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sRAGE and the risk for incident heart failure: The Atherosclerosis Risk in Communities Study

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Abstract

Background—Experimental studies in animals suggest that circulating soluble receptor for advanced glycation end-products (sRAGE) decrease oxidative stress, inflammation and fibrosis. The association between sRAGE and incident heart failure has not been systematically examined in a prospective study.

Methods—We conducted a prospective analysis of a subsample of 1,086 participants from the Atherosclerosis Risk in Communities Study who attended visit 2 (1990–1992) without a history of coronary heart disease, stroke, or heart failure and with measured plasma sRAGE levels. Incident heart failure was defined as death from heart failure or hospitalization due to heart failure during a median of 20 years of follow up.

Results—In this sample of a community-based population (mean age 63 years, 60% women, 78% white), there were 126 incident cases of heart failure. Lower levels of sRAGE were

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CONFLICT OF INTEREST

None

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significantly associated with an increased risk of heart failure; the adjusted hazard ratios (95% confidence intervals) of heart failure were 1.0 (reference), 1.81 (0.94–3.49), 1.57 (0.80–3.08) and, 3.37 (1.75–6.50), for 4th, 3rd, 2nd and 1st quartile respectively (P for trend=0.001). We did not observe significant interactions by diabetes status or by race or obesity status.

Conclusions—Lower circulating levels of sRAGE are independently associated with the development of heart failure in a community-based population. Our results add to the growing evidence that sRAGE is a valuable predictor of cardiovascular disease.

Advanced glycation end products (AGEs) are a group of compounds generated under hyperglycemic conditions, oxidative stress, and hypoxia. AGEs bind to the cellular receptor for AGEs (RAGE) and lead to generation of reactive oxygen species (ROS), and activation of intracellular second messengers involved in inflammation and fibrosis.^{1, 2} Non-AGE ligands to the RAGE that also elicit inflammatory responses have been reported and include: high mobility group box-1 (HMGB1) and s100/calgranulins.^{3, 4}

The soluble receptor for advanced glycation end products (sRAGE) is the isoform of RAGE found in serum and is formed by proteolytic cleavage of RAGE. The relevance of sRAGE is that it competes with cellular RAGE for binding of AGEs and other ligands such as HMGB1⁵ and therefore may reduce the activation of the RAGE mediated pro-inflammatory and pro-fibrotic signaling pathways.^{6, 7} In fact, experimental models have demonstrated that administration of sRAGE reduces immune and inflammatory responses.⁸

Given that the pathogenesis of heart failure includes insult to myocardial tissue through oxidative stress, inflammation and fibrosis, all of which are related to the activity of RAGE pathway⁹; we hypothesized that sRAGE levels are related to future heart failure risk. The goal of the current study was to examine the prospective association between sRAGE and risk of heart failure among individuals without history of cardiovascular disease, heart failure or stroke.

METHODS

Study Population

The ARIC Study is an ongoing cohort study of 15,792 initially middle-aged adults recruited from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland.¹⁰ The first examination of participants took place from 1987 to 1989, with three follow-up visits, occurring approximately three years apart, and a fifth visit in 2011–2013. The study population for the present study is comprised of a subsample of participants who attended visit 2 (1990–1992). Briefly, a random sample of 1,289 participants with normal kidney function (glomerular filtration rate >60 ml/min/1.73 m²) was selected from the 14,348 participants who attended visit 2. For the current study we excluded participants with race/ethnicity other than black or white, and persons with a history of coronary heart disease, stroke or heart failure at baseline. The final sample size was 1,086 adults. The characteristics of the participants included in the current analyses and those excluded are presented in the Supplemental Table 1.

All participants provided written informed consent and the institutional review boards at each clinical site approved the study.

Measurements of sRAGE

sRAGE was measured in stored plasma samples using a commercially available ELISA kit (R&D Systems, Minneapolis, MN). The intra- and inter-assay coefficients of variation for the assay were 2.8% and 9.6%, respectively. In addition, measurement of sRAGE levels has been reported to be highly reliable, with an intra-class correlation 0.76 and Pearson's correlation 0.78 when measurements were compared 3 years apart.¹¹

Assessment of Incident Heart Failure

Incident heart failure was defined as death from heart failure in any position on the death certificate or as the first heart failure hospitalization with ICD-9 code 428 or ICD-10 code I50 in any position of the hospital discharge summary obtained during the ongoing active surveillance for all cardiovascular-related hospitalizations and deaths for all ARIC participants. For the current analyses follow up information was available up to December 31st of 2011.

