ORIGINAL ARTICLE

Time course of endogenous nitric oxide inhibitors in severe sepsis in humans

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ABSTRACT

Aim. Asymmetric and symmetric dimethylarginines (ADMA and SDMA, respectively) are protein breakdown markers; both compete with arginine for cellular transport and both are excreted in urine. Moreover, ADMA is a non-selective inhibitor of nitric oxide (NO) synthase that is metabolized by a specific hydrolase in which the activity during stress remains controversial. While an increase in ADMA is known to be associated with adverse events, little is known about SDMA. We investigated plasma ADMA and SDMA levels during ICU stay to reveal the time course of endogenous NO inhibition in patients with sepsis.

Methods. A post hoc analysis from a prospective random controlled trial conducted in three ICUs was performed to study the pathophysiological pathways of sepsis. ADMA, SDMA, the ratio of ADMA/SDMA (a marker of ADMA catabolism), arginine, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C reactive protein (CRP) were measured on days 1, 3, 6, 9, 12 and at discharge in 72 consecutive severely septic patients.

Results. Fasting basal glycemia, creatinine, IL-6, TNF-α, CRP, ADMA, and SDMA were higher than normal. The ADMA/SDMA ratio was decreased by 50%, and arginine levels were low. ADMA levels were related to the total Sequential Organ Failure Assessment (SOFA) scores and arginine levels, and inversely related to IL-6 and CRP levels. SDMA levels were related to Simplified Acute Physiologic Scores II (SAPS II), SOFA scores, blood urea, creatinine, and arginine levels. The ADMA/SDMA ratio was inversely related to IL-6 levels. In 58 ICU survivors, creatinine, IL-6, and CRP levels decreased over time; ADMA levels increased, SDMA levels remained stable, and the ADMA/SDMA ratio increased. In 14 non-survivors, creatinine, IL-6, TNF-α, CRP, and ADMA levels were stable, whereas the SDMA levels increased and the ADMA/SDMA ratio remained low. In both ICU survivors and non-survivors, the levels on the last ICU day confirmed the data trends. SDMA, but not ADMA, was associated with ICU mortality.

Conclusion. ADMA catabolism appears to be activated by inflammation; its increase during the advanced septic phase in surviving patients may suggest an endogenous inhibition of NO synthesis during the full-blown septic phase. In severe sepsis, SDMA, but not ADMA, appears to be a marker of alterations in vital functions and mortality.

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Key words: Sepsis - Nitric oxide - Critical illness.

Symmetric and asymmetric dimethylarginines (SDMA and ADMA, respectively) are synthesized during the methylation of protein arginine residues in a process catalyzed by the protein arginine methyltransferase I (ADMA) and II (SDMA).[1] ADMA and SDMA are released for proteolytic degradation during physiological protein turnover.[1, 2] Both are eliminated by renal excretion,[3] but the main metabolic route for ADMA is decomposition to citrulline and dimethylamine

in a reaction catalyzed by dimethylarginine dimethylaminohydrolase (DDAH). DDAH is highly expressed in the liver, kidney, pancreas and endothelial cells. Under normal conditions, their plasma levels are similar.

Dimethylarginines may interfere with nitric oxide (NO) synthesis by competing with arginine for cationic amino acid transporters of the y+ system.[4] ADMA is also an endogenous nonselective inhibitor of endothelial and inducible NO synthase.[5-7] Increased catabolism combined with renal and hepatic dysfunction cause increases in ADMA (and SDMA) levels, which may result in decreased NO production.[8-11]

Clinical evidence suggests that a high ADMA level is a predictor of adverse outcomes in critically ill patients,[1, 8-10] surgical patients,[11] end-stage renal disease,[12] coronary heart disease,[13, 14] and idiopathic pulmonary arterial hypertension.[15] Interestingly, the administration of NG-monomethylarginine, a pharmacological nonspecific NO synthase inhibitor analogous to ADMA, increased mortality rates in septic patients,[16] indicating an adverse effect of nonselective NO inhibition. Moreover, stress and related factors, *e.g.*, cytokines and hyperglycemia, affect DDAH activity in a manner that remains controversial.[17-19, 20] It is of interest to clarify the endogenous regulation of anti-NO synthesis in sepsis.

