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Soluble Receptor for Advanced Glycation End-products Levels in Chronic Heart Failure and Its Correlation to Left Ventricular Ejection Function

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Abstract

The Receptor for Advanced Glycation End-products (RAGE), a multi-ligand member of the immunoglobulin superfamily, is a ubiquitous receptor present on epithelial, neuronal, vascular and inflammatory cells. AGEs have been implicated in vascular and myocardial dysfunction and in development of atherosclerosis but little are known about the role of the AGE-RAGE system in heart failure. The main objective of the study was to assess sRAGE plasma levels in patients with Chronic Heart Failure (CHF) focusing on patients with severe reduction of left ventricle function. We measured sRAGE plasma levels in 389 patients with CHF and 319 stable patients with Coronary Artery Disease (CAD). Patients with CHF had significantly lower values of soluble RAGE in respect to stable CAD population. The linear regression analysis showed that LVEF (Left Ventricularv Ejection Fraction) significantly correlated with sRAGE plasma concentrations; sRAGE plasma levels were significantly lower in patients with severe left ventricular systolic dysfunction compared with those with ejection Fraction ≥ 30%. Our data support a positive correlation between soluble RAGE plasma levels and left ventricular ejection fraction in the CHF population; we demonstrated that in subjects with CHF and severe left ventricular systolic dysfunction, soluble RAGE plasma concentrations were significantly lower in comparison with patients with moderate left ventricular dysfunction. This study suggests the possibility that soluble RAGE can be considered a new element to be used in prognostic stratification in patients affected by CHF.

Keywords: Chronic heart failure; Coronary artery disease; Soluble RAGE; Left ventricular ejection fraction

Introduction

Advanced glycation end products (AGEs) are a heterogeneous and complex group of biochemical compounds, which cause a wide range of deleterious effects, which are mediated by cellular receptor, especially the receptor for advanced glycation end products (RAGE) [1-3]. AGEs seem to play an important role for the development and/or progression of cardiovascular disease (CVD) mainly through induction of oxidative stress and inflammation [4]. Complication arising from atherosclerosis, characterized by superimposed hypoxia and ischemia-reperfusion (I-R) injury, are potent and rapid generators of AGEs [5].

The Receptor for Advanced Glycation End-products (RAGE), a multi-ligand member of the immunoglobulin superfamily, is a ubiquitous receptor present on epithelial, neuronal, vascular and inflammatory cells, usually expressed at low levels in homeostasis and to increased degrees at sites of stress or injury [4]. RAGE is widely studied both in animal models and in human subjects [6,7]. Advanced glycation endproducts engage their receptor in cells of the blood vessel wall, thereby activating mechanisms linked to the development of vascular lesions. Park et al., report a model of accelerated and advanced atherosclerosis in diabetic mice deficient for apolipoprotein E and showed that treatment of these mice with the soluble extracellular domain of the receptor for advanced glycation end-products completely suppressed diabetic atherosclerosis in a glycemia- and lipid-independent manner [8]. Wautier et al., also report that blockade of RAGE inhibits AGE-induced impairment of endothelial barrier function, and reverse, in large part, the early vascular hyperpermeability observed in diabetic rats. Inhibition of AGE- and diabetes-mediated hyperpermeability by antioxidants, both *in vitro* and *in vivo*, suggested the central role of AGE-RAGE-induced oxidant stress in the development of hyperpermeability [9,10]. The coding sequence of sustained interaction of AGEs-RAGE may trigger RAGE-dependent cellular activation, induce oxidative stress, and promote inflammatory-proliferative responses leading to vascular dysfunction [11,12].

RAGE has a C-truncated secretory isoforms (soluble RAGE), that circulates in plasma, and which has at least two variants: one that is secreted from cells, endogenously secreted RAGE (esRAGE), and another that is formed by proteolytic cleavage by matrix metalloproteinases from the cell-surface, cleaved-RAGE (cRAGE) [13]. The soluble isoform (sRAGE) acts as a decoy receptor for RAGE ligands, and is thought to afford protection against inflammation.