Other Measurements

Smoking history and alcohol consumption were assessed during interviews with the participants. Participants were asked to bring all medications, which were coded by trained personnel. We defined history of cardiovascular disease as: self-reported myocardial infarction or stroke before visit 1, or silent myocardial infarction (diagnosed by electrocardiographic changes), adjudicated myocardial infarction or revascularization (at or before visit 2). Prevalent heart failure was defined as self-reported treatment for heart failure or hospitalization for heart failure at or before visit 2. Diabetes was defined as self-reported physician diagnosis or hemoglobin A1c (HbA1C) $\geq 6.5\%$. Using standardized methods, height, weight, waist circumference, and blood pressure were measured. C-reactive protein (CRP) was measured in stored plasma samples using an immunoturbidimetric assay on the Siemens BNII autoanalyzer (Dade Behring). Frozen whole blood samples collected at ARIC visit 2 (1990–1992) were thawed and assayed for HbA1c using a high performance liquid chromatography instruments (Tosoh Corporation, Tokyo, Japan). The CV for quality control replicate samples (N=259) was 1.4%. Gamma-glutamyltransferase (GGT), as surrogate marker of oxidative stress, was measured in serum or plasma using Roche GGT reagent on the Roche Modular P Chemistry analyzer. The laboratory inter-assay CV is 5.1% at a value of 39 U/L and 2.9% at a value of 171 U/L.

Statistical Analyses

Baseline levels of sRAGE were categorized into quartiles. We used the Kaplan-Meier method to assess the difference in the overall risk (cumulative incidence) of heart failure by quartiles of sRAGE. Cox proportional hazards models were used to estimate the independent association between quartiles of sRAGE and the risk of heart failure. Model 1 included age, race, and sex. Model 2 included all variables in Model 1 plus biological factors associated with sRAGE levels: body mass index (BMI) categories, CRP (categories) and gamma

glutamyl-transferase (U/L). Model 3 included all variables in Model 2 plus factors associated with heart failure risk: diabetes (yes/no), hypertension (yes/no), current blood pressure medication use, current alcohol consumption (yes/no), and current smoking (yes/no). We additionally adjusted for fasting glucose in sensitivity analyses.

To characterize the shape of the association of sRAGE with incident heart failure, we implemented a piece-wise linear spline model with 5 knots. In this model, we adjusted for age, sex and race and truncated sRAGE at the 99th percentile. The model was centered at the 75th percentile of sRAGE. In addition, because of the established substantial difference in the levels of sRAGE in blacks compared to whites^{12, 13}, we also implemented race-stratified spline models, centered at the race-specific 75th percentile of sRAGE.

Because it has been postulated that the role of sRAGE for disease may be particularly important for persons with diabetes^{14, 15}, we conducted a sensitivity analyses stratified by diabetes status. We also tested for interaction by obesity status.

Finally, using Harrell's C statistic, we evaluated the incremental value of sRAGE for the prediction of heart failure compared to a modified ARIC Heart Failure (HF) Risk Score (which included age, sex, race, systolic blood pressure, use of blood pressure medications, diabetes, smoking status, heart rate and BMI).¹⁶ We also used the Stata "idi" and "nri" program to estimate the integrated discrimination improvement (IDI), and net reclassification improvement (NRI), respectively. All analyses were conducted using Stata 13.1

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The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

RESULTS

Baseline characteristics of the study population by overall and race-specific quartiles of sRAGE are shown in Table 1. Blacks had substantially lower levels of sRAGE and a higher prevalence of diabetes and hypertension. Regardless of the race/ethnicity the following were factors associated with low levels of sRAGE: male sex, diabetes and hypertension, higher BMI, higher CRP, and higher GGT levels.

During a median follow-up of 20 years, there were 126 cases of heart failure among the 1086 study participants in our subsample. The cumulative incidence of heart failure by quartile of baseline sRAGE is shown in Figure 1.

Persons in the lowest quartile of sRAGE had a significantly higher risk of heart failure compared to persons in the upper quartiles, even after multivariable adjustment (Table 2). The fully adjusted HRs of heart failure were 1.0 (reference), 1.81 (95% CI 0.94–3.49), 1.57 (95% CI 0.80–3.08) and, 3.37 (95% CI 1.75–6.50), for the 4th, 3rd, 2nd and 1st quartiles of sRAGE, respectively (P-for-trend=0.001). The results remained almost identical after additional adjustment for fasting glucose.