Few data are available on the plasma variations of dimethylarginines during the clinical course of stressed patients. To the best of our knowledge, ADMA has only been measured at admission and either on day 7 [10] or the second, seventh, and the last day in the ICU, and only a single study [8] has measured the role of SDMA in these patients. Here, we investigated if the time course of plasma ADMA and SDMA concentrations could offer insight on the endogenous modulation of NO synthesis during the favorable or adverse clinical course of patients with severe sepsis and septic shock. We particularly focused on the interplay between the metabolic pathways of cytokines and dimethylarginines, aiming to verify if, as recently described for laboratory animals [20] and less severe patients,[19] cytokines would induce the elimination of dimethylarginines and have an effect on the degree of inhibition of NO synthesis during early and late phases of sepsis.

Materials and methods

The results presented in this paper originate from a post hoc analysis of data collected between December 2004 and March 2007 from three Italian university hospital intensive care units (ICUs). All data were collected during a randomized controlled clinical trial (RCT) that had investigated whether prevention of hyperglycemia affected some metabolic pathways involved in the pathophysiology of severe sepsis and septic shock (namely the coagulation- fibrinolysis system [21, 22] and the NO pathway).[23] The results of this RCT have already been published.[21-23]

This study was approved by the institutional review boards of each hospital. Written informed consent was obtained from each subject before enrollment or was delayed until recovery if one was unable to express her/his will due to his/her condition.

Study population: Consecutively admitted patients were enrolled if they met the criteria for severe sepsis.[24] Exclusion criteria were as follows: 1) age younger than 16 years; 2) hematological malignancies or bone marrow transplantation; 3) diabetes; and 4) likelihood of early death because of the underlying disease. In a previous paper [23] and in the present analysis, we excluded patients with artificial renal support or with only basal dimethylarginines assays. Because we found no effects of tight glycemic control on clinical and all relevant biochemical variables (except for blood glucose), or in ADMA [23] and SDMA [25] (see ESM) plasma levels during the ICU stay, we pooled data of the two glucose strategies. As a part of the intensive care, parenteral/enteral/mixed nutrition (25 kcal/kg ideal body weight) was given as soon as it was tolerated.

Measurements: The demographic and clinical details of all patients were recorded at baseline, including severity of illness, using the Simplified Acute Physiologic Score II [26] (SAPS II), and morbidity, using the Sequential Organ Failure Assessment score [27] (SOFA). The SOFA score was also determined at each sampling time. Blood was sampled [23] for glucose (measured every 4 hours or more frequently when indicated), creatinine, ADMA, SDMA, arginine, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP) levels were measured immediately

after enrollment (D0-fasting) and on the third (D3), sixth (D6), ninth (D9), twelfth (D12) and on the last ICU day (Last). Plasma arginine, ADMA and SDMA levels were determined by employing high-performance liquid chromatography (HPLC) as previously described.[23, 28] The reference levels [28] in 77 healthy volunteers (38 male, age 41±16 years, creatinine 0.76±0.13 mg/100 mL) were: arginine 77.2±1.0 μmol/L, ADMA 0.46±0.13, SDMA 0.41±0.09, and ADMA/SDMA ratio 1.19±0.38. According to the reference ratio, at any level of dimethylarginine appearance and renal function, an increase/decrease of ADMA with respect to plasma SDMA level could indicate lower or higher activity of DDAH.[5, 19] Thus, we used the ADMA/SDMA ratio as a rough indicator of ADMA metabolism.

Fasting basal levels were compared to normal values. We determined the relationship between D0-D12 dimethylarginine levels and the pre-existing comorbidities, diagnosis, SAPS II, daily SOFA scores, sepsis status and blood parameters (mean daily glucose concentration, creatinine, urea, bilirubin, platelets, white blood cells, pH, arginine, IL-6, TNF-α, and CRP levels). Finally, we investigated whether dimethylarginine levels were related to ICU mortality.

