

ORIGINAL INVESTIGATION

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# sRAGE and early signs of cardiac target organ damage in mild hypertensives

Andrea Maria Maresca<sup>1\*†</sup>, Luigina Guasti<sup>1†</sup>, Sara Bozzini<sup>2</sup>, Christian Mongiardi<sup>1</sup>, Nicolò Tandurella<sup>1</sup>, Rossana Corso<sup>1</sup>, Francesco G. Zerba<sup>2</sup>, Alessandro Squizzato<sup>1</sup>, Leonardo Campiotti<sup>1</sup>, Francesco Dentali<sup>1</sup>, Catherine Klersy<sup>3</sup>, Anna M. Grandi<sup>1</sup> and Colomba Falcone<sup>2,4</sup>

## Abstract

**Background:** Soluble Receptor for Advanced Glycation End Products (sRAGE) may be considered a marker inversely related to inflammation and its participation has been established in patients with advanced atherosclerotic vascular diseases. However, it is still unknown whether sRAGE reduction could be early metabolic change in the first stage of hypertension and initial hypertension-associated cardiac damage. We sought to determine the sRAGE values in otherwise healthy, untreated and recently diagnosed mild hypertensives and evaluate their association with blood pressure (BP) values, metabolic parameters, and with subclinical initial signs of cardiac target organ damage (TOD).

**Methods:** sRAGE were measured in 100 hypertensive and 100 normotensive subjects matched for age, gender and body mass index (BMI), submitted to a clinic visit and both ambulatory BP monitoring and echocardiography to determine the presence of initial cardiac TOD (presence of signs of left ventricular hypertrophy: left ventricular mass indexed for height<sup>2.7</sup> (LVMI) > 48 g/m<sup>2.7</sup> for men and > 44 g/m<sup>2.7</sup> for women and/or increased left atrial volume 4-chamber indexed for body surface area (LAVi) > 34 ml/m<sup>2</sup>).

**Results:** sRAGE levels were similar between hypertensive and normotensive subjects and were not significantly correlated with office and 24-h BPs values. However, when subgrouping the hypertensive patients in Hyp-TOD and Hyp-withoutTOD, sRAGE was found to be different among the three groups ( $p = 0.030$ ), being lower in the Hyp-TOD group than the values of both Hyp-withoutTOD ( $p = 0.038$ ) and normotensives ( $p = 0.038$ ). In hypertensive patients sRAGE was negatively related with both LVMI ( $r = -0.239$ ,  $p = 0.034$ ) and LAVi ( $r = -0.315$ ,  $p = 0.005$ ) and was independently related to cardiac TOD also in multivariable analysis.

**Conclusions:** In this population of mild hypertensives, low circulating sRAGE may be a very early marker of initial TOD, suggesting the possible participation of oxidative stress in initial cardiac changes in human hypertension.

**Keywords:** sRAGE, Inflammation, Oxidative stress, Mild hypertension, Cardiac target organ damage, Left ventricular mass index, Left atrial volume index

## Background

The interaction between Advanced Glycation End products (AGEs) with their cell-bound receptors (RAGE) results in oxidative stress-related stimuli and may contribute to vascular disease; indeed, this interaction leads to structural modification and functional alteration of the

extracellular matrix proteins, promote the generation of reactive oxygen species (ROS) and consequently activates mitogen-activated protein kinase (MAPK) and nuclear factor kappa-B (NF- $\kappa$ B) signaling, followed by production of several inflammatory and/or profibrotic factors which are involved in the progression of atherosclerosis [1].

sRAGE is found to be negatively associated with baseline inflammation [2] but its role in development of cardiovascular diseases and organ damage (OD) is still controversial.

\*Correspondence: andrea.maresca@uninsubria.it

<sup>†</sup>Andrea M. Maresca and Luigina Guasti contributed equally to the study

<sup>1</sup> Research Center on Dyslipidemia, Department of Medicine and Surgery, University of Insubria, Varese, Italy

Full list of author information is available at the end of the article



In previous studies, lower levels of sRAGE were found in metabolic disorders and vascular diseases (hypertension, coronary artery disease and peripheral artery disease) when compared to healthy controls [1–6]; conversely it has been reported that sRAGE are elevated in type 1 and type 2 diabetes, in patients with renal impairment [7] and were associated with incident events in a cardiovascular disease population [8].

