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Effects of a recruitment maneuver on plasma levels of soluble RAGE in patients with diffuse acute respiratory distress syndrome: a prospective randomized crossover study

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Take-home message: The authors describe the first kinetics study of plasma sRAGE after a recruitment maneuver in ARDS. These findings support the value of sRAGE as a marker of short-term response to therapeutic interventions and reinforce sRAGE as a biomarker of ARDS.

Prior abstract publication/presentation: Partial results of this study were presented as an oral communication during the conference "Congrès de la Société de Réanimation de Langue Française" (2014) and during the annual congress of the European Society of Intensive Care Medicine (2014).

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Abstract *Purpose:* The soluble form of the receptor for advanced glycation end-products (sRAGE) is a promising marker for epithelial dysfunction, but it has not been fully characterized as a biomarker of acute respiratory distress syndrome (ARDS). Whether sRAGE could inform on the response to ventilator settings has been poorly investigated, and whether a recruitment maneuver (RM) may influence plasma sRAGE remains unknown. *Methods:* Twenty-four patients with moderate/severe, nonfocal ARDS were enrolled in this prospective monocentric crossover study and randomized into a "RM-SHAM" group when a 6-h-long RM sequence preceded a 6-h-long sham evaluation period, or a "SHAM-RM" group (inverted sequences). Protective ventilation was applied, and RM consisted of the application of 40 cmH_2O airway pressure for 40 s. Arterial blood was sampled for gas analyses and sRAGE measurements, 5 min pre-RM (or 40-s-long sham period), 5, 30 min, 1, 4, and 6 h after the RM (or 40-s-long sham period). *Results:* Mean PaO_2/FiO_2, tidal volume, PEEP, and plateau pressure were 125 mmHg, 6.8 ml/kg (ideal body weight), and 13 and 26 cmH_2O, respectively. Median baseline plasma sRAGE levels were 3,232 pg/ml. RM induced a significant decrease in sRAGE ($-1{,}598 \pm 859$ pg/ml) in 1 h ($p = 0.043$). At 4 and 6 h post-RM, sRAGE levels increased back toward baseline values. Pre-RM sRAGE was associated with RM-induced oxygenation improvement (AUC 0.84). *Conclusions:* We report the first kinetics study of plasma sRAGE after RM in ARDS. Our findings reinforce the value of plasma sRAGE as a biomarker of ARDS.

Keywords
Soluble receptor for advanced glycation end-products (sRAGE) · Recruitment maneuver · Acute respiratory distress syndrome · Biomarker

Introduction

Acute respiratory distress syndrome (ARDS), a major cause of respiratory failure and death in critically ill patients [1], is characterized by diffuse alveolar epithelial and lung endothelial injury leading to increased permeability pulmonary edema [2, 3]. Despite recent therapeutic advances [4–6], neither effective pharmacologic therapies nor fully characterized biomarkers have yet been identified [7–9].

A biomarker should have pathophysiological significance, provide a diagnosis, assess disease severity or risk, and guide clinical interventions [10, 11]. The receptor for advanced glycation end-products (RAGE), a member of the immunoglobulin superfamily, is a transmembrane receptor that can bind multiple ligands, e.g., advanced glycation end-products, high-mobility group box-1, and S100 proteins. RAGE–ligand interaction results in intracellular signaling, which leads to activation of the proinflammatory transcription factor nuclear factor-κB (NF-κB) [12]. This cellular activation is related to inflammatory processes or tissue injury, and RAGE is now recognized as a marker of alveolar type (AT) I cell injury [13, 14]. Elevated sRAGE levels during ARDS are not influenced by associated sepsis but correlate with diffuse CT scan damage and mortality in patients ventilated with high tidal volumes [15], and sRAGE levels are reported to decrease when PaO_2/FiO_2 increases during the resolution of ARDS [16]. The Berlin definition of ARDS does not include any specifications about the distribution of bilateral infiltrates [3]; however, the expert panel suggests that this area may deserve additional investigation [3]. In this perspective, measuring sRAGE might help to identify subgroups of ARDS patients with poor clinical outcomes [15, 16].