In recent years, the role of AGEs in the pathogenesis of cardiovascular diseases became recognized. AGEs have been implicated in vascular and myocardial dysfunction [14,15] and in the development of atherosclerosis [16,17]. Little is known about the role of the AGE-RAGE system in heart failure (HF) [18,19]. Epidemiological evidence suggesting foundamental association between AGE-RAGE and heart failure in human subject [20]; including the finding that high serum levels of the specific AGE pentosidine were found to be an independent

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prognostic factor for heart failure [21]. Recent study reported that plasma sRAGE is an independent prognostic factor for heart failure [22] and showed a robust association between NR-proBNP with sRAGE [23].

The main objective of the study was to assess sRAGE plasma levels in patients with Chronic Heart Failure and left ventricle (LV) dysfunction, focusing on patients with severe LV dysfunction.

Material and Methods

Study population

The population of this study consists of 389 patients (326 men and 63 women; mean age of 57 ± 10 years) with CHF followed in the University Hospital of Pavia. CHF patients enrolled in the study were selected according to the presence of depressed LVEF (≤45%). In the meantime, we enrolled 319 stable patients with documented CAD at angiography (249 men and 70 women; mean age of 64 ± 10 years) with normal LV systolic function. We excluded from the study patients with acute heart failure or acute coronary syndrome within 3 months, patients with acute inflammatory states, or with exacerbations in the act of infectious diseases, chronic inflammatory or autoimmune diseases, patients with known malignancies, patients with renal or hepatic impairment and patients with macroalbuminuria.

Patients included in the study underwent the following investigations: an accurate anamnesis with identification of the major cardiovascular risk factors; cardiology consultation including check of baseline blood pressure; peripheral venous blood sample for determining the concentration of sRAGE, exercise stress test and echocardiography. Data collection included age and body mass index (BMI), no data about diet or physical activity were collected. Patients with positive exercise stress test underwent diagnostic coronary angiography using standard techniques. CAD was defined as angiographic evidence of stenosis in any epicardial coronary artery of ≥50% of diameter.

The cardiovascular risk factors were defined as follows: hypertension (systolic pressure>140 mmHg or diastolic pressure>90 mmHg or antihypertensive therapy), family history of CAD (coronary artery disease in a first degree relative under the age of 60 years), tobacco smoke, hyperlipidemia, and diabetes mellitus. With regard to cigarette smoking, subjects were grouped under the headings 'always' or 'never': group 'always' were included subjects who had smoked daily for at least 1 year. We considered dyslipidemic patients with cholesterol levels above 200 mg/dl or in treatment with lipid-lowering drugs. The diagnosis of diabetes mellitus has been placed in patients previously treated with dietary treatments, which had received oral antidiabetic agents or insulin or had a fasting plasma glucose value greater than 126 mg/dL.

We used as control group patients who visited our affiliated hospitals or clinics for a physical check-up. Controls were characterized by no history of angina and other heart disease, a normal resting ECG, and normal exercise ECG stress testing. They were matched with patients by age (data previously reported) [24].

All subjects signed an informed consent form before the study. The study was conducted in accordance with the guidelines of the Declaration of Helsinki for human research and the guidelines of our local ethics committee.

Echocardiography

Conventional echocardiography and tissue Doppler imaging were performed. M-mode, two-dimensional and Doppler echocardiographic examinations were performed with an ultrasonographic system equipped with a multi-frequency transduction. All images were stored digitally and analyzed off-line with EchoPac PC Dimension software (GE Medical). LV ejection fraction was calculated from apical two- and four-chamber views using LV volumes by the modified biplane Simpson rule. LV end-diastolic volume and LV end-systolic volume were indexed to body surface area. Peak early (E) and late (A) filling velocities, E/A ratio, and E velocity deceleration time were measured from the LV-inflow pattern at the tips of the mitral valve at end expiration. Measurement of systolic pulmonary artery pressure was performed using the maximal regurgitant velocity at the tricuspid valve by continuous Doppler.

Measurements of soluble receptor of advanced glycation end products

Venous blood samples (3 ml) were collected, during ambulatory evaluation of patients, in Vacutainer tubes containing EDTA as anticoagulant for determination of plasma levels of sRAGE and lipid parameters. The samples were centrifuged at 1000*g* for 30 and immediately divided into aliquots.