Statistical analysis

To assess the differences in each variable over time and their determinants, we used a linear mixed model for repeated measures based on each single patient. Non-normally distributed variables were log-transformed for the analysis. The model took into account the effect of time as a within-subject factor, with centers and the center-patients interaction fitted as random to correct for differences in the size of the treatment effect across centers. In addition, we used Student's t-test or the Mann-Whitney U test as needed to assess differences between groups, and the chi-square test was used to compare categorical data. To assess the determinants of ICU mortality, we used a logistic regression for basal values and a linear mixed model for D0-D12 values. In both cases, we report the odds ratios (OR) and their 95% confidence intervals (CI). We considered $P<0.05$ as statistically significant. Statistical analysis was done using Stata Statistical Software, release 9.2 (Stata Corporation,

TABLE I.—*Demographics, clinical characteristics and the fasting profile of biochemical markers at ICU admission.*

Male sex - No. (%)	47 (65.2)
Age - yr	62.2±14.3
BMI - kg/m^2	26.2±6.0
IBW - kg	63.7±7.5
ICU Admission type - No. (%)	
Medical	46 (66.6)
Surgical Unscheduled	21 (30.4)
Surgical Scheduled	2 (2.9)
Infection site - No. (% of patients)	
Pulmonary	35 (48.6)
Abdominal	18 (25.0)
Urinary tract	10 (13.8)
Others	17 (23.6)
Severe Sepsis - No. (%)	14 (19.4)
Septic Shock - No. (%)	58 (80.5)
SAPS II score - points	41.7±13.3
SOFA score - points	8.9±3.1
SOFA score (organ system > 3 points)	
Respiratory Failure - no (%)	43 (59.7)
Coagulation Failure - no (%)	11 (15.2)
Hepatic Failure - no (%)	6 (8.3)
Cardiovascular Failure - no (%)	53 (73.6)
Neurological Failure - no (%)	3 (4.2)
Renal Failure - no (%)	3 (4.2)
Blood glucose - mg/dL	144.6±41.0
Creatinine - mg/dL	2.1±1.7
Arginine - μmol/L (Norm: 55-95)	61.3 [45.8-80.9]
IL-6 - pg/mL (Norm: 0.19-12.00)	234.2 [62.3-449.8]
TNF-α - pg/mL (Norm: 3.75-18.25)	39.6 [16.7-94.5]
CRP - μg/mL (Norm: 0.15-6.55)	162.4 [110.0-228.3]
ADMA - μmol/L (Norm: 0.33-0.59)	0.96±0.41
SDMA - μmol/L (Norm: 0.31-0.49)	2.05±1.09
ADMA/SDMA (Norm: 0.89-1.42)	0.54±0.23

Values are presented as mean±SD or median [interquartile range]. BMI: Body-Mass Index; IBW: ideal body weight; ICU: intensive care unit; SAPS II: simplified acute physiological score; SOFA: sepsis-related organ failure assessment; IL-6: interleukin-6; TNF-·: tumor necrosis factor-·; CRP: C-reactive protein; ADMA: asymmetric dimethylarginine; SDMA: symmetric dimethylarginine; Norm: normal range.