Hypertension is one of the major risk factors in the development of atherosclerosis and vascular events including stroke, coronary artery disease and peripheral artery disease [9, 10]. Subclinical organ damage is detectable at cardiac site and various vascular districts focusing various parameters including coronary calcifications, carotid intima-media thickness, microalbuminuria, retinal vascular changes and is associated with increased cardiovascular risk in hypertension [11, 12]. In particular, the cardiac chamber morpho-functional changes are early signs of potentially evolving overt cardiac failure and atrial fibrillation and ultrasound evaluation allows to identify individuals at high risk due to presence of subclinical cardiac alterations in front of mild to moderate BP elevations [13].

The increasing emphasis on early prevention [9, 10] has prompted the need to focus on patient populations presenting at the early stages of hypertension. Despite the finding of altered sRAGE in high cardiovascular risk populations, there are very few data about the correlation between sRAGE and hypertension disease, in particular it has not been shown whether sRAGE may be reduced in the very early stage of hypertension-associated cardiac damage. Therefore, we sought to determine the sRAGE values in otherwise healthy patients with mildly increased blood pressure (BP) levels and, as a secondary endpoint, evaluate their association with both BP values and metabolic parameters, and with subclinical initial signs of cardiac target organ damage (TOD).

## Methods

We studied 100 consecutive hypertensive patients referred to our hypertension outpatient clinic (Department of Medicine and Surgery, University of Insubria, Varese, Italy) by general practitioners from October 2016 to September 2017, with office blood pressure  $\geq 140/90$  mmHg and 24-hour (24-h) ambulatory blood pressure monitoring (ABPM) values  $\geq 130/80$  mmHg [9]. Moreover, 100 subjects with BP  $< 140/90$  mmHg and 24-h ABPM values  $< 130/80$  mmHg were evaluated for a clinical check up and were matched for age, gender and BMI (to avoid possible confounding factors such as overweight and obesity) and enrolled in the study as normotensive controls. As for inclusion criteria, all the patients presented without overt cardiovascular diseases, diabetes and chronic

kidney disease, were not smokers and with no history of chronic obstructive pulmonary disease or obstructive sleep apnoea, and were never treated with antihypertensive drugs or statins. Subjects with office systolic BP  $> 160$  mmHg and/or diastolic BP  $> 100$  mmHg and/or body mass index (BMI)  $\geq 35$  kg/m<sup>2</sup>, subjects who did not show a good window for echocardiographic examination and patients with secondary forms of hypertension were excluded by this study.

All the subjects gave an informed consent to the study which was approved by the local Ethics Committee.

All the subjects underwent a clinic visit including clinical history, anthropometric parameters examination, BMI and waist circumference (cm). Metabolic syndrome was defined according to AHA criteria [14]. Office BP was considered the mean of at least three recordings taken at the time of first visit [9]. All the subjects were submitted to 24-h ABPM, to central BP evaluation, to an echocardiographic examination and to laboratory testing.

## ABPM

ABPM was performed on the non-dominant arm using the Spacelabs Healthcare 90207 (Issaquah, WA, USA). The device was programmed to obtain BP readings at 15-min intervals during the whole recording. The recording was then analyzed in order to obtain 24 h, daytime and night-time average systolic, diastolic blood pressure and heart rate. In 12 subjects the valid measurements were  $< 70\%$  and the subjects repeated the monitoring within 1 week. As for inclusion criteria, all hypertensive patients showed values  $> 130/80$  mmHg and normotensives showed values below 130/80 mmHg [9].

## Ultrasound examination

Every echocardiographic examination was performed by a single operator by Esaote My-Lab 30 CV ultrasound system (Esaote, Firenze, Italy) using a 2–4 MHz transducer. Examiner was blinded to the results of BP and blood tests. Left ventricle (LV) end-diastolic diameter (LVEDD), LV posterior wall thickness (PWT), and interventricular septum wall thickness (ISWT) were obtained by M-Mode analysis and LV end-diastolic volume (LVEDV) was determined according to the recommendations of the European Association of Echocardiography/American Society of Echocardiography [15]. Systolic function parameters such as ejection fraction (EF), mid-wall-fractional-shortening (MWFS) were estimated using the over cited recommendations. Relative wall thickness (RWT) was calculated and concentric geometry was defined as a RWT  $> 0.42$ . The left ventricular mass (LVM) was calculated [15] and indexed for body surface area (LVM/BSA) and for height<sup>2.7</sup>. LV hypertrophy was defined as left

ventricular mass index (LVMI:  $LVM/Height^{2.7}$ )  $> 48 \text{ g}/\text{m}^{2.7}$  for men and  $> 44 \text{ g}/\text{m}^{2.7}$  for women.