All laboratory tests were performed in blind. The serum total cholesterol and triglycerides were determined using a standard enzymatic procedure. HDL cholesterol was determined enzymatically after precipitation of other lipoproteins with dextran sulfate magnesium. Blood glucose was determined by the method of glucose oxidase. Plasma levels of sRAGE were determined using a kit for the immunoadsorption enzyme is commercially available (Quantikine, R & D Systems) according to manufacturer's protocol. Briefly, a monoclonal antibody against sRAGE has been used to capture sRAGE from plasma. sRAGE captured was marked with a polyclonal anti-human sRAGE. After washing, the plates were incubated with streptavidin-HRP, developed on an appropriate substrate and OD450 was determined using a plate reading immunoadsorption enzyme. The measurements were made in duplicate and the results compared. The values of the coefficients of variation intra-and inter-determination were respectively less than 6% and <8%.

Statistical analysis

All statistical analysis was performed using the statistical packages SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc (Mariakerke, Belgium). The hypothesis of normal distribution for continuous variables was tested according to Kolmogorov-Smirnov statistics. Continuous variables are expressed as mean ± standard deviation in the case of Gaussian distribution and as median (interquartile range) in the case of variables with non-normal distribution. The data were analyzed using the Student *t*-test for paired Mann-Whitney or the EU. The category variables were compared using the chi-square test.

A linear regression analysis was performed to evaluate the possible correlation between plasma sRAGE and clinical-instrumental variables. Statistical significance was defined as $p<0.05$.

Results

The target population was composed of 389 patients with CHF (326 men and 63 women, mean age 57 ± 10 years) and 319 stable CAD patients (249 men and 70 women, mean age of 64 ± 10 years) without CHF and with preserved LVEF. The clinical and instrumental

characteristics of the two populations under consideration are shown in Table 1.

The 7% of CHF patients are in NYHA class IV, 51% of patients are in NYHA class III and 42% of patients are in NYHA class II; no CHF patients are in NYHA class I.

Patients with CAD had a higher mean age compared with CHF patients and there are higher prevalence of male, hypertensive, dyslipidemic, smokers and diabetic subjects.

In terms of drug therapy the two populations were different, in particular in the CHF population there is a higher prevalence of subjects treated with beta-blockers, ACE inhibitors/ARBs and diuretics, and lower prevalence of subjects treated with calcium channel blockers, nitrates and statins.

Patients with CHF had significantly lower values of sRAGE in respect to stable CAD population (659 pg/ml, 470-920 pg/ml; 950 pg/ml, 730-1200 pg/ml respectively, P<0.05). The concentration of sRAGE in plasma was significantly lower (P<0.01) in CAD and CHF cases than in control subjects [1335 (936-1954) pg/mL] as previously reported [24].

We also performed stepwise regression analysis to determine whether this association was independent from the effect of common cardiovascular risk factors and current treatment. The results showed that levels of sRAGE remained related to the manifestation of heart disease (p<0.001), even after adjusting for these confounding variables.

In the population with CHF, 242 patients (62%) had non-ischemic cardiomiopathy (by hypertension, valve disease, congenital heart disease and previous infections) and 147 patients (38%) had post-ischemic cardiomiopathy. Of the 147 patients with post-ischemic cardiomiopathy 27% of patients had one-vessel disease, 31% of patients had two-vessel disease, 42% of patients had 3 vessels disease. The clinical characteristics of the two groups of patients are shown in Table 2.

The two populations showed a different distribution of risk factor for CAD: patients with ischemic etiology were more hypertensive, dyslipidemic, diabetic and smokers than those with non-ischemic cardiomiopathy. The plasma concentration of sRAGE was similar in the two populations under consideration (674 pg/ml, 460-1076 pg/ml in patients with non-ischemic cardiomiopathy vs. 598 pg/ml, 432-949 pg/ml in patients with post-ischemic cardiomiopathy, p=ns).

The correlation analysis performed to evaluate which clinical-instrumental parameters were associated with plasma levels of sRAGE in CHF patients showed that LVEF significantly correlated with sRAGE plasma concentrations, both in the group of patients with ischemic or non-ischemic etiology (R=0.32; p<0.05) (Table 3 and Figure 1).