Whether sRAGE could help to tailor therapy or to predict response to therapy (e.g., ventilator settings) in patients with ARDS remains unknown, and few data are available to date on the influence of ventilator settings on plasma sRAGE during ARDS. In a retrospective analysis of patients enrolled in a randomized controlled trial [15], baseline plasma levels of sRAGE were associated with mortality in those receiving high tidal volumes [12 ml/kg ideal body weight (IBW)], supporting the hypothesis of a protective effect of lower volumes. As part of a lung-protective ventilation strategy, recruitment maneuvers (RM) can be applied to increase arterial oxygenation, net alveolar fluid clearance (AFC), and alveolar recruitment [17–20]. Lung morphology, as assessed by loss of aeration distribution patterns on CT scan, predicts the response to RM in ARDS, and patients presenting with nonfocal morphology are more likely to respond to RM [21]. To date, the kinetics of plasma sRAGE levels after RM have never been investigated in the clinical setting [22], and whether sRAGE may serve as a marker of the short-term response to ventilator settings (e.g., by predicting the response to RM with regard to oxygenation improvement after RM) remains unexplored.

We hypothesized that RM would result in decreased plasma sRAGE in ARDS. Our study was therefore designed to determine short-term effects of RM on plasma sRAGE in patients with diffuse ARDS, and to test sRAGE as a predictor of response to RM.

Partial results of this study were presented as an oral communication during the conference "Congrès National de la Société de Réanimation de Langue Française" (2014) [23] and during the annual congress of the European Society of Intensive Care Medicine (2014) [24].

Materials and methods

Setting

The protocol for this monocenter, single-blind, crossover randomized controlled trial was approved by our institutional review board (Comité de Protection des Personnes Sud Est VI, AU948). Next-of-kin written consent was obtained for all participants, followed whenever possible by patient consent as soon as they regained the capacity to provide it. There was no deviation from the approved protocol.

Patients

Patients were eligible if they were over 18 years old and admitted to the ICU within 24 h of moderate or severe ARDS onset, according to the Berlin definition [3]. ARDS criteria had to be simultaneously met within 1 week of a known clinical insult [3]. Only patients with diffuse (nonfocal) lung CT scan morphology were enrolled. Two independent radiologists performed the qualitative CT analysis according to the "CT scan ARDS study group" criteria [25–27]. Patterns of loss of aeration distribution were characterized, and nonfocal pattern was identified with diffuse or patchy loss of aeration [17].

Patients were ineligible if they had a history of allergy to cisatracurium, acute complications of diabetes due to severe hyperglycemia (diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic syndrome), dialysis for end-stage kidney disease, Alzheimer's disease, amyloidosis, evolutive solid neoplasm; intracranial hypertension, bronchopleural fistula, or pneumothorax was suspected or confirmed; they received long-term oxygen therapy or respiratory support for chronic respiratory disease; they had already received RM since ARDS diagnosis. Only patients with stabilizing hemodynamic status (defined as the absence of preload dependence and a recent trend for decreasing blood lactate levels and norepinephrine requirements) were eligible.

Interventions

Patients were assigned into two groups: a "RM-SHAM" group when an RM sequence preceded a sham evaluation period, and a "SHAM-RM" group, in which patients received a sham sequence first; each sequence was 6-h long and included a 2-h wash-out period (Fig. 1).

RM consisted of the application of 40 cmH_2O continuous positive airway pressure for 40 s [19] in patients under deep sedation and neuromuscular blockade by cisatracurium (intravenous bolus of 0.15 mg/kg followed by a continuous infusion of 37.5 mg/h, in both "RM-SHAM" and "SHAM-RM" groups).

All patients received lung-protective ventilation (see Electronic Supplementary Material). Fraction of inspired oxygen and positive end-expiratory pressure (PEEP) were maintained unchanged during the experimental period. Apart from the experimental procedures, intensive care management was conducted using standard protocols; weaning from mechanical ventilation, sepsis management, and the use of sedative agents were based on available guidelines [4, 28, 29].

Biologic sample collection and measurements

During both sequences, arterial blood was sampled from an indwelling catheter, 5 min before RM (or a 40-s-long sham period) and 5, 30 min, 1, 4, and 6 h after RM (or a 40-s-long sham period). Blood gases were immediately analyzed after sample collection. Other samples were centrifuged at $1{,}000 \times g$ for 15 min; supernatant was kept frozen at − 80 °C until analysis. Plasma levels of sRAGE were measured in duplicate using commercially available ELISA kits (R&D Systems, Minneapolis, MN). The personnel responsible for performing sRAGE assays had no knowledge of the clinical data and of the randomization group.