LV diastolic function analysis required information derived from trans-mitral and myocardial Tissue Doppler analysis (TDI). LV diastolic function analysis included the measurement of transmitral early diastolic peak flow velocity (E), the late diastolic flow velocity (A), their ratio (E/A). TDI was used to obtain the LV myocardial longitudinal velocities in the apical four-chamber view with a 2-mm sample volume placed on the basal segment of postero-septal, antero-lateral, inferior and anterior segment during diastole (E'/A'). The (E/E') ratio of the LV was determined using a mean of E' obtained between septal and lateral values [22]. Left Atrium diameter (LAD, mm) was measured using the modified Simpson's method. Maximum left atrium areas, except for the confluence of pulmonary veins and the left atrial appendage, were traced in apical 2- and 4-chamber (4C) views at end systole of the LV (LAV, ml). Left atrial volume-4 chamber-LAV-4C was indexed for body surface area (LAVi,  $\text{ml}/\text{m}^2$ ) and was left atrial volume was considered to be increased if  $LAVi > 34 \text{ ml}/\text{m}^2$ . The intraobserver and interobserver variabilities in our laboratory were 4% and 6%, respectively.

Cardiac TOD was defined as the presence of signs of left ventricular hypertrophy: (LVMI  $> 48 \text{ g}/\text{m}^{2.7}$  for men and  $> 44 \text{ g}/\text{m}^{2.7}$  for women) and/or increased left atrial volume ( $LAVi > 34 \text{ ml}/\text{m}^2$ ).

#### Routine laboratory examination

Every patient underwent blood and urinary tests including white blood cell and neutrophil count, C-reactive protein (CRP), lipid profile (total, low-density and high-density cholesterol, triglycerides), fasting glucose, microalbuminuria. The homeostasis model assessment of insulin resistance index (HOMA-IR) was calculated [16]. The glomerular filtration rate (GFR) was calculated according to the modification of diet in renal disease formula  $< 45 \text{ ml}/\text{min}/1.73 \text{ m}^2$  [17].

#### Laboratory examination of sRAGE

In patients and controls, blood samples were taken in ethylenediaminetetraacetic acid (EDTA) containing tubes after a 14-h overnight fasting for sRAGE quantification. Blood samples were centrifuged at 1000g for 30 min and immediately divided into aliquots. Plasma specimens were then frozen and stored at  $-20 \text{ }^\circ\text{C}$  until analysis (which were performed at the Molecular Medicine Research Center, University of Pavia, Pavia, Italy). Plasma sRAGE levels were determined using a commercially available enzyme-linked immunosorbent assay

kit (Quantikine; R&D systems) according to the manufacturer's protocol [14]. Briefly, a monoclonal antibody against sRAGE was used to capture sRAGE from plasma. Captured sRAGE was detected with a polyclonal anti-human sRAGE antibody. After washing, plates were incubated with streptavidin-HRP, developed with appropriate substrate, and OD450 was determined using an enzyme-linked immunosorbent assay plate reader. The intra-assay and inter-assay coefficients of variation values were  $< 6\%$  and  $< 8\%$ , respectively. Measurements were performed in duplicate and the results were averaged.

#### Statistical analysis

Statistical analysis was performed using the SPSS package for Windows (version 18, Chicago, Illinois, USA). Continuous variables were presented as mean  $\pm$  SD and were compared using *t* test for two independent samples as they showed a normal distribution. Differences in proportions were compared using the chi2-test. Pearson's correlation coefficient was used for determining the correlation between different parameters. In the case of non normal distribution of variables, data are reported as median and interquartile range (IQR) and comparisons were made using Mann-Whitney-U test and Spearman correlation analysis.

sRAGE were also evaluated according to the presence or absence of cardiac TOD in hypertensive patients, using ANOVA with LSD post hoc test. In hypertensives, a multivariable general linear regression model was fitted to investigate whether sRAGE was independently associated with subclinical cardiac TOD (LVMI and LAVi), while adjusting for 24-h BP parameters (24-h systolic BP), age, BMI, and HOMA-IR.

A 2-sided *p*-value of less than 0.05 was considered statistically significant.