The spline model demonstrated an “L” shaped association, largely consistent with analyses using quartiles and showed an increased risk of heart failure for those with low levels of sRAGE with some evidence of threshold effect at 1,200 pg/ml (Figure 2). The results were largely consistent in race-stratified analyses (Figure 2 B and C) and we did not observe a statistically significant difference.

We assessed whether the observed association of sRAGE and heart failure was different by diabetes or obesity status (Table 3). Results were very consistent in diabetes-stratified analyses with similar patterns of association observed in individuals with and without diabetes (p for heterogeneity=0.55). Analyses stratified by obesity status (Table 3) and adjusted for diabetes status suggested that among individuals with obesity the risk of heart failure with low sRAGE levels seemed higher (HR=11.2, 95% CI 1.45–86.32) compared to individuals without obesity (HR=2.62, 95% CI 1.20–5.71); however this interaction was not significant (p for heterogeneity=0.08).

The area under the curve (AUC) using the ARIC HF Risk Score (which included age, sex, race, systolic blood pressure, use of blood pressure medications, diabetes, smoking status, heart rate and body mass index) was 0.77, and when sRAGE was added the AUC was 0.78, with a significant, but small, improvement of 0.02 (95% CI 0.002–0.03), p value 0.03. The integrated discrimination improvement (IDI) was 0.007 (p value 0.05) and the net reclassification improvement (NDI) was 0.32 (p value < 0.001).

Discussion

In this community-based population of middle-aged individuals without clinically evident cardiovascular disease and normal kidney function we found that low levels of sRAGE were independently associated with increased risk of heart failure over a median of 20 years of follow up. Furthermore, addition of sRAGE to the ARIC heart failure prediction model resulted in a small but significant improvement in prediction. As it has been postulated, low sRAGE levels were significantly correlated with more inflammation and oxidative stress, as measured by higher c-reactive protein and GGT, respectively.

The rationale for studying the role of the AGE-RAGE pathway in the development of cardiovascular disease is grounded in a number of studies that first postulated that among persons with diabetes, the hyperglycemia induced vascular damage was, at least in part, due to the accumulation and cross-linking of advanced glycation endproducts to proteins in

vessel walls.¹⁴ These studies were followed by others describing the presence and role of the receptor to AGE (RAGE) in a number of cells of different tissues such as vascular endothelial cells, kidney, nerves, and which demonstrated that binding to cellular RAGE induced inflammation, thrombosis, and accelerated atherosclerosis.¹⁷ Experimental studies have demonstrated blockade of RAGE suppresses the development of atherosclerosis^{17, 18}, and leads to an antiinflammatory phenotype.⁶ The role of soluble forms of the RAGE, sRAGE and esRAGE, which also serve as receptors for these ligands are not completely understood. It has been postulated that sRAGE may act as an extracellular decoy ligand that prevents binding of AGE or other ligands to the cellular RAGE, and therefore the levels of sRAGE convey a protective environment, whereby higher levels indicate higher protection¹⁹. However, others have postulated that sRAGE release may be part of the regulatory mechanism, and therefore their levels may reflect the ongoing activation of the axis, whereby production of RAGE leads to increase shedding of sRAGE into the circulation and thus higher levels indicate higher overall activity of the axis^{5, 20}.

Our results are consistent with other epidemiologic studies demonstrating the inverse association sRAGE levels and risk of disease and death. Low levels of sRAGE have been associated prospectively with risk of diabetes¹², coronary heart disease¹², atherosclerosis^{13, 21} and mortality.¹² In addition, low levels of esRAGE, another soluble receptor of AGE, have been cross-sectionally associated with heart failure presence²². However, other studies have found associations between sRAGE and outcomes to be in the opposite direction, e.g. high levels of sRAGE were associated with an increased risk of various cardiovascular outcomes^{15, 23, 24}, including severity of heart failure^{25, 26}. Explanations for the inconsistent findings are largely speculative and highlight our incomplete understanding of the regulatory mechanisms of sRAGE. Potential factors that may explain the heterogeneity of the findings include the study population (with respect to disease status and medication use), the baseline levels of AGE, RAGE, and the duration of follow up. Indeed, our analyses using splines suggest an “L” shaped association, with a graded inverse relationship between sRAGE levels and the risk of heart failure up to a certain point after which it flattens. While we cannot draw firm conclusions given the small sample size at the tails of the distribution, these analyses highlight the relevance of the baseline levels and the range of levels of sRAGE in the study population and the possibility of a threshold effect that should be corroborated in future studies. In addition, most of the prospective studies demonstrating an association between high levels of sRAGE and risk of cardiovascular outcomes have been shorter than our study and have included individuals with existing disease. Similarly, differences in findings across studies may be related to the pre-existing conditions that may modify the observed association. In our study, the association between sRAGE levels and the risk of heart failure seemed to be stronger among people with obesity compared to their counterparts. Due to the limited sample size of our study, the subgroup analyses were, however, secondary in nature and the lack of precision of these estimates can be appreciated by the large confidence intervals.