The population of patients with CHF was considered according to LVEF value and we identified 232 patients (60%) with LVEF ≥ al 30% (moderate systolic dysfunction) and 157 patients (40%) with LVEF<30% (severe left ventricular systolic dysfunction).

Higher prevalence of hypertension and a lower prevalence of dyslipidemia were found in patients with severe left ventricular systolic dysfunction. The plasma creatinine levels were on average higher in subjects with greater impairment in heart failure. Notably, there is a great difference in sRAGE mean value if we consider CHF patients with severe LV dysfunction (LVEF<30%) with respect to those with LVEF ≥ 30%. sRAGE plasma levels were significantly lower in patients with

	CHF patients n=389	CAD patients=319	P
Age, year	57 ± 10	64 ± 10	<0.01
Male, n%	326 (84%)	249 (78%)	<0.01
BMI, kg/m^2	24 ± 3	25 ± 3	Ns
Smoking, n%	175 (45%)	185 (58%)	<0.05
Hypertension, n%	245 (63%)	217 (68%)	<0.05
Dyslipidemia, n%	226 (58%)	265 (83%)	<0.01
Diabetes mellitus, n%	90 (23%)	102 (32%)	<0.01
Medical treatment			
Beta-blocker, n%	342 (87%)	239 (75%)	<0.01
ACE-inhibitor, n%	323 (83%)	169 (53%)	<0.01
Nitrates, n%	171 (43%)	182 (57%)	<0.01
Ca-antagonist, n%	74 (19%)	86 (27%)	<0.05
Diuretic, n%	319 (82%)	128 (40%)	<0.01
Statin, n%	198 (51%)	255 (80%)	<0.01
LVEF, %	35 ± 7	58 ± 5	<0.01
LVV, ml	198 ± 83	94 ± 58	<0.01
Total cholesterol, mg/dl	192 ± 43	189 ± 40	<0.05
HDL cholesterol, mg/dl	45 ± 13	48 ± 22	Ns
Triglycerides, mg/dl	149 ± 60	152 ± 54	Ns
Creatinin, mg/dl	1.6 ± 0.4	1.1 ± 0.5	<0.05
WBC, n/ul	8650 ± 1264	7468 ± 1456	Ns
Hemoglobin, g/l	11.2 ± 2.2	12.3 ± 2.5	Ns
sRAGE, ng/ml	659 (470-920)	950 (730-1200)	<0.05

CHF=Chronic Heart Failure; CAD=Coronary Artery Disease; LVEF=Left Ventricular Ejection Fraction; LVV=Left Ventricle Volume; WBC=White Blood Cells

Table 1: Characteristics of the study population.

	Non-ischemic CHF N=242	Post-ischemic CHF N=147	P
Age, year	54 ± 14	61 ± 10	<0.01
Male, n%	193 (80%)	133 (90%)	<0.01
BMI, kg/m^2	24 ± 12	23 ± 12	Ns
Smoking, n%	99 (41%)	76 (52%)	<0.05
Hypertension, n%	136 (56%)	109 (74%)	<0.05
Dyslipidemia, n%	119 (49%)	107 (72%)	<0.01
Diabetes mellitus, n%	44 (18%)	46 (31%)	<0.01
CAD extension			
1-Vessel, n%	/	40 (27%)	
2-Vessel, n%	/	46 (31%)	
3-Vessel, n%	/	61 (42%)	
LVEF, %	35 ± 6	36 ± 8	Ns
LVV, ml	187 ± 89	203 ± 92	Ns
Medical treatment			
Beta-blocker, n%	213 (87%)	129 (87%)	Ns
ACE-inhibitor, n%	191 (82%)	125 (85%)	Ns
Nitrates, n%	73 (30%)	98 (66%)	<0.01
Ca-antagonist, n%	29 (12%)	45 (31%)	<0.01
Diuretic, n%	48 (20%)	31 (21%)	Ns
Statin, n%	75 (31%)	123 (84%)	<0.01
Total cholesterol, mg/dl	198 ± 57	184 ± 56	<0.05
HDL cholesterol, mg/dl	48 ± 22	46 ± 23	Ns
Triglycerides, mg/dl	144 ± 60	156 ± 52	Ns
Creatinine, mg/dl	1.2 ± 0.4	1.9 ± 0.5	Ns
WBC, n/ul	7654 ± 1089	8543 ± 1875	Ns
Hemoglobin, g/l	13.4 ± 2.3	12.2 ± 2.9	Ns
BNP, pg/ml	330 ± 237	411 ± 187	Ns
sRAGE, ng/ml	674 (460-1076)	598 (432-949)	Ns