#### Results

The hypertensive patients and normal subjects had similar age ( $45.5 \pm 6.3$  vs.  $45.5 \pm 6.0$ ,  $p = 0.767$ , respectively), sex distribution (male sex: 46% vs 38%,  $p = 0.315$ , respectively), BMI ( $25.9 \pm 4.2 \text{ kg}/\text{m}^2$  vs  $25.8 \pm 4.2 \text{ kg}/\text{m}^2$ ,  $p = 0.558$ , respectively) and waist circumferences (males:  $96.2 \pm 7.3 \text{ cm}$  vs  $93.3 \pm 8.8$ ,  $p = 0.140$ ; females:  $88.6 \pm 10.8$  vs  $89.5 \pm 11$ ,  $p = 0.666$ , in hypertensive and normotensive subjects, respectively). The metabolic syndrome was observed in 23% of hypertensive and 7% of normotensive subjects ( $p = 0.003$ ).

The office, 24-h BP values and arterial tonometry parameters are detailed in Table 1.

At standard laboratory findings, fasting glucose ( $93.7 \pm 10.2$  and  $94 \pm 9.1 \text{ mg}/\text{dl}$ , in hypertensives and normotensives, respectively;  $p = 0.846$ ) and GFR ( $81 \pm 12$  vs

**Table 1 Office, 24-h BP values and arterial tonometry parameters in hypertensive and normotensive subjects**

	Hypertensive patients (n = 100)	Normotensive subjects (n = 100)	p
Office SBP (mmHg)	136.5 ± 14.3	120.3 ± 9.6	< 0.001
Office DBP (mmHg)	89.1 ± 8.9	76.1 ± 7.1	< 0.001
Office PP (mmHg)	47.4 ± 8.6	44.2 ± 7.7	0.001
Office heart rate (beats/min)	72.8 ± 10.7	69.4 ± 10.1	0.012
24-h SBP (mmHg)	131.3 ± 7.9	116.9 ± 6.6	< 0.001
24-h DBP (mmHg)	85.3 ± 5.5	72.8 ± 5.1	< 0.001
24-h PP (mmHg)	46.0 ± 6.6	44.0 ± 5.6	0.004
Daytime SBP (mmHg)	136.9 ± 8.6	122.7 ± 7.4	< 0.001
Daytime DBP (mmHg)	90.5 ± 5.9	78.2 ± 5.8	< 0.001
Daytime PP (mmHg)	46.3 ± 6.8	44.4 ± 6.2	0.006
Nighttime SBP (mmHg)	120.9 ± 8.8	106.9 ± 7.7	< 0.001
Nighttime DBP (mmHg)	75.7 ± 7.3	63.6 ± 5.7	< 0.001
Nighttime PP (mmHg)	45.2 ± 6.7	43.3 ± 6.5	0.014
24-h HR (beats/min)	74.5 ± 8.7	71.1 ± 8.3	0.010
Daytime HR (beats/min)	79.3 ± 9.7	75.9 ± 9.3	0.023
Nighttime HR (beats/min)	66.5 ± 8.2	63.6 ± 7.8	0.020

SBP systolic blood pressure, DBP diastolic blood pressure, PP pulse pressure, HR heart rate

83.9 ± 12.4 ml/min/1.73 m<sup>2</sup> p = 0.479, in hypertensives and normotensives, respectively) were similar in the two groups whereas HOMA-IR [2.8 (1.5–4.9) vs 2.24 (1.1–3.36); p = 0.005] and microalbuminuria [0.8 (0.4–1.4) vs 0.6 (0.3–0.9); p = 0.008] were higher in hypertensive patients. The circulating white blood cells, lipid parameters (except for triglycerides) and CRP values did not differ between hypertensive and normotensive subjects (see Additional file 1: Table S1).

#### Echocardiographic parameters in hypertensive and normotensive subjects

Although the morphological and functional properties of left atrium and left ventricle were found within the normal ranges in most of mild hypertensive and normotensive subjects, the interventricular septum, posterior wall thickness and left ventricular mass indexed for BSA were increased in mild hypertensives, whereas the mid-wall-fractional-shortening and the E/A were reduced the hypertensive group; the left atrium parameters were similar between hypertensive and normotensive subjects. Echocardiographic parameters are detailed in Table 2.