To our knowledge, although our study is small, it is the largest and longest prospective study examining the association between sRAGE and incident heart failure among individuals without existing cardiovascular disease. Our study was a random sample of the ARIC cohort and we benefited from the rigorous case ascertainment, comprehensive risk factor

measurement, and standardized data collection on important confounders. The results of the risk of heart failure among ARIC participants have been published before by Agarwal S. et al,¹⁶ our results of the cumulative incidence of heart failure (11%) is the same as that reported by Agarwal using the 13,555 ARIC participants.

There are some limitations of the current study. First, given our small size we had limited ability to examine differences in the effect of sRAGE levels on the risk of heart failure among subgroups (e.g. blacks, people with obesity or diabetes). Additionally, we aimed to have parsimonious models and limited the number of confounders and mediators included in multivariable models, therefore the possibility of residual confounding cannot be eliminated. Second, given the observational nature of the study, we cannot conclude the sRAGE is a causal factor in the development of heart failure, and our recent work on the genetics of sRAGE suggests that sRAGE is a marker of cardiovascular disease but not an independent causative factor.²⁷ Third, we only had a single measurement of sRAGE to characterize exposure status, however, we have demonstrated in our study population, that sRAGE levels track well over time, Pearson's correlation 0.78 when measurements were compared 3 years apart.¹¹ Fourth, we relied on hospitalization records or death certificates to ascertain heart failure, this outcome has been recently validated by ARIC investigators²⁸, who demonstrated that the outcome is highly specific: 92.5% of the hospitalizations with ICD-9 code CM428 were validated as acute decompensated heart failure, however we do not anticipate that any misclassification is differential by sRAGE level. Finally, we only had measurement of sRAGE, there may be other measures that might help us fully characterize the role of the AGE-RAGE related pathway in heart failure.

In conclusion, low levels of sRAGE were strongly and independently associated with increased risk of heart failure in a community based sample of middle-aged adults. Our findings must be confirmed but suggest that sRAGE may be valuable as a predictor of future heart failure, a condition associated with a substantial and rapidly-growing public health burden²⁹. In addition our results support the hypothesis that antagonists of the RAGE pathway may provide important targets for the prevention and treatment of heart failure in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Cumulative incidence of heart failure by baseline sRAGE quartiles (presented from lowest to highest)

Figure 2.

Adjusted* HRs (95% CI) for incident heart failure by baseline sRAGE, overall (A), for whites (B), and for blacks (C), using a piece-wise linear spline model

*A: Adjusted for race, age and sex. B and C: Adjusted for age and sex. Reference: 75th percentile. Data truncated at 10th and 90th race-specific percentiles.

Table 1
Baseline characteristics of the study population by quartiles of sRAGE (pg/mL) overall and stratified by race groups