Table 2 Characteristics of post-ischemic CHF and non-ischemic CHF patients.

	All patients		Non-ischemic		Ischemic	
	R	P	R	p	R	p
Age	0.14	Ns	0.14	ns	0.04	Ns
Body mass index	0.03	Ns	0.03	ns	0.03	Ns
Cardiac frequency	-0.01	Ns	0.01	ns	0.03	Ns
Systolic pressure	-0.07	Ns	0.09	ns	-0.01	Ns
Diastolic pressure	-0.03	Ns	-0.05	ns	-0.04	Ns
LVEF	0.32	<0.05	0.38	<0.05	0.42	<0.05
Total cholesterol	-0.12	Ns	0.01	ns	-0.03	Ns
HDL cholesterol	-0.01	Ns	0.02	ns	-0.03	Ns
LDL cholesterol	-0.07	Ns	0.01	ns	-0.04	Ns
Triglycerides	-0.11	Ns	-0.01	ns	0.02	Ns
Creatinine	0.28	Ns	0.14	ns	0.06	Ns
Glycemia	0.06	Ns	0.06	ns	0.07	Ns
Hemoglobin	0.03	Ns	0.03	ns	0.08	Ns
WBC	-0.07	Ns	-0.07	ns	0.05	Ns
ALT	0.05		0.046	ns	0.023	Ns
AST	0.02		0.020	ns	-0.053	Ns

Table 3: Linear regression analysis to evaluate which clinical-instrumental parameters were associated with plasma levels of sRAGE in all patients and divided on the basis of presence of previous ischemic events.

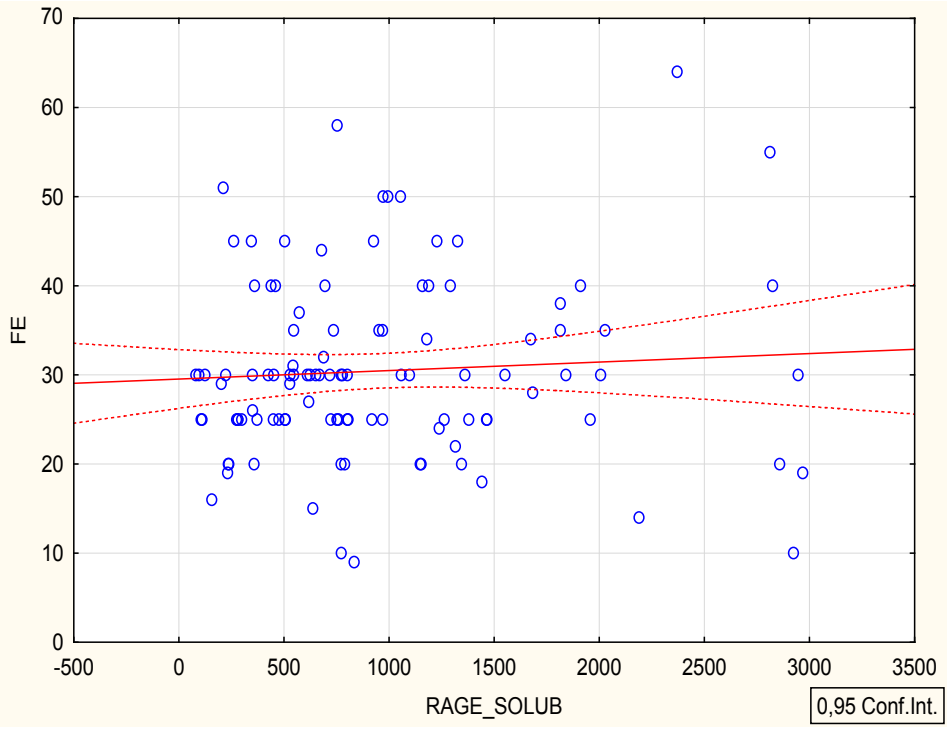

Figure 1: Scatter plot about correlation between sRAGE and LVEF in CHF patients.

severe left ventricular systolic dysfunction compared with those with LVEF ≥ 30% (580 pg/ml 356-780 pg/ml versus 690 pg/ml, 534-1143 pg/ml respectively, p<0.05).