Study outcomes

The primary outcome was plasma levels of sRAGE, as measured 1 h after RM. Secondary outcomes included the kinetics of plasma sRAGE during the first 6 h after RM and the predictive value of baseline sRAGE on the response to RM (as defined, a priori, as a 20 % increase in PaO_2 1 h after RM [17]).

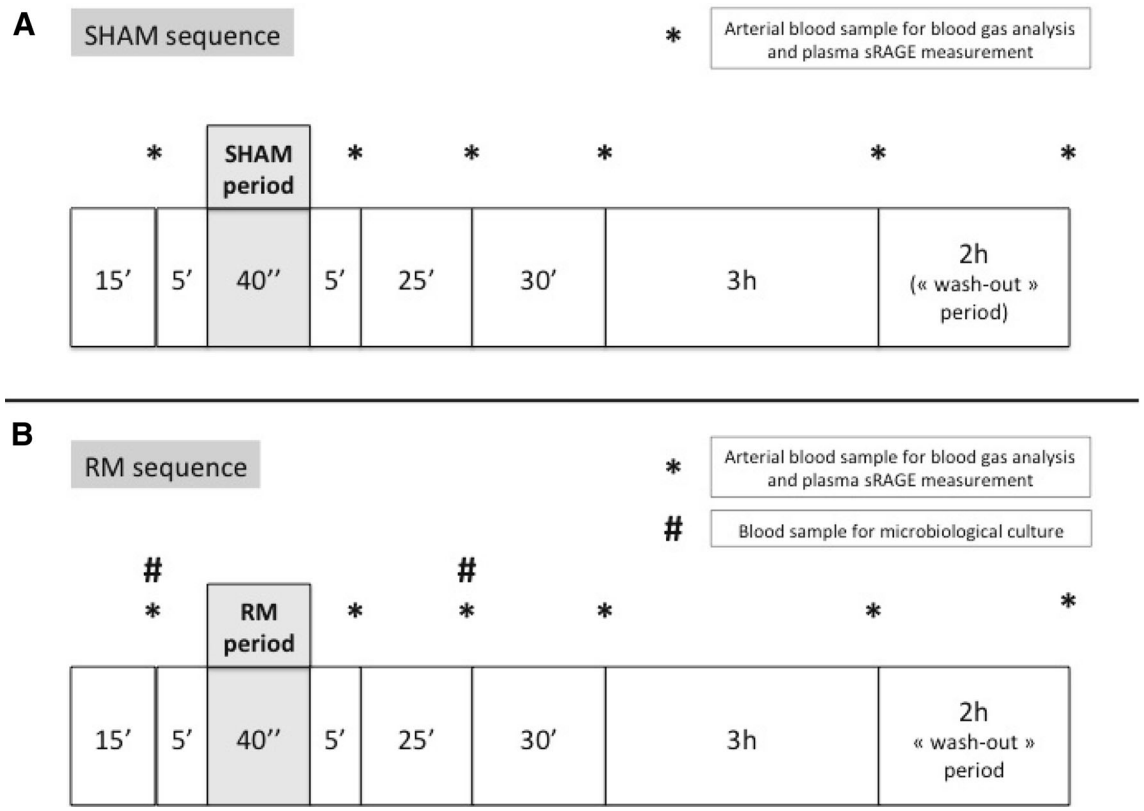

Fig. 1 Schematic representation of **a** sham sequence and **b** RM sequence. Depending on randomization results, patients underwent these sequences in different orders

Statistical analysis

All analyses were performed using Stata software (v13, StataCorp, College Station, TX). Qualitative data are expressed as numbers and percentages, and quantitative data as mean, standard deviation (SD) (or SEM for sRAGE for graph readability) or median and interquartile range (IQR). To compare baseline characteristics between groups, Student's *t* test or the Mann–Whitney test was considered for quantitative parameters according to *t* test hypotheses (normality assumption using the Shapiro–Wilk test and homoscedasticity with the Fisher–Snedecor test). Proportions were compared among groups using the Chi square test or Fisher's exact test. Considering a crossover design and repeated correlated data, a complete random-effects model was used to study the longitudinal evolution of sRAGE (aim analysis): (1) taking into account between- and within-subject variability (random subject effects: random intercept and slope), and (2) evaluating fixed effects: group, time-points evaluation, and their interaction,