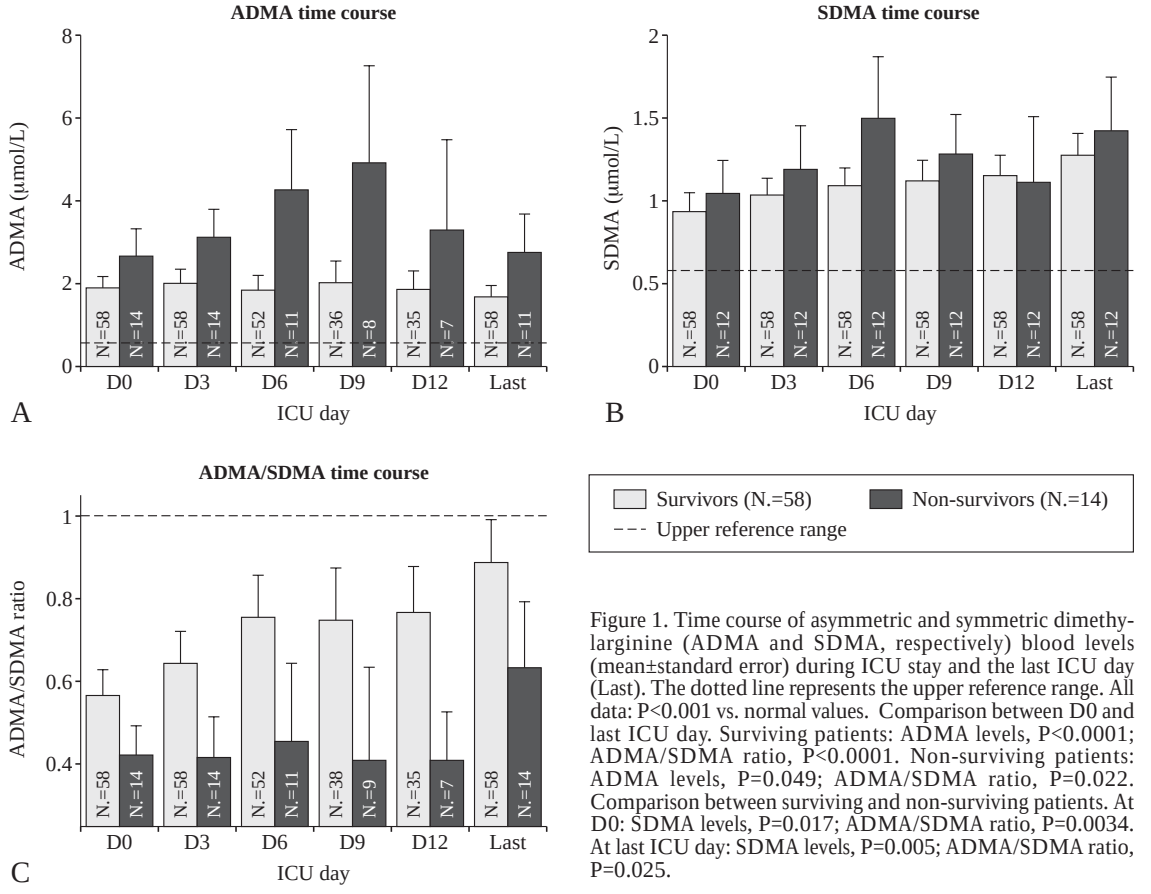

Figure 1. Time course of asymmetric and symmetric dimethylarginine (ADMA and SDMA, respectively) blood levels (mean±standard error) during ICU stay and the last ICU day (Last). The dotted line represents the upper reference range. All data: P<0.001 vs. normal values. Comparison between D0 and last ICU day. Surviving patients: ADMA levels, P<0.0001; ADMA/SDMA ratio, P<0.0001. Non-surviving patients: ADMA levels, P=0.049; ADMA/SDMA ratio, P=0.022. Comparison between surviving and non-surviving patients. At D0: SDMA levels, P=0.017; ADMA/SDMA ratio, P=0.0034. At last ICU day: SDMA levels, P=0.005; ADMA/SDMA ratio, P=0.025.

College Station, TX). Results are given as mean±standard deviation or as median (interquartile range) when the data was normally or not normally distributed, respectively.

Results

Of the 90 patients enrolled in the trial, 18 were excluded from the analysis for a length of stay less than 3 days. Thus, 72 patients had at least D0 and D3 samples and were included in the analysis. Demographics, clinical characteristics and biochemical markers profile at ICU admission are presented in Table I. Ventilation, cardio-circulatory therapy and energy supply (1,279±544 kcal, IU insulin 55.2±98.4 per day) was provided. The arginine dose at full strength supply ranged from about 3 (Enteral) to 4 (Parenteral) g/day.

Basal fasting glycemia, creatinine, IL-6, TNF-α and CRP levels were higher than normal, and arginine levels were at the lower limit of normal. ADMA and SDMA levels were 2- and 5-fold higher, respectively, than in healthy volunteers, and the ADMA/SDMA ratio was decreased by 50%. The mean clinical and biochemical data during the study period (D0-D12) and the ICU outcome are shown in Table II. The daily trend of ADMA, SDMA and the ADMA/SDMA ratio is shown in Figure 1.

In the multivariate linear mixed effects model (Table III, P<0.001 for all reported variables), ADMA levels were only directly related to the total SOFA score and arginine levels and was inversely related to IL-6 and CRP levels. SDMA levels were related to the SAPS II score, the SOFA score, and blood urea, creatinine, and arginine levels. The ADMA/SDMA ratio was inversely related to IL-6 levels.