When the hypertensive patients were subgrouped according to the presence (Hyp-TOD) or absence (Hyp-withoutTOD) of early signs of cardiac TOD, fifteen

**Table 2 Echocardiographic parameters in hypertensive and normotensive subjects**

	Hypertensive patients (n = 100)	Normotensive subjects (n = 100)	p
ISWT (mm)	10.0 ± 1.5	9.2 ± 1.3	0.001
PWT (mm)	8.8 ± 1.2	8.2 ± 1.5	0.001
LVEDD (mm)	45.5 ± 4.3	45.9 ± 4.8	0.440
LVEDV (ml)	94.4 ± 25.6	92.0 ± 27.0	0.698
LVM (g)	146.1 ± 38.4	133.1 ± 35.6	0.056
LVM/BSA (g/m <sup>2</sup> )	78.6 ± 15.5	72.9 ± 15.5	0.017
LVMi (g/m <sup>2.7</sup> )	35.0 ± 7.3	32.8 ± 7.4	0.065
RWT	0.40 ± 0.1	0.36 ± 0.1	< 0.001
EF (%)	63.1 ± 4.9	63.6 ± 5.3	0.984
MWFS	17.0 ± 3.7	19.5 ± 4.6	< 0.001
E/A	1.1 ± 0.3	1.3 ± 0.6	0.028
Septum E'/A'	0.9 ± 0.3	1.1 ± 0.4	< 0.001
Septum E/E'	7.2 ± 1.6	7.2 ± 5.6	0.993
Lateral E'/A'	1.3 ± 0.5	1.5 ± 0.5	0.094
Lateral E/E'	5.1 ± 1.4	5.1 ± 1.4	0.651
LAD (mm)	33.1 ± 4.1	33.2 ± 4.1	0.710
LAV 4C (ml)	40.4 ± 12.8	38.9 ± 13.7	0.479
LAVi (ml/m <sup>2</sup> )	21.9 ± 6.2	21.1 ± 6.9	0.507

ISWT interventricular septum wall thickness, PWT posterior wall thickness, LVEDD left ventricle end-diastolic diameter, LVEDV left ventricle end-diastolic volume, LVM left ventricle mass, LVM/BSA left ventricle mass indexed for body surface area, LVMi left ventricular mass index (i.e. LVM indexed for height: LVM/Height<sup>2.7</sup>), RWT relative wall thickness, EF ejection fraction, MWFS mid-wall-fractional-shortening, E transmittal early diastolic peak flow velocity, A late diastolic flow velocity and E' and A' are the parameters obtained by Tissue Doppler analysis, LAD left atrium diameter, LAV 4C left atrial volume-4 chamber, LAVi left atrial volume-4 chamber indexed for body surface area

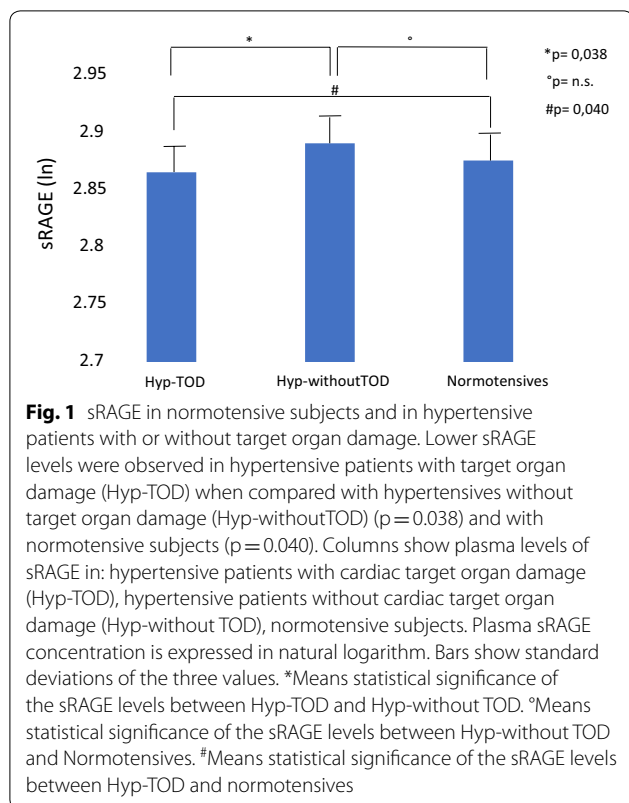
subjects showed left ventricular hypertrophy and/or left atrium enlargement. In particular, LVMi was in Hyp-TOD: 42.878 ± 9.456 g/m<sup>2.7</sup> vs. in Hyp-withoutTOD: 33.259 ± 5.733 g/m<sup>2.7</sup> (p = 0.002), and LAVi: 28.855 ml/m<sup>2</sup> vs. 20.632 ± 4.884 ml/m<sup>2</sup> (p < 0.001).