RAGE	Overall (N=1,086)				Whites (N=857)				Blacks (n=229)			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Quartiles												
Mean [Range], pg/mL	550.7 [714.1]	840.9 [714.7–966.3]	1116.2 [966.4–1271.8]	1700.8 [1272]	641.8 [796.1]	924.8 [796.6–1047.9]	1193.1 [1050.6–1352.6]	1775.7 [1353.1]	393.5 [493.2]	587.4 [494.3–670.4]	773.2 [672–891.4]	1219.9 [894]
Male, %	47.6	44.1	41.3	29.8*	54.2	41.1	45.3	26.5*	33.3	42.1	40.4	31.0
Mean age (years)	56.5	56.2	56.5	56.3	56.7	56.6	56.8	56.2	56.3	55.4	55.9	54.9
Black, %	46.9	20.2	11.4	5.9*	0	0	0	0	100	100	100	100
Diabetes, %	16.9	12.5	10.3	5.2*	11.2	11.2	7.5	5.1	21.1	24.6	22.8	13.8
Mean BMI (kg/m ²)	30.0	27.9	27.2	26.6*	29.1	27.4	26.9	25.5*	31.5	29.5	29.6	27.7*
C-reactive protein, %												
<1 mg/L	17.0	29.0	35.4	39.3*	18.2	32.7	36.0	41.4*	14.0	24.6	22.8	31.0
1–2.99 mg/L	33.9	34.9	34.7	33.8	36.5	37.9	33.6	33.5	28.1	26.3	33.3	34.5
3 mg/L	49.1	36.0	29.9	26.8	45.3	29.4	30.4	25.1	57.9	49.1	43.9	34.5
Mean glucose (mg/dL)	114.0	111.4	108.9	102.7*	108.2	108.4	107.3	102.3*	121.8	119.5	125.1	111.9
Mean GGT (U/L)	35.6	32.3	23.2	20.6*	32.6	30.5	22.4	20.5*	43.1	35.9	32.4	23.0*
Current smoker, %	15.1	21.7	19.6	15.8	16.8	17.8	20.6	14.9	19.3	19.3	19.3	22.4
Current drinker, %	54.6	58.1	63.8	60.3	70.1	64.0	70.1	62.3	29.8	29.8	35.1	31.0
Hypertension, %	33.9	24.6	21.8	17.3*	26.6	18.2	19.2	14.4*	47.4	42.1	38.6	41.4

* p-for-trend across quartiles of sRAGE <0.05

Table 2
Adjusted Hazard Ratios (95% Confidence Intervals) of Incident Heart Failure by Quartiles of sRAGE

sRAGE Quartile, [Range, pg/mL]	Q1 [<714.1]	Q2 [714.7–966.3]	Q3 [966.4–1271.8]	Q4 [>1272.1]	P value for linear trend [†]
Events	52	29	31	14	
Model 1	4.01 (2.14 – 7.53) *	2.19 (1.14 – 4.19) *	2.24 (1.19 – 4.23) *	1 (Reference)	<0.001
Model 2	3.04 (1.58 – 5.82) *	1.68 (0.86 – 3.29)	1.74 (0.90 – 3.34)	1 (Reference)	0.001
Model 3	3.37 (1.75 – 6.50) *	1.57 (0.80 – 3.08)	1.81 (0.94 – 3.49)	1 (Reference)	0.001

Model 1: adjusted for race, age, and sex

Model 2: adjusted for variables in Model 1+ C-reactive protein (mg/L, categories), BMI (kg/m², categories), and GGT (U/L)

Model 3: adjusted for variables in Model 2 and diabetes, systolic blood pressure, blood pressure medication, alcohol use, and smoking

* p<0.05 compared to reference group (sRAGE Q4)

[†]Test for trend was performed by modeling the category median as a continuous variable.

Table 3
Adjusted Hazard Ratios (95% Confidence Intervals) of Incident Heart Failure by Quartiles of sRAGE in Population Subgroups

sRAGE, pg/mL [Range]	Q1 [<710.5]	Q2 [710.5 – 965.2]	Q3 [965.2 – 1264.2]	Q4 [>1264.2]	P value for linear trend [†]
Diabetes					
No n=940	3.54 (1.64 – 7.63)*	1.86 (0.84 – 4.10)	2.20 (1.03 – 4.69)	1 (Reference)	0.002
Yes N=113	3.48 (0.68 – 17.82)	0.93 (0.20 – 4.41)	0.82 (0.17 – 3.99)	1 (Reference)	0.09
Obesity					
No n=760	2.62 (1.20 – 5.71)*	0.92 (0.40 – 2.10)	2.08 (1.02 – 4.25)*	1 (Reference)	0.10
Yes N=293	11.2 (1.45 – 86.32)*	7.65 (0.97 – 60.30)	3.19 (0.39 – 26.2)	1 (Reference)	0.001

Adjusted for race, age, sex, C-reactive protein (mg/L), BMI(kg/m²), GGT, diabetes, hypertension, blood pressure medication, alcohol use, and smoking

* p<0.05 compared to reference group (sRAGE Q4)

[†] Test for trend was performed by modeling the category median as a continuous variable.