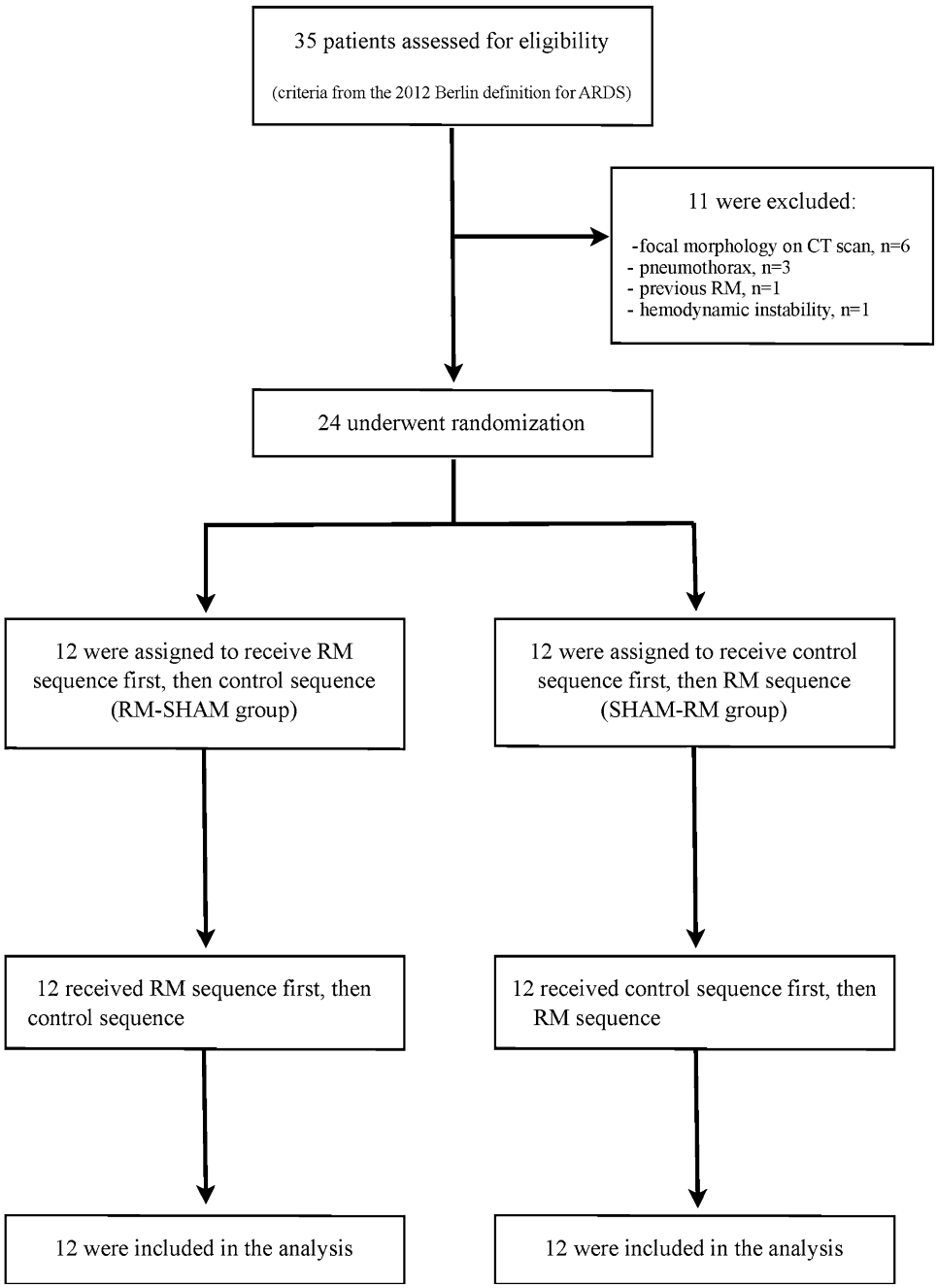

Fig. 2 Assessment, randomization, and follow-up of patients included in the DAMAGE study

period, treatment, sequence, and possible carryover. Residual normality was checked for all models. This analysis was completed by standard crossover statistical analyses with the pkcross routine in Stata. The default parameterization estimates overall mean, period effects, treatment effects, and sequence effects, assuming possible carryover effects. As sRAGE was not normally distributed, values were log-transformed in order to achieve normality and to allow the correct use of the statistical approach. Receiver-operating characteristic (ROC) curve was computed and area under the curve was used to evaluate how well the model distinguished non-response from response to RM. Confidence intervals (CIs) for areas under ROC curve were calculated using non-parametric assumptions. Several indexes were calculated (Youden, Liu, and efficiency) to propose the threshold value that optimized the sensitivity and the specificity of sRAGE to predict the response. The study of relations between quantitative parameters (sRAGE with outcomes) was improved by calculating correlation coefficients (Pearson or Spearman according to statistical distribution); $p < 0.05$ (two-sided) was considered statistically significant.

