-blocker use ($P = 0.624$), CCB use ($P = 0.160$), ACEI use ($P = 0.325$), statin use ($P = 0.600$), and nitrate use ($P = 0.353$) in that two groups of patients (see **Table 1**). Such outcomes also denote that main cardiovascular risk elements, like smoking ($P = 0.447$), hypertension ($P = 0.282$) as well as diabetes mellitus ($P = 0.254$), have no significant differences among two groups.

Table 1. Underline attributes among the three various patients groups.

	Group one middle age population age < 65 years old (n = 34)	Group two elderly population age > 65 years old (n = 34)	P value
Age (years)	55 \pm 4.4	71 \pm 4.7	0.000
Male/female	24/10	23/11	0.801
BMI (kg/m ²)	25 \pm 3.1	24 \pm 2.8	0.182
Hypertension (%)	15 (44)	20 (58)	0.282
Diabetes mellitus (%)	9 (26)	5 (14)	0.254
Smoking (%)	15 (44)	18 (52)	0.447
EF (%)	60.3 \pm 8.8	61.3 \pm 7.4	0.660
Aspirin use (%)	24 (71)	17 (50)	0.109
Beta-blockers' use (%)	14 (41)	12 (35)	0.624
ACE inhibitors' use (%)	3 (8)	6 (17)	0.325
CCB use (%)	8 (23)	14 (41)	0.160
Statins use (%)	19 (55)	17 (50)	0.600
Nitrate use (%)	17 (50)	21 (61)	0.353
SBP (mmHg)	123.4 \pm 17.6	128.5 \pm 19.4	0.254
DBP (mmHg)	74.8 \pm 12.2	71.8 \pm 11.9	0.193

Abbreviations: BMI, basal metabolism index; EF, ejection fraction; D-D, D-dimer; ACEI, angiotensin converter enzyme inhibitor; CCB, calcium channel blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Measurement of blood profile degrees among the whole patients.

Preoperative blood profiles of the whole subjects are shown in **Table 2**. In the two groups, it can be seen that there is no significant differences among serum TC ($P = 0.088$), HDL-C ($P = 0.219$), LDL-C ($P = 0.212$), TG ($P = 0.059$), Hb ($P = 0.464$), FPG ($P = 0.091$), as well as UA ($P = 0.453$) between two groups. Blood coagulation profiles (platelet ($P = 0.178$) and FIB ($P = 0.977$)) in these two groups have no statistical difference, however D-D ($P = 0.007$) showed significant discrepancies between younger and elderly patients.

Outcomes are shown as the mean \pm standard deviation. For investigating the concentration of sRAGE, VCAM-1, as well as S100A12 in arterial blood prior to and after coronary angiography, immunohistochemistry was conducted. In group one, it is revealed in **Table 3** that prior to coronary angiography, average

Table 2. Blood profile and lipid degrees in patients.

	Group one middle age population age < 65 years old (n = 34)	Group two elderly population age > 65 years old (n = 34)	P value
Hb (g/l)	135.1 \pm 24.1	143.2 \pm 57.8	0.464
Platelet ($10^9/L$)	215.8 \pm 79.3	180.7 \pm 72.5	0.178
D-D ($\mu g/mL$)	0.42 \pm 0.49	0.81 \pm 1.06	0.007
Fibrinogen (mmol/l)	2.7 \pm 0.69	2.7 \pm 1.18	0.977
TC (mmol/l)	4.2 \pm 0.91	4.5 \pm 0.81	0.088
HDL-C (mmol/l)	1.4 \pm 1.7	1.0 \pm 0.22	0.219
LDL-C (mmol/l)	2.7 \pm 0.7	2.9 \pm 0.63	0.212
TG (mmol/l)	2.1 \pm 1.75	1.5 \pm 0.66	0.059
FPG (mmol/l)	5.8 \pm 1.7	5.2 \pm 1.1	0.091
UA (mmol/l)	351.1 \pm 106.5	330 \pm 91.1	0.453

Abbreviations: Hb, hemoglobin; D-D, D-dimer; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; FPG, fasting plasma glucose; UA, uric acid.

Table 3. Concentration of S100A12, VCAM-1, sRAGE in arterial blood prior to and after CAG in younger patients.