ICU mortality was related to admission and D0-D12 levels of SDMA (logistic regression,

TABLE II.—*Differences in clinical characteristics and average profile of biochemical markers during the study period (D0-D12) between ICU survivors and not survivors.*

ICU outcome	ICU survivors 58	ICU non-survivors 14	P
D0 - D12			
Septic Shock - no (%)	49 (84.5)	14 (100.0)	0.115
*Mean SOFA score** - points	5.5±2.8	10.5±3.1	<0.001
*Worst SOFA score** - points	9.7±2.7	12.6±2.7	<0.001
*Total SOFA score** - points	33.8±23.0	50.9±37.7	<0.001
Blood glucose - mg/dL	135.7±31.9	134.9±43.7	0.90
*Creatinine** - mg/dL	1.4±1.2	2.5±1.4	<0.001
Arginine - μmol/L (Norm: 55-95)	73.3 [56.7-99.6]	72.8 [58.8-87.9]	0.45
*IL-6** - pg/mL (Norm: 0.19-12.00)	49.7 [22.1-118.9]	146.7 [39.5-444.7]	0.0004
TNF-α - pg/mL (Norm: 3.75-18.25)	20.9 [13.8-32.9]	17.3 [13.2-42.6]	0.67
CRP - μg/mL (Norm: 0.15-6.55)	72.6 [29.8-124.6]	81.6 [44.0-168.8]	0.06
*ADMA** - μmol/L (Norm: 0.33-0.59)	1.05±0.39	1.22±0.48	0.0067
*SDMA** - μmol/L (Norm: 0.31-0.49)	1.93±1.25	3.54±2.16	<0.0001
*ADMA/SDMA** (Norm: 0.89-1.42)	0.68±0.32	0.42±0.22	<0.0001
ICU STAY* - days	23.8±17.2	15.7±9.4	0.001

Values are presented as mean ± SD or median [interquartile range]. ICU: intensive care unit; SOFA: sepsis-related organ failure assessment; IL-6: interleukin-6; TNF-·: tumor necrosis factor-·; CRP: C-reactive protein; ADMA: asymmetric dimethylarginine; SDMA: symmetric dimethylarginine; Norm: normal range. *P<0.05 survivors vs. non-survivors.

OR=1.83 [1.09-3.08], P=0.023 and OR=2.32 [1.26-4.26], P=0.007, respectively) but not to ADMA levels. Compared to survivors, the 14 patients who died in the ICU had a higher number and degree of organ failure, higher mean levels of creatinine, IL6, ADMA, and SDMA (Figure 1, Table II) and a lower mean ADMA/SDMA ratio. Creatinine, IL-6, TNF-α, CRP and ADMA levels did not change during the study period (linear mixed model, P=0.299, 0.291, 0.470, 0.116, and 0.196, respectively), SDMA showed a daily increase of 0.105 μmol/L (P=0.048; Figure 1), and the resulting ADMA/SDMA ratio did not significantly change (P=0.314). On the contrary, levels of creatinine (linear mixed model, daily reduction=0.064 mg/dL, P<0.001), IL-6 (daily reduction=12.094 pg/mL, P<0.001), and CRP (daily reduction=8.846 μg/mL, P<0.001) progressively decreased in the 58 surviving patients who were discharged from the ICU. ADMA rose significantly (daily increase=0.013 μmol/L, P<0.001), while the high level of SDMA remained stable (P=0.219; Figure 1). As a result, the ADMA/SDMA ratio rose significantly (daily increase=0.017 points, P<0.001; Figure 1).

On the last ICU day of all patients, measurements were taken after D12 in 23 of the 58 surviving patients as well as 7 of the 14 non-surviving patients (Table IV). The ADMA levels and the ADMA/SDMA ratio on the last ICU day were increased compared to baseline levels in both surviving and non-surviving patients (Figure 1). Moreover, SDMA levels and the ADMA/SDMA ratio were different in surviving and non-surviving patients. Arginine levels were within normal ranges in both groups; however, the SOFA score and the levels of creatinine, IL-6, and CRP were lower in patients who survived.