The characteristics of the two populations are represented in Table 4.

Stepwise regression analysis show that levels of sRAGE remained related to the magnitude of left ventricular dysfunction, dichotomized the value of 30%, even after adjusting for clinical-instrumental parameter (p<0.01).

Discussion

In this study we set out to assess the plasma levels of sRAGE in a large population of patients with Chronic Heart Failure. Our data support the presence of a positive correlation between plasma sRAGE and LVEF in the CHF population: we demonstrated that in subjects with CHF and severe left ventricular systolic dysfunction (LVEF<30%), sRAGE plasma concentrations were lower than in patients with moderate left ventricular dysfunction. Reduced sRAGE levels were found as respect to patients with stable CAD. No significantly difference was found between patients with different etiology of CHF.

	LVEF ≥ 30% n=232	LVEF<30% n=157	p
Age, y	57 ± 10	57 ± 10	ns
Male, n%	189 (81%)	137 (86%)	ns
BMI, kg/m^2	24 ± 3	25 ± 3	ns
Smoking, n%	105 (45%)	70 (44%)	ns
Hypertension, n%	122 (53%)	123 (78%)	<0.01
Dyslipidemia, n%	144 (62%)	82 (52%)	<0.01
Diabetes, n%	49 (21%)	41 (26%)	ns
Medical treatment:			
Beta-blocker, n%	205 (88%)	137 (87%)	ns
ACE-inhibitor, n%	207 (89%)	116 (74%)	<0.01
Nitrates, n%	101 (44%)	70 (49%)	ns
Ca-antagonist, n%	49 (21%)	35 (16%)	<0.05
Diuretic, n%	189 (81%)	130 (83%)	ns
Statin, n%	120 (52%)	78 (50%)	ns
Total cholesterol, mg/dl	192 ± 48	193 ± 50	ns
HDL cholesterol, mg/dl	45 ± 13	45 ± 13	ns
Triglycerides, mg/dl	144 ± 64	155 ± 59	ns
Creatinine, mg/dl	1.4 ± 0.4	1.9 ± 0.7	<0.05
WBC, n/ul	7460 ± 1286	7845 ± 1326	ns
Hemoglobin, g/l	12.4 ± 2.4	11.1 ± 2.5	ns
sRAGE, ng/ml	690 (534-1143)	580 (356-780)	<0.05

Table 4: CHF population divided according to LVEF value (cutoff 30%).

The role of sRAGE in systemic and coronary atherosclerotic disease has been amply demonstrated both in animal and human studies [8,9]. We better define the role of sRAGE in humans: in our case-control study plasma sRAGE were lower in CAD patients compared to those without CAD [25]. These observations were subsequently confirmed by an analysis of the population of the "Dallas Heart Study" in which the presence of calcification in coronary arteries is inversely related to plasma sRAGE [26]. In addition, low levels of sRAGE have been found in patients with atherosclerotic disease with lower limb location as well as in patients with carotid intimal proliferation [27].

The current study extends the analysis of the role of sRAGE in patients with chronic heart failure. Our data suggest that in CHF population, the plasma concentrations of sRAGE are not significantly affected by the presence of post-ischemic etiology, but these levels seems to be correlated to myocardial dysfunction expressed by a severe reduction of LVEF.

In a prospective study Koyoama et al. concluded that sRAGE serum levels are related to worse prognosis of HF and to more severe clinical condition, specifically in relation to NYHA functional class and NT-proBNP levels [28]. In the current study, we extended these findings to show an association between sRAGE and LVEF.