Serum Protein	Group one (middle age population) age < 65 years old (n = 34)		P value
	Average level before CAG	Average level after CAG	
S100S12 ($\mu g/L$)	7.3 \pm 7.1	7.1 \pm 6.9	0.383
VCAM-1 ($\mu g/L$)	95.3 \pm 77.2	114.3 \pm 92.5	0.007
sRAGE (ng/L)	95.3 \pm 78.5	102.4 \pm 72.89	0.093

Abbreviations: VCAM-1, vascular cell adhesion molecule-1; sRAGE, soluble receptor of advanced glycation end products.

concentration of sRAGE was 95.3 ± 78.5 ng/L, average concentration of VCAM-1 is 95.3 ± 77.2 μ g/L, and average concentration of S100A12 is 7.3 ± 7.1 μ g/L. After coronary angiography, average concentration of SRAGE is 102.4 ± 72.89 ng/L, average concentration of VCAM-1 is 114.3 ± 92.5 μ g/L, and average concentration of S100A12 is 7.1 ± 6.9 μ g/L. Significant enhancement in concentration of serum VCAM-1 ($P = 0.007$) in post CAG arterial blood can be seen. However, the findings of serum concentration S100A12 ($P = 0.383$) and sRAGE ($P = 0.093$) in post CAG arterial blood keeps comparatively uninterrupted.

In group two, it is revealed in **Table 4** that prior to coronary angiography, average concentration of sRAGE is 83.8 ± 53.1 ng/L, VCAM-1 is 77.4 ± 59.4 μ g/L, and S100A12 is 6.0 ± 5.0 μ g/L. After coronary angiography, average concentration of sRAGE is 94.1 ± 45.5 ng/L, VCAM-1 is 77.9 ± 53.1 μ g/L, and S100A12 is 6.3 ± 5 μ g/L. Significant enhancement in concentration of serum sRAGE ($P = 0.019$) in post CAG arterial blood can be seen. However, the findings of serum concentration S100A12 ($P = 0.218$) and VCAM-1 ($P = 0.450$) in post CAG arterial blood that keeps comparatively uninterrupted.

It can be seen that group two (elderly patients) possessed significant increased concentration of serum sRAGE among the post CAG arterial blood. Concentration of serum VCAM-1 among post CAG arterial blood of group 1 (younger patients) had been significantly promoted. Such outcomes indicated that either concentration of sRAGE or VCAM-1 in arterial blood had been significantly promoted in both younger patients and elderly patients with CAD who underwent CAG.

4. Discussion

Inflammation is also an essential component of atherosclerosis, as the process leads to the activation and recruitment of inflammatory cells, endothelial cell dysfunction and plaque formation [12]. During endothelial injury context, it is going to further induce pro-inflammatory reaction, linked with inflammatory biomarkers output.

Table 4. Concentration of S100A12, VCAM-1, sRAGE in the arterial blood prior to and after CAG in elderly patients.

Serum Protein	Group two (elderly population) age > 65 years old (n = 34)		P value
	Average level before CAG	Average level after CAG	
S100S12 (μ g/L)	6.0 ± 5.0	6.3 ± 5	0.218
VCAM-1 (μ g/L)	77.4 ± 59.4	77.9 ± 53.1	0.450
sRAGE (ng/L)	83.8 ± 53.1	94.1 ± 45.5	0.019

Abbreviations: VCAM-1, vascular cell adhesion molecule-1; sRAGE, soluble receptor of advanced glycation end products.

VCAM-1 is an immunoglobulin-like adhesion molecule expressed on activated endothelial cells [13].

According to Weinkau *et al.*, VCAM-1 is a crucial marker of vascular endothelial injury and the degrees are enhanced via indicating VCAM-1 expression among endothelial cells [14]. Several latest researches also show that large elevation among concentration of VCAM-1 is able to be motivated by the inflammatory cytokines [15] [16].

Enhanced expression of the VCAM-1 among vascular endothelial cells after CAG disseminates adherence as well as integration of leukocytes to vascular wall [17]. VCAM-1 motivates migration of appendiculate leukocytes alongside vascular endothelial appearance, and motivate diffusion of glossy muscle cells; as such, it can be supposed that VCAM-1 is able to be comprised in further pathogenesis of atherosclerosis because of endothelial injury [16] [18]. Saidi *et al.* [19] once claimed that among patients with atherosclerosis, harms of endothelial cells own correlation with elevation of VCAM-1 degree.

Regarding our findings, there is significant and independent correlation of enhanced concentration of VCAM-1, had been significantly higher after CAG in younger patients (group 1). However, the concentration of VCAM-1 in elderly patients (group 2) was slightly elevated after CAG, but not significant.

The outcomes of us are consistent with that of Saidi *et al.* The overall enhancement in concentration of VCAM-1 is linked with aggressive attribute of CAG process; and the large enhancement in concentration of VCAM-1 in group 1 sheds light on that with the increasing severity of atherosclerosis, the elevation in concentration of VCAM-1 is higher. As a result of this, CAG can possibly incite further atherosclerosis' pathogenesis among patients having more serious atherosclerotic plague.

While previous researches indicated that sRAGE can reflect increased activity among RAGE system as effects of ligand motivation mediate sRAGE up regulation [20] and sRAGE has been concealed in parallel with RAGE [21] [22]. The sRAGE is a RAGE's isoform that is short of the intracellular field, hence intracellular signaling [23]. On the contrary, sRAGE spreads in blood and is thought to indicate RAGE and inflammatory practice [24].