TABLE III.—*Dimethylarginine plasma level determinants during the study period (D0-D12).*

	ADMA		SDMA		ADMA/SDMA ratio	
	R	P	R	P	R	P
SAPS II score	0.11	0.14	0.40*	<0.001	0.01*	0.43
Daily SOFA score	0.02	0.19	0.62*	<0.001	0.14	0.75
Worst day SOFA	0.08	0.31	0.44*	<0.001	0.26	0.76
Total SOFA score	0.22*	<0.001	0.50*	<0.001	0.01	0.61
Blood urea	0.15	0.18	0.62*	<0.001	0.18	0.56
Creatinine	0.09	0.11	0.50*	<0.001	0.31	0.24
Arginine	0.38*	<0.001	0.14*	<0.001	0.2	0.09
IL-6	-0.31*	<0.001	-0.02	0.40	-0.24*	<0.001
CRP	-0.28*	<0.001	0.05	0.81	-0.21	0.42

ADMA: asymmetric dimethylarginine; SDMA: symmetric dimethylarginine; SAPS II: Simplified acute physiology score II; SOFA: sepsis-related organ failure assessment; IL-6: interleukin-6; CRP: C-reactive protein; R: correlation coefficient between variables. *variables significantly (P<0.05) related.

TABLE IV.—*Clinical characteristics and average profile of biochemical markers in the last ICU day of ICU survivors and non-survivors.*

ICU outcome	ICU survivors 23	ICU non-survivors 7	P
*Mean SOFA score** - points	3.8±2.0	10.8±3.9	<0.001
*Creatinine** – mg/dL	1.3±1.4	2.7±1.7	0.009
Arginine - μmol/L (Norm: 55-95)	82.5[61.8-97.0]	61.9[52.3-89.6]	0.26
IL-6 * - pg/mL (Norm: 0.19-12.00)	37.7 [15.9-73.9]	172.5 [54.4-466.5]	0.001
CRP * - μg/mL (Norm: 0.15-6.55)	55.5 [25.8-111.5]	107.8 [56.9-170.8]	0.04

Values are presented as mean±SD or median [interquartile range]. ICU: intensive care unit; SOFA: sepsis-related organ failure assessment; IL-6: interleukin-6; CRP: C-reactive protein; Norm: normal range. *P<0.05 survivors vs. non-survivors.

Discussion

In this study, SDMA was found to be directly related to indicators of organ failure severity, whereas ADMA was found to be inversely related to proinflammatory cytokines. Moreover, a significant daily increase in ADMA levels and a concurrent reduction in renal failure and markers of inflammation were observed in ICU survivors.

There are several interesting reasons to study methylarginines in critically ill patients: 1) methylarginines are markers of nuclear protein breakdown;[4] 2) they may also interfere with NO synthesis [4-7] (as for this property, ADMA might have a role in the outcome,[4, 8] whereas little attention has been paid to SDMA); and 3) the impact of systemic inflammatory reaction on ADMA catabolism remains controversial [17-20, 29] and, due to ADMA activity, it is of interest to clarify the time course of the endogenous regulation of NO inhibitors in patients with severe sepsis.[11]

The main prerequisite for any study on this topic is a population of highly stressed, critically ill patients, i.e., patients admitted with severe sepsis and septic shock. Indeed, our cohort was at significant high risk; approximately 50% of our patients had pneumonia, 25% had peritonitis, and 80% were admitted for septic shock. The severity of the patients at admission and the number and degree of organ failures (Table I) resulted in a high level of treatment, substantial mortality and long ICU stays (Table II).

In this setting, we found that ADMA and

SDMA fasting plasma levels on the day of admission were 2- and 5-fold higher, respectively, than in healthy volunteers (and higher than reported in less severely ill patients).[8, 9, 11] The rise in ADMA levels was not as evident as for SDMA, which is consistent with the only study on SDMA levels in septic patients.[10] As a consequence, the ADMA/SDMA ratio was decreased by 50%.

The determinants of both dimethylarginine levels during full-blown stress reaction (Table III) were arginine plasma levels and the severity of organ failure (as previously described only for ADMA).[8, 10] The SDMA concentration was also strongly and independently related to the presence of renal failure. This finding is hardly surprising because urinary excretion is the main process of elimination in humans.[3] Curiously, both ADMA levels and the ADMA/SDMA ratio were inversely related to the levels of inflammatory markers CRP and IL-6. This result is in apparent contrast to the assumed down-regulation of DDAH during oxidative stress and cytokine release.[17, 29] In fact, the reduced DDAH activity should raise the ADMA level, not lower it. However, our findings fit with recent reports in cultured smooth muscle cells [20] and in infected medical ward patients,[19] in which inflammation, and particularly IL-6, were found to play an important inductive role for DDAH. Thus, a high level of IL-6 should induce the DDAH enzyme, which will, in turn, lower ADMA levels.