#### sRAGE in hypertensives with and without echocardiographic signs of subclinical TOD and normotensive subjects

sRAGE levels were similar between hypertensive and normotensive subjects (2.891 ± 0.259 ln-sRAGE vs 2.876 ± 0.263 ln-sRAGE p = 0.691, respectively). However, when subgrouping the hypertensive patients in Hyp-TOD and Hyp-withoutTOD, sRAGE was found to be different among the three groups (p = 0.030), being lower in the Hyp-TOD group than the values of both Hyp-withoutTOD (p = 0.038) and normotensives (p = 0.040) (Fig. 1).

sRAGE was not significantly correlated with office and 24-h BPs values (sRAGE and office BPs: r = 0.032, p = 0.768 and r = 0.019, p = 0.864 for systolic and diastolic BP, respectively; sRAGE and 24-h BPs: r = 0.028,





$p=0.794$  and  $r=0.048$ ,  $p=0.654$  for 24-h systolic and diastolic BPs, respectively). In hypertensives (Hyp-TOD + Hyp-withoutTOD), sRAGE was negatively related with both LVMi ( $r=-0.239$ ,  $p=0.034$ ) and LAVi ( $r=-0.315$ ,  $p=0.005$ ) (Fig. 2a, b, respectively).

In multivariable analysis, in hypertensive group (Hyp-TOD + Hyp-withoutTOD), when entering sRAGE as dependent variable, and subclinical cardiac TOD, 24-h systolic BP, mean age, BMI, and HOMA-IR as independent variables, a significant association was observed (model  $p$  for ANOVA  $p=0.019$ ,  $R=0.354$ ,  $R$  square = 0.100). The association was significant for TOD ( $\beta=-0.233$ ,  $p=0.04$ ) whereas the other variables did not fit the model (24-h systolic BP:  $\beta=-0.022$ ,  $p=0.844$ ; mean age:  $\beta=0.152$ ,  $p=0.197$ ; BMI:  $\beta=-0.050$ ,  $p=0.659$ ; and HOMA-IR:  $\beta=-0.188$ ,  $p=0.107$ ).

## Discussion

### Main results

To our knowledge this is the first study exploring the relationship between circulating sRAGE and subclinical cardiac TOD in otherwise healthy, untreated patients with a recent diagnosis of mild hypertension. As expected according to inclusion and exclusion criteria, mean morphological and functional parameters of left cardiac chambers were found within the normal

ranges in most of the patients in both the mild hypertensives and the normotensive subjects. Among the group of patients at the early stage of the hypertensive disease, fifteen patients showed early echographic signs of cardiac TOD, being LVMi and/or LAVi increased above the normal ranges. Although sRAGE were similar between mild hypertensives and normotensives, and not related to either office or 24-h BP values, when subgrouping the population of mild untreated hypertensives according to the presence or absence of TOD, reduced sRAGE levels were observed in the Hyper-TOD group with early alteration in cardiac parameters.

Although only fifteen patients had LVMi and/or LAVi increased above the normal ranges, the correlation between sRAGE and subclinical cardiac TOD was confirmed also in the multivariable analysis.