Only few data are available on the variability of sRAGE levels in critically ill patients [14–16], with standard deviations around 2,000 pg/ml. When considering alpha and beta risks of 5 % (bilateral) and 20 %, respectively, enrolling 12 patients in each group would allow the detection of a 1,700 pg/ml difference in sRAGE

Table 1 Baseline characteristics of the patients

Characteristic	Study population ($N = 24$)	RM-SHAM group ($N = 12$)	SHAM-RM group ($N = 12$)	p
Male sex, *n* (%)	17 (71)	8 (67)	9 (75)	1
Age (years)	56 ± 3	59 ± 5	54 ± 4	0.5
Body mass index (kg/m^2)	25.5 ± 1.5	26.1 ± 2	25 ± 2.4	0.7
SOFA	12.5 ± 3.6	12.1 ± 2.5	13 ± 4.5	1
APACHE II	26.8 ± 6.6	27.7 ± 5.3	26 ± 7.8	0.6
Lung injury score	3.2 ± 0.3	3.1 ± 0.4	3.2 ± 0.2	0.7
Coexisting conditions, *n* (%)				
Atherosclerosis	5 (21)	2 (17)	3 (25)	1
Hypertension	8 (33)	3 (25)	5 (42)	0.7
Any alcohol intake	3 (13)	2 (17)	1 (8)	0.5
Current smoking	4 (17)	1 (8)	3 (25)	0.6
COPD	4 (17)	3 (25)	1 (8)	0.6
Asthma	1 (4)	0 (0)	1 (8)	1
Hematologic neoplasms	5 (21)	2 (17)	3 (25)	1
Solid cancer	1 (4)	0 (0)	1 (8)	1
Dyslipidemia	2 (8)	0 (0)	2 (17)	0.5
Chronic renal failure	2 (8)	2 (17)	0 (0)	0.5
Diabetes	5 (21)	3 (25)	2 (17)	1
Associated conditions, *n* (%)				
Sepsis	23 (96)	12 (100)	11 (92)	1
Severe sepsis	18 (75)	10 (83)	8 (67)	0.6
Septic shock	14 (58)	7 (58)	7 (58)	1
SIRS	24 (100)	12 (100)	12 (100)	1
Severe trauma	1 (4)	1(8)	0	1
Pneumonia	20 (83)	10 (83)	10 (83)	1
Aspiration	4 (17)	1 (8)	3 (25)	0.6
Ongoing therapy, *n* (%)				
Statin	5 (21)	2 (17)	3 (25)	1
Cisatracurium	17 (71)	9 (75)	8 (67)	1
Corticosteroid	6 (25)	1 (8)	5 (42)	0.2
Enteral tube feeding	19 (79)	10 (83)	9 (75)	1
Biologic status				
CRP (mg/L), median [IQR]	138 [90–212]	156 [102–258]	138 [77–202]	0.5
PCT (μg/L), median [IQR]	4 [1–13]	4 [1–11]	3 [1–13]	0.9
Total proteins (g/L)	55 ± 9	55 ± 9	56 ± 9	0.9
Prealbumin (g/L)	1.1 ± 2.5	1.1 ± 1.4	0.1 ± 0.1	0.7
PINI, median [IQR]	69 [10–288]	133 [15–450]	50 [6–126]	0.2

Data are expressed as mean ± standard deviation, unless otherwise indicated. *p* values were calculated in order to detect differences between the two groups (RM-SHAM and SHAM-RM). The body mass index is the weight in kilograms divided by the square of the height in meters. Lung injury (or Murray) score can range from 0 to 4, with higher values indicating more severe lung injury. Percentages may not exactly total 100 % because of rounding

COPD chronic obstructive pulmonary disease, *SIRS* systemic inflammatory response syndrome, *CRP* C-reactive protein, *PCT* procalcitonin, *PINI* prognostic inflammatory and nutritional index, *SOFA* Sequential Organ Failure Assessment, *APACHE II* Acute Physiology and Chronic Health Evaluation II

levels (measured 1 h after RM) between groups for a null correlation coefficient, a 1,200 pg/ml difference for a 0.5 coefficient, and a 2,400 pg/ml difference at the end of the crossover period. If an interaction effect of the first period over the second one was observed, only results from the first period were considered.