To further clarify the metabolism of dimethylarginines, we divided the patients according to their ICU outcome (Figure 1). During the first 12 days of sepsis (Table II), ICU survivors had a logical decrease in creatinine, IL-6, and CRP levels. In contrast, levels of creatinine, IL-6, TNF-α, and CRP remained high in patients who did not survive the ICU. In the latter group, high basal SDMA levels were increased, whereas ADMA levels did not increase as expected due to high catabolic appearance, progression of renal failure, and a possible sub-clinical septic liver involvement. Consequently, the resulting ADMA/SDMA ratio remained very low (0.42).

In contrast, the SDMA remained stable in patients who survived, and the ADMA levels showed a moderate, but significant, daily increase from the basal levels; as a consequence, the ADMA/SDMA ratio increased. This finding was an unexpected if we consider the presumably decreased appearance of methylarginine (reduced protein catabolism) and the improved renal excretion (creatinine decrease). Nonetheless, our finding is similar to the results from the only available study on both methylarginines in ICU surgical patients.[8]

Thus, in the acute phase of sepsis, notwithstanding a significant increase, the ADMA levels were consistently reduced with respect to SDMA levels, suggesting a consistent catabolism. In an advanced phase in patients who began to improve from sepsis, ADMA catabolism showed a decreasing trend.

We further investigated the dimethylarginines levels by pooling together the values on the last ICU day. In ICU survivors, stress reaction (IL-6 and CPR) and organ failure (creatinine and SOFA scores) recovered with respect to admission values, whereas in patients who did not survive, this recovery did not happen. Interestingly, survivors at the late phase of the inflammatory process had plasma ADMA levels that were increasing, instead of decreasing, and had an ADMA/SDMA ratio that, though increasing, remained below normal values (0.89). This result supports the hypothesis that the DDAH enzyme, which is highly expressed along with a cytokine burst in full-blown stress reactions (inhibiting the endogenous ADMA increase), relapses as the cytokine-associated infectious process subsides.[19] This finding suggests that ADMA is contained during the early septic phase and increases in advanced septic phases with favorable outcomes (*i.e.*, a possible early preservation of NO production, followed by an endogenous increase of NO synthesis inhibition), which may, at least in part, explain the adverse effects of the administration of an ADMA analogue at the early stage of sepsis when it is supplied to elicit an acute and non-selective inhibition of NO.[16]

Studies in critically ill patients have shown that ADMA is an independent predictor of ICU mortality for the most severe cases [8] and that an increase in ADMA between days 0 and 2 and in the last days of ICU stay is significantly related to ICU mortality.[9] Inconsistent with previous studies,[8-10] the SDMA level in our severely septic patients appeared to be a more robust independent pre-

dictor of both organ failure and ICU mortality compared to ADMA level. Even if modestly hypocaloric, our nutritional regimen was able to normalize the plasma concentration of L-arginine during sepsis. Arginine supply, which is a determinant of both dimethylarginine levels (Table III), is supposed to overcome the deleterious effects of high ADMA levels on vital functions.[30] This could explain the observed clinical improvement notwithstanding the increase of ADMA levels and highlights the complexity of the pathophysiology of sepsis.

The main limitation of our study is that it was a post hoc analysis of data from a randomized study on tight glycemic control [23] that showed no impact on ADMA metabolism. For this reason, we pooled data of patients who were given two different treatment regimens. The case-mix was a homogeneous group of severely septic patients, and all of the described clinical and biochemical variables (with the exception of blood glucose) showed no differences between the tight glycemic control or conventional treatment.[23, 25] Thus, pooling the patients resulted in a large dataset that allowed a deeper insight into dimethylarginine metabolism in patients with sepsis.

Conclusions

In conclusion, this study produced three main findings: 1) SDMA, rather than ADMA, was found to be a marker of alterations in vital functions and mortality rate in patients with severe sepsis; 2) inflammatory markers were negatively associated with ADMA levels and the ADMA/SDMA ratio, possibly indicating activation of ADMA catabolism by inflammation; and 3) when the stress reaction subsided the moderate increase in plasma ADMA concentration along with normal arginine plasma levels suggest a reduction in initially high ADMA catabolism and thus a possible strengthening of the endogenous inhibition of NO synthesis.

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