### sRAGE and hypertension organ damage (OD)

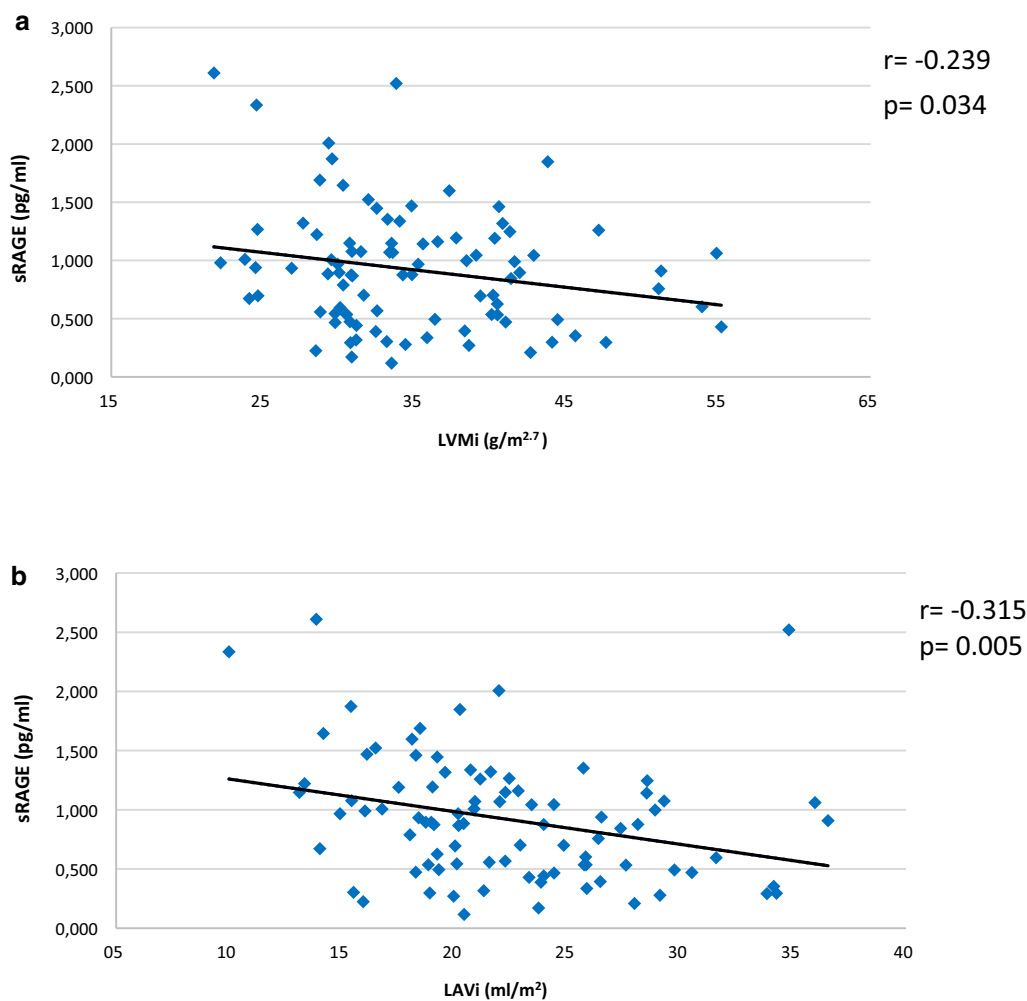
Our study report the association of sRAGE with very early left ventricle and left atrium modification, in a relatively young (with ages within a relatively narrow range) and otherwise healthy mild hypertensives, suggesting that decreased sRAGE levels may occur very early in the development of the hypertensive disease.

In literature there are no univocal results about the role of sRAGE in cardiovascular disease, beyond that the origin and progression of OD.

Previously, sRAGE decreased plasma levels were described in a population of hypertensive patients including severe stages of hypertension [5] and left ventricular hypertrophy (indexed for body surface area) correlated inversely with sRAGE in a group of long-lasting treated hypertensive disease [18]. As confounding factors, the latter study included older patients among the 81 presenting with left ventricular hypertrophy and a large percentage of patients with coronary artery disease [25]. A relationship between sRAGE and left ventricular hypertrophy was also reported in patients with chronic kidney disease with severely impaired GFR [19].

Decreased sRAGE levels were also found to be associated with high carotid intima-media thickness (IMT) of the common carotid artery and with carotid plaque calcifications in 284 subjects without history of atherosclerosis disease, suggesting a role of sRAGE in vascular inflammation and in early-stage atherosclerosis [20]. This hypothesis is supported by the evidence that sRAGE may be implicated in impaired glucose metabolism in patients with primary hypertension [21].

Conversely, Heier et al. showed in a 5 years follow up study a possible protective effect of high levels of sRAGE against inflammation but not for carotid atherosclerosis in a cohort of adolescents and young adults with diabetes type 1 [22]. Moreover, Paradelo-Dobarro et al. showed



**Fig. 2** Relationship between sRAGE and left ventricular mass index and left atrial volume index in hypertensives. Figure 2 shows, in the hypertensive group, the relationship between sRAGE and left ventricular mass index (LVMi) (left ventricular mass indexed for height-g/m<sup>2.7</sup>-) (a) and left atrial volume index (LAVi) (left atrial volume-4 chamber-indexed for body surface area-ml/m<sup>2</sup>-) (b)

that while AGEs and sRAGE are bad prognostic biomarkers for acute heart failure (HF), they serve as useful markers of HF progression, suggesting the role of the axis AGE-RAGE activation in cardiac organ damage [23].

#### sRAGE, oxidative stress and inflammation

Circulating sRAGE values have been negatively associated to inflammation in humans. Indeed, low sRAGE levels have been associated with elevated circulating inflammatory markers such as CRP and white blood cells in large patient populations [2, 4, 22].

Oxidative stress and autophagy were found to be related to both cardiac hypertrophy and heart failure in a distinct manner in animal models [24]. Myocyte hypertrophy induced in rats after pressure overload was the

result of autophagy impairment induced by oxidative stress [25]. Moreover AGEs can cause endothelial dysfunction via decreased endothelial nitric oxide synthase expression and increased oxidative stress in human coronary artery endothelial cells by activation of the mitogen-activated protein kinases p38 and ERK1/2 [26].