Results

Study population

From June 2012 through October 2013, 35 patients with moderate to severe ARDS were assessed for eligibility, and 24 were included (Fig. 2). Data on the primary outcome were available for all. Pneumonia was the most common cause of ARDS. First plasma samples for the study were drawn a median of 1 [IQR 1, 2] day after ICU admission and a median of 18 [10, 22] h after intubation.

At baseline in the whole cohort ($N = 24$), mean (±SD) PaO_2/FiO_2 was 125 ± 38 mmHg, mean tidal volumes were 6.8 ± 0.9 ml/kg IBW, PEEP was 13.4 ± 3 cmH_2O and plateau pressure was 26 ± 4 cmH_2O. Baseline characteristics are reported in Table 1. No difference was found in baseline plasma sRAGE between patients receiving and those not receiving cisatracurium prior to randomization [3,597 (2,718, 4,501) pg/ml versus 3,636 (2,941, 10,070), respectively, $p = 0.55$]. There was no difference in baseline plasma sRAGE between patients receiving and those not receiving corticosteroids at randomization [3,603 (3,005, 6,431) versus 3,583 (2,715, 4,837) pg/ml, respectively, $p = 0.96$].

Kinetics of plasma sRAGE after RM

Baseline plasma sRAGE levels, as measured 5 min before RM or sham period depending on treatment order, were 3,551 [2,866, 4,765] and 3,203 [2,650, 3,661], respectively ($p = 0.15$).

Longitudinal data analysis based on a mixed statistical model confirmed a significant decrease in plasma sRAGE 1 h after RM [−1,545 (−1,931, −1,029), $p = 0.049$] (Fig. 3). Figure 3 summarizes the evolution of mean plasma sRAGE levels during both sequences; all measured sRAGE concentrations are reported in Table 2 (Electronic Supplementary Material). A "time" effect was found in the evolution of sRAGE levels ($p = 0.001$): the decrease in sRAGE was more pronounced when RM was applied during the first sequence, but the decrease after RM was significant in both first ($p = 0.015$) and second ($p = 0.01$) sequences.

Oxygenation and respiratory parameters and their variation in both sequences are summarized in Table 3 (Electronic Supplementary Material); no difference was found between the two sequences, apart from lower inspiratory plateau pressure 5 min after RM as compared with sham sequence. No change in mean arterial pressure or in norepinephrine dose over time was found to be significant in our study ($p = 0.11$ and 0.9, respectively),