In addition, the sRAGE can be generated by two distinctive methods, endogenous secreted being a splice variant, esRAGE [22] or being a laminated variant [23] [24] [25]. A least expression of RAGE below regular conditions exists while it highly enhances in cellular pressure [26]. As discussed in the above part that sRAGE indicate RAGE practice.

Regarding this research, a significant and independent correlation of enhanced concentration of sRAGE, had been significantly higher after CAG in elderly (group 2). From a flip side, the concentration of sRAGE in younger (group 1) was slightly elevated after CAG, but not significant.

It can be found that significant enhancement of sRAGE after CAG in the group two revealed higher RAGE practice. Therefore, indicating higher inflam-

matory practice that is linked to process of CAG. Additionally, VCAM-1 and RAGE are involved in the same immunoglobulin super family [5] [27], endothelial injury because of CAG process is able to motivate inflammatory response. Integration of inflammatory response and AGEs-RAGE communication induces VCAM-1 expression among endothelial cells [15] [16]. In elderly, CAG procedures may promote endothelial injury through significant enhancement of inflammatory process (RAGE practice) and secondary VCAM-1 expression among endothelial cells.

There are significant differences between the elderly and the younger in post CAG serum inflammatory biomarkers output, which reflects the degree of causes of vascular endothelial injury varies substantially across age period.

The observed enhancement in sRAGE and VCAM-1 has been assumed to be independent of any underline attributes, blood coagulation profile, and cardiovascular risk elements since no significant discrepancy exist between two groups (see **Table 1** and **Table 2**). Only D-D ($P = 0.007$) showed significant discrepancies between younger and elderly patients. It can be explained that elderly has higher risk of thrombus formation.

The vascular endothelium homeostasis plays an important role. Any structural or functional abnormality in the vascular wall (involving the extracellular matrix, vascular smooth muscle or endothelium) that occurs during aging may contribute to the increased risk of thrombosis in the elderly, particularly at hero thrombosis [28]. In addition, some researches show that sRAGE own higher affinity for heparin binding [19] [29] [30]. Because the whole patients are managed with heparin being part of CAG process, likelihood exists that concentration of sRAGE in post CAG-blood samples keeps lower than reality. In this case, it is foreseeable that large enhancement during concentration of sRAGE in elderly with additional risk of thrombus formation may require additional clinical management, such as administration of heparin post CAG procedure.

CAG process was aggressive diagnostic approach which share different mechanism of endothelial injury in elderly and younger patients. Especially in elderly, because of activation of inflammatory response and AGEs-RAGE axis induces VCAM-1 expression among endothelial cells. Such context will result in elderly has more pathways leading to endothelial injury. Combine with higher risk of thrombus formation, It can be hypothesized that group two may expose to higher risk of exacerbation in atherosclerosis plaque formation after CAG procedure.

No large shift exists during concentration of S100A12 prior to and after CAG. This may be caused via seizing of pro-inflammatory receptor as well as s100A12 [9]. Hence, indicating lower concentration of S100A12. An additional plausible interpretation would be because of the sample subjects' health profile. One research also revealed that a serum S100A12 focus keeps higher in patients having ACS than patients having steady CAD [31]. As subjects in the research are majorly patients having CAD, degree of S100A12 cannot react as sensitive.

5. Conclusion

A large and independent correlation of enhanced concentrations of sRAGE and VCAM-1, enhance the causation between endothelial injury and CAG process, particularly in patients with atherosclerotic illness. Therefore, CAG revealed both elderly and younger patients having CAD to larger risk of atherosclerosis that further exacerbates current status, although it reveals that both groups do not share the same pathogenesis pathway. Elderly has higher risk of greater exacerbation compared to the younger patients. As such, precautionary methods to guard against aforementioned risk should be conducted before, meanwhile and after CAG process, like additional use of heparin and others measures. Other non-aggressive diagnostic instruments are preferred by patients having CAD, like Cardiac ECT and dual source CT. However, future related clinical researches ought to be carried out for assessing the whole benefits of using non-aggressive diagnostic instruments rather than CAG. The research is practical in helping people aged over 65 years old to prevent themselves from vascular endothelial injury.

Limitations

Despite the achievements in present study, there are some limitations that must be highlighted. This research has employed a cross-sectional approach using a small sample size, thus affecting the external validity of research. Therefore, it is suggested for future researches to conduct multi-center prospective longitudinal researches upon bigger population to reconfirm the observation. Furthermore, this research has used the shifts in concentration sRAGE to be a direct indicator of RAGE practices. Further researches can measure expression of RAGE in a direct way. In addition, it may be crucial when these results were measured via expression of VCAM-1 upon arterial tissues rather than concentration of VCAM-1 among soluble pattern.

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