In our patients with newly diagnosed and mild stage of hypertension, the finding of sRAGE reduction in the subgroup of patients presenting with initial cardiac TOD, although the small number size, may supports the hypothesis that reduced sRAGE may be an early metabolic sign related to subclinical anatomical cardiac remodeling in hypertension, as a marker of increased oxidative stress, even though do not directly supported by our data.

Although sRAGE was not associated with incidence of atrial fibrillation in the AIRC study [2], it has been demonstrated that oxidative stress and inflammation may affect adverse atrial structural and electrical remodeling that lead to the onset and maintenance of atrial fibrillation [27] and high sRAGE were associated with favorable clinical outcome after catheter ablation in diabetic patients [28]. Moreover, when stratified according to glycated hemoglobin (HbA1c), patients with prediabetes (HbA1c 5.7% to 6.4%) exhibited subclinical atrial alterations associated with sRAGE [29].

It has been suggested in animal models that antioxidant treatment could have a role in prevention of early myocardial hypertrophy [25]. It is well known that drugs such as statins may interfere with the pro-inflammatory immune cell attitude through Angiotensin II AT1 receptor expression modulation [30–32] and statin have been shown to be associated with decreased incident atrial fibrillation episodes after cardioversion [33]. Moreover, various cardiovascular drugs may modify advanced-glycation-end-products and sRAGE levels [34, 35]. In our study no patients had suffered episodes of atrial fibrillation or was on therapy with anti-inflammatory drugs or antihypertensives or statins which could have influenced the oxidative status or morphofunctional atrial changes of the patients.

Therefore, in this patient population of untreated and mild, recently diagnosed hypertensive patients, low circulating sRAGE may be a very early marker of initial TOD.

## Additional file

**Additional file 1: Table S1.** Circulating white blood cells and lipid parameters in hypertensive and normotensive subjects.

## Abbreviations

A: late diastolic flow velocity; ABPM: ambulatory blood pressure monitoring; AHA: American Heart Association; BMI: body mass index; BP: blood pressure; BSA: body surface area; CRP: C-reactive protein; DBP: diastolic blood pressure; E: transmitral early diastolic peak flow velocity; EDTA: ethylenediaminetetraacetic acid; EF: ejection fraction; GFR: glomerular filtration rate; HbA1c: glycated hemoglobin; HDL: high density lipoprotein; HF: heart failure; HOMA-IR: homeostasis model assessment of insulin resistance index; HR: heart rate; IMT: intima-media thickness; IQR: interquartile range; ISWT: interventricular septum wall thickness; LAD: left atrium diameter; LAV: left atrial volume; LAVI: left atrial volume 4-chamber indexed for body surface area; LDL: low density lipoprotein; LVEDD: left ventricle end-diastolic diameter; LVEDV: left ventricle end-diastolic volume; LVH: left ventricular hypertrophy; LVM: left ventricular mass; LVMi: left ventricular mass index; MWFS: mid-wall-fractional-shortening; OD: organ damage; PP: pulse pressure; PWT: posterior wall thickness; RWT: relative wall thickness; SBP: systolic blood pressure; SD: standard deviation; sRAGE: soluble Receptor for Advanced Glycation End products; TD: tissue doppler analysis; TOD: target organ damage; 4C: 4-chamber.

## Authors' contributions

AMM, LG participated in coordination and study design, draft the manuscript, read and approved the final paper. AMM, CF, CM, NT, RC, FZ participated in study design, data collection and interpretation, draft the manuscript read and approved the final paper. AS, LC, FD participated in study design, draft the manuscript, read and approved the final paper. AMG participated in study design, data interpretation, read and approved the final paper. AMM, CK participated in data interpretation and performed statistical analysis of the final paper. All authors read and approved the final manuscript.

## Author details

<sup>1</sup> Research Center on Dyslipidemia, Department of Medicine and Surgery, University of Insubria, Varese, Italy. <sup>2</sup> Interdepartmental Center for Research in Molecular Medicine (CIRMC), University of Pavia, Pavia, Italy. <sup>3</sup> Clinical Epidemiology and Biometry, IRCCS Policlinico San Matteo, Pavia, Italy. <sup>4</sup> Department of Cardiology, Istituti Clinici di Pavia e Vigevano University Hospital, Pavia, Italy.

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Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Consent for publication

Not applicable.

## Ethics approval and consent to participate

Informed consent was obtained from all subjects and the study was approved by "Insubria" Ethics Committee.

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