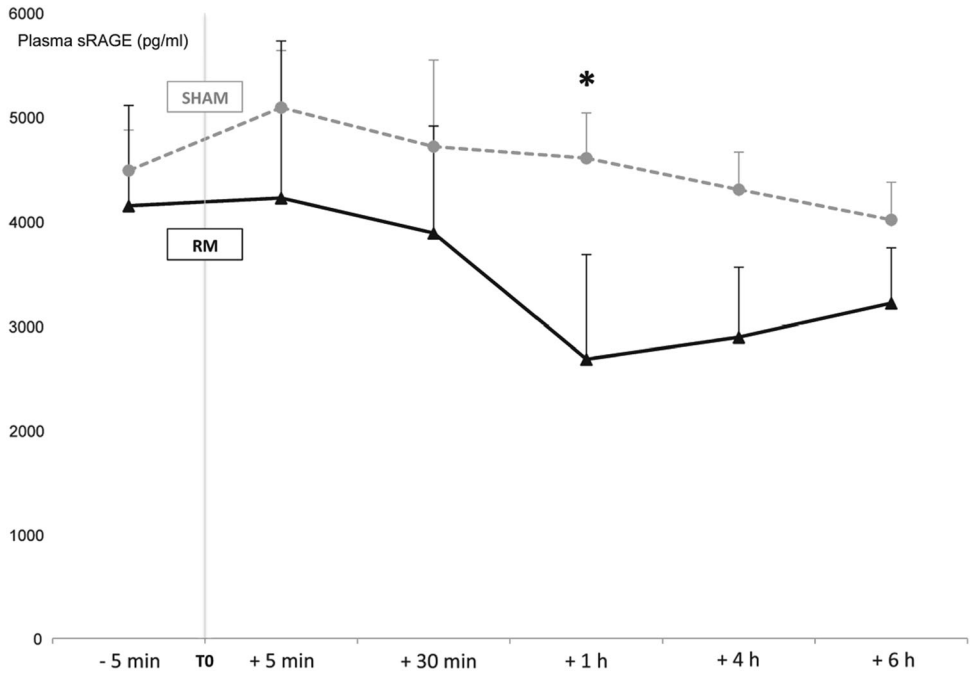

Fig. 3 Mean values ± standard error of the mean (SEM) for plasma levels of sRAGE (in pg/ml) at study timepoints in both randomization sequences. Time is expressed with regards to the application of the 40-s-long recruitment maneuver (RM) or the equivalent sham period (defined as T0). *$p < 0.05$

Baseline plasma sRAGE and response to RM

A total of eight patients responded to RM, i.e., had a 20 % improvement in PaO_2 1 h after RM (Fig. 4a). The area under the ROC when baseline plasma sRAGE was used to differentiate response from non-response to RM was 0.84 (95 % confidence interval 0.66–1) (Fig. 4b). A cut-off value of 4,501 pg/ml had a sensitivity of 83 % (95 % CI 36–99) and a specificity of 83 % (95 % CI 59–96).

Patient outcome

No significant correlation was found between plasma sRAGE as measured at baseline and main patient outcomes, except between baseline sRAGE (but not post-RM sRAGE) and the number of ventilator-free days at day 28 (Spearman's rank correlation coefficient $\rho = 0.4$; $p = 0.03$) (Table 4, Electronic Supplementary Material). Correlations between patient outcome and "delta" sRAGE (defined as the difference between plasma sRAGE as measured 1 h after RM and plasma sRAGE as measured before RM) were not statistically significant (Table 4, Electronic Supplementary Material).

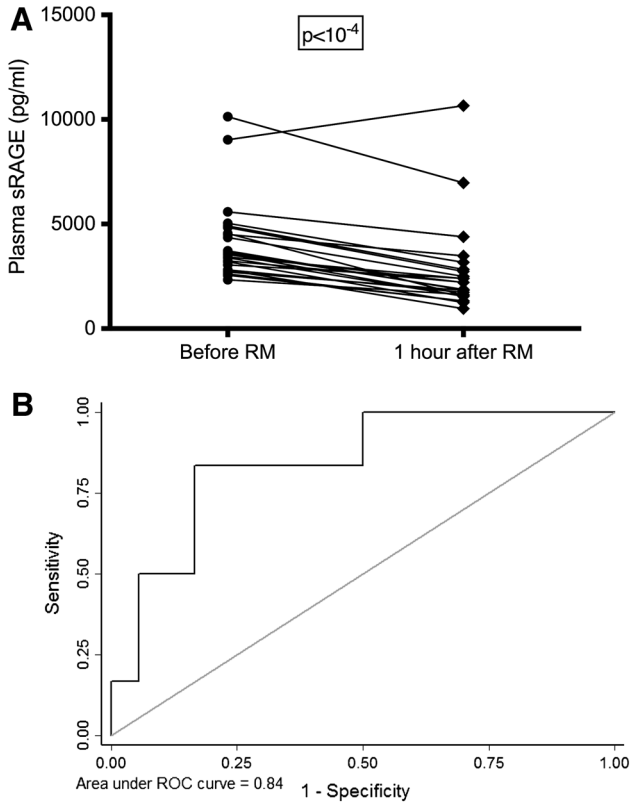

Fig. 4 **a** Individual values of plasma sRAGE (pg/ml), as measured before and 1 h after the recruitment maneuver (RM). **b** Receiver-operating characteristic curve of baseline plasma sRAGE levels in differentiating between the response and the absence of response to a recruitment maneuver. The area under the receiver-operating characteristic curve was 0.84 (95 % CI 0.66–1) for a cut-off value of 4,501 pg/ml, with a sensitivity of 83 % (95 % CI 36–99) and a specificity of 83 % (95 % CI 59–96)

Discussion

We report here the kinetics of RM-induced changes in plasma sRAGE, a marker of AT I cell injury [13, 14]. A significant but transient decrease in sRAGE was observed in patients with diffuse ARDS, and baseline sRAGE was associated with response to RM.