The pathophysiological mechanism that would link low levels of sRAGE with the development of left ventricular dysfunction cannot be inferred from this study. However several observations would support a role of ligands of RAGE with the development of clinical syndrome characterized by heart failure. In the first instance a number of risk factors for HF such as age, diabetes mellitus, and renal failure are characterized by accumulation of AGE. This factor could induce the development of systolic and diastolic dysfunction of the left ventricle through the development of cross-links between intra-extracellular proteins such as elastin, laminin and collagen conformation changes affecting therefore ability to create changes in both structural and functional myocardial infarction [29]. AGEs are able to changing the properties of the extracellular matrix such as hydrophilicity and the turnover elasticity [30]. On the other hand the effects of AGEs in vascular endothelium is certainly a key element to accelerate the susceptibility to atherosclerotic lesions, thrombotic and an increase in left ventricular after load through increased rigidity of blood vessels.

In our population with severe left ventricular systolic dysfunction was observed a higher prevalence of hypertension and a lower prevalence of dyslipidemia. We previously demonstrates that plasma sRAGE levels are decreased in patients with essential hypertension and are inversely related to pulse pressure indicating the possibility that sRAGE may play a role in arterial stiffening and its complications [31]. The plasma creatinine levels were on average higher in subjects with greater impairment in heart failure. AGEs accumulate in patients with decreased renal function and through its receptor RAGE exert various toxic effects [27] and it has been demonstrated that serum sRAGE levels increase in patients with decrease renal function [32]. However, in our present study the correlation analysis, performed to evaluate which clinical-instrumental parameters were associated with plasma levels of sRAGE in CHF patients, showed that serum creatinine not correlated with sRAGE plasma concentrations, both in the group of patients with ischemic or non-ischemic etiology.

In this study we found significantly lower sRAGE plasma levels in CHF population in respect to CAD patient. We also found that the presence of previous CAD documentation are not a determining factor in influencing levels of sRAGE in patients with CHF. In fact patients with CHF and documented CAD had sRAGE concentrations similar to non ischemic CHF patients. The low levels of sRAGE in our population with CHF may reflect the greater severity of endothelial dysfunction, and therefore may not be independent of the extent of CAD. In addition, this hypothesis seems to be supported by the observation that levels of sRAGE showing a direct correlation with LVEF values.

The significant reductions in coronary flow reserve sometimes ascribed to disease of the microcirculation in patients with CHF, despite the angiographic evidence of coronary epicardial free, may justifying the similar levels of sRAGE in non-ischemic patients with respect to post-ischemic ones. These studies have assessed the coronary perfusion using the most modern techniques at our disposal, such as myocardial scintigraphy or MRI (Magnetic Resonance Imaging) [33-35].

In the interpretation of our data is necessary to consider a limitation: we measured in our population, only the share of total sRAGE, having used a detection system that cannot discriminate between specific splice variants of sRAGE. It should therefore be aware that decreased levels of sRAGE measured by this method could be due to a reduction of circulating sRAGE isoforms. The results of our research will also share the limitations of observational compared studies. Indeed, we have evaluated an association and not a causal relationship or predictability.

Further prospective studies in this direction will allow us to discriminate whether sRAGE is to be considered a marker of risk/disease or a real modulating factor. In this regard the studies of animal models would seem to attribute to sRAGE a direct role in altering the natural history of disease. If this hypothesis is confirmed in humans RAGE could become an important new therapeutic target in the prevention and treatment of coronary artery disease and heart failure.

In conclusion, lower sRAGE plasma levels may be expression of more severe ventricular dysfunction. It was hypothesized that sRAGE may be the next C reactive protein in CAD [36]; even more this study suggests the possibility that sRAGE can be considered a new element to be used in prognostic stratification of CHF population.

Because the results of the present study are consistent with a

role of RAGE in CHF patients with severe ventricular dysfunction, future studies are needed to further examine how levels of the soluble form of RAGE could influence endothelial dysfunction and vascular inflammation. Specifically, studies on the interrelationships between plasma sRAGE concentration and levels of inflammatory proteins such as CRP, TNF-alpha, IL-6 or NFkB.

Disclosure

The authors declare no conflict of interest.

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