In our study, RM has a significant biological impact, with rapid and transient decrease in plasma sRAGE. Previous studies raised the question of RM-induced exacerbation of epithelial [30, 31] and endothelial [32] injury, increasing alveolar-capillary permeability in non-responders [17]. Furthermore, if RM is applied to an inhomogeneous lung parenchyma, its deleterious effects may be amplified, predisposing alveolar cells to deformation during lung distension and causing nonphysiological stress and strain [33]. Our results could be in contradiction with previous data [30, 31], but whether RM-induced fall in sRAGE could reflect a beneficial epithelial effect of RM remains uncertain, and our findings warrant further investigation.

Our measurements support the hypothesis of a rapid but transient decrease in sRAGE release from the alveolar structure to the systemic circulation after RM. The extrapolation of such findings to pathophysiological hypotheses remains hazardous. Multiple mechanisms seem implicated in sRAGE expression but they remain underinvestigated to date. In a recent experimental study in a rat model of endotoxin-induced lung injury, higher RAGE mRNA levels were rapidly induced after RM as compared to controls [22]. These results are not incompatible with ours. As a matter of fact, RAGE mRNA participates in the expression of full-length RAGE but sRAGE expression implicates additional complex regulation by proteases [34]. Such a regulation could be influenced by the accumulation of various RAGE ligands and oxidative stress [34–37], resulting in high expression of full-length RAGE. Thus, less cleavage of full-length RAGE by proteases could explain, at least in part, a decrease in sRAGE levels in our study. Unfortunately, the respective effects on plasma sRAGE of the type, the abruptness, and the duration of the RM were beyond the scope of our study [22].

The response to RM was defined a priori by an increase in PaO_2 as measured 1 h after RM [17], and a cut-off value of 4,501 pg/ml predicted response to RM with good sensitivity and specificity. This finding is compatible with previous results, in particular with a cut-off value of plasma sRAGE that could distinguish between nonfocal and diffuse lung morphology in ARDS [16]. In

our study, few patients responded to RM, i.e., improved their oxygenation with RM, but a decrease in plasma sRAGE was observed almost in all (23 out of 24 patients) (Fig. 4a). In an ex vivo model of isolated perfused human lung, alveolar sRAGE was inversely associated with AFC rate [38]. If sRAGE reflects AFC, then the effect of RM on sRAGE could provide indirect information on AFC, even in cases of unchanged PaO_2/FiO_2 [19]. The measurable oxygenation benefit of RM may be mainly dependent on the pressure level required to reverse atelectasis [19]. An RM-induced increase in regional AFC may simply mean that regional alveolar edema is reduced as fluid is "pushed out" from the alveoli during RM application. If RM pressure level is not high enough to simultaneously reverse atelectasis, the resulting change in oxygenation may be minor. However, there would still be a regional, RM-associated benefit with respect to AFC, which may be measurable through the change in sRAGE.

Our study has limitations. First, this was a relatively small, single-center study, partly due to protocol complexity. Second, as there was no change in PEEP levels during the whole study period, and because few data only are available to date in the existing literature [15], how PEEP levels influence plasma sRAGE remains to be investigated. In addition, whether this response is associated or not with effective alveolar recruitment or changes in systemic inflammation was not investigated in our study. Next, although results at baseline are consistent with the absence of a corticosteroid or cisatracurium effect on plasma sRAGE, future studies are needed to investigate this specific issue. Also, we cannot exclude that a transient RM-induced decrease in pulmonary blood flow could result in decreased sRAGE release from the lung. Finally, AFC evaluation relies on edema fluid aspirates with assessment of differences in total protein levels over time [17, 39]. As this measurement would have hampered the expected beneficial effects of RM by causing alveolar de-recruitment, it was not assessed in our study.

Our findings add to the growing body of evidence supporting sRAGE as a biomarker during ARDS and represent one more step toward better characterizing sRAGE as a tool to tailor ventilation in ARDS [21]. Whether monitoring plasma sRAGE could be beneficial in the management of ARDS patients by reflecting lung response to therapy (e.g., ventilator strategy) remains unknown, but is currently under investigation in a large randomized controlled trial of lung imaging for ventilator setting in ARDS [40].

In conclusion, we report the first kinetics study of plasma levels of sRAGE after RM in ARDS. Plasma sRAGE decreased significantly 1 h after RM before evolving toward its baseline levels between 4 and 6 h, and baseline sRAGE was associated with response to RM, i.e., improved oxygenation. Our findings reinforce the value of plasma sRAGE as a biomarker of ARDS, and they may stimulate more research on the assessment and validation of sRAGE as a surrogate marker of response to clinical interventions during ARDS.

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