Journal of Critical Care 38 (2016) 68–72

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Plasma adrenomedullin in critically ill patients with sepsis after major surgery: A pilot study

Tim-Philipp Simon, MD [a], Lukas Martin, MD [a], Sabine Doemming, MD [a], Andreas Humbs [a], Christian Bruells, MD [a], Ruedger Kopp, MD [a], Oliver Hartmann, ScD [b], Joachim Struck, ScD [b], Andreas Bergmann, ScD [b], Gernot Marx, MD [a], Tobias Schuerholz, MD [a,*]

[a] Department of Intensive Care and Intermediate Care, University Hospital RWTH Aachen, Pauwelsstr. 30, 52074 Aachen, Germany
[b] Sphingotec GmbH, Neuendorfstraße 15A, 16761, Hennigsdorf, Germany

ARTICLE INFO

Keywords:
Adrenomedullin
Sepsis
Biomarker
Surgical
Intensive care

ABSTRACT

Purpose: Adrenomedullin is released by different tissues in hypoxia, oxidative stress, and inflammation and is found in general and medical patients and, recently, in sepsis patients in emergency departments. The aim of this study was to evaluate biologically active adrenomedullin that mirrors directly the active peptide levels in plasma of surgical intensive care unit (ICU) patients with sepsis.
Materials and methods: In this single-center observational pilot trial, 42 ICU patients with sepsis and 14 patients after major surgery were included after sepsis diagnosis or ICU admission.
Results: Patients (66% male) were 70 (median) (interquartile range [IQR], 61-77]) years old and had a body mass index of 26.2 (24.2-29.4) kg/m^2. The ICU and hospital length of stay was 8 (1-22) and 17 (8-21) days, respectively. Eight patients had sepsis, 19 developed severe sepsis, and 15 suffered from septic shock. Adrenomedullin increased with severity (sepsis: 25.8 pg/mL [IQR 20.3-40.2], severe sepsis: 84.2 pg/mL [IQR 42.7-118.5], septic shock: 119.7 pg/mL [IQR 83.8-172.6]; $P < .0001$). Higher adrenomedullin was associated with poor 90-day outcomes ($P = .019$) and more frequent vasopressor use ($P = .001$).
Conclusions: This is the first study investigating adrenomedullin in patients with sepsis following major surgery. Higher adrenomedullin on admission is associated with increased vasopressor need and mortality after 90 days. Thus, adrenomedullin may be a useful additional parameter in surgical patients with sepsis.

1. Introduction

More than 1 000 000 cases of sepsis are diagnosed in hospitalized patients each year in the United States. The incidence of sepsis is still increasing primarily because of the growing and aging population and the associated increases in comorbidities [1]. Sepsis is not only a problem in the United States; it is one of the leading causes of mortality and morbidity worldwide with a number of reports from several European countries also [2].

Despite the increased attention focused on sepsis and numerous experimental and clinical trials, the morbidity and mortality of sepsis remain high. Early detection and diagnosis are key points in the treatment of sepsis.

Many biomarkers have been investigated, and different experimental treatment strategies have failed to reduce the mortality associated with sepsis [3].

Adrenomedullin (ADM) is a 52–amino acid peptide that was first isolated from a human pheochromocytoma [4] and participates in a variety of physiological and pathophysiological processes including sepsis. In bacterial sepsis, ADM expression has been described in different vascular systems including the lungs, blood vessels, and kidney and is released by different tissues in hypoxia, oxidative stress, and inflammation [5]. In most cells, ADM stimulation leads to the accumulation of cAMP and thus contributes to vasodilation and the loss of resistance. In infections induced by cytokines, lipopolysaccharide, and hypoxia, increased ADM levels have been demonstrated in animals and humans [5]. From animal experiments, it appears that the most relevant action of ADM is decreasing capillary leakage and hyperpermeability during septic shock [6,7].

In clinical studies, associations between increased ADM blood concentrations in sepsis and increased morbidity and mortality have been found [8-11].

The prognostic value of ADM has been described in general patient populations, in medical patients, in patients following thoracic surgery, and particularly recently in patients with suspected sepsis in the emergency department [12-14], but the prognostic value has not yet been described in patients with sepsis following major surgery. Especially in patients undergoing major surgery, it is important to discriminate between postsurgical

* Corresponding author at: Department of Intensive Care and Intermediate Care, University Hospital Aachen, Pauwelsstr. 30, 52074, Aachen, Germany. Tel.: +49 241 80 80444; fax: +49 241 80 3380444.
E-mail address: tschuerholz@ukaachen.de (T. Schuerholz).

http://dx.doi.org/10.1016/j.jcrc.2016.10.017
0883-9441/

inflammation and infection as early as possible. Furthermore, in critically ill surgical patients, important factors in therapy are the abilities to predict the severity of disease and to assess the patients' prognoses.

Thus, we conducted a prospective, observational study to evaluate the ADM levels in the plasma of surgical intensive care unit (ICU) patients using a novel assay that specifically measures bioactive adrenomedullin (bio-ADM). We compared bio-ADM levels with conventionally used parameters like C-reactive protein, procalcitonin, and white blood count.

2. Material and methods

2.1. Population and study protocol

We conducted a prospective, observational clinical pilot trial in the surgical intensive care department of the University Hospital RWTH Aachen, Germany. We enrolled 42 ICU patients with clinical signs of sepsis according to the Society of Critical Care Medicine definitions [15]. All 42 patients underwent major surgery before enrollment and developed sepsis in the postoperative course. Of the 42 ICU patients, 8 patients had sepsis, 19 developed severe sepsis, and 15 suffered from septic shock. We enrolled 14 patients admitted routinely to the ICU directly after major surgery as a control group to evaluate the effect of surgery on bio-ADM levels (Table 1). Four (7%) of 56 patients underwent major trauma surgery, 9 (16%) of 56 patients underwent major brain surgery, 15 (27%) of 56 patients underwent major cardiothoracic surgery, and 28 (50%) of 56 patients underwent major abdominal surgery.

The study was approved by the local ethical committee of the University Hospital RWTH Aachen (EK 021/14). All patients or their legal representatives provided written informed consent. Ethylenediaminetetraacetic acid plasma samples to determine single bio-ADM levels were drawn within 16 hours after patients were classified as having sepsis. In the control group, samples were drawn up to 5 hours after ICU admission. CRP and PCT were measured at the same point of time that the bio-ADM levels were determined and were also measured afterward as clinical routine but were not taken into analysis. The laboratory and clinical parameters were recorded for all patients and presented in the "Results" section. The 28- and 90-day mortalities were recorded. Acute Physiology and Chronic Health Evaluation Score (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were calculated for all patients. Two patients were excluded because of unknown 90-day survival statuses.

2.2. Bio-ADM measurement

All bio-ADM measurements were performed in a blinded manner in the laboratories of Sphingotec GmbH, Hennigsdorf, Germany, with a previously described, commercially available immunoassay [12]. Briefly, a 1-step sandwich-coated tube chemiluminescence immunoassay based on acridinium NHS-ester labeling was used for the detection of human ADM in the plasma.

Mouse monoclonal antibodies (ABs) directed against the middle region of ADM in the solid phase and labeled mouse monoclonal ABs directed against the amidated C-terminal moiety of ADM were used in the assay. To label the anti–C-terminal antibodies (1 g/L), the samples were incubated with MACN-acridinium-NHS (*N*-hydroxysuccinimide)-ester (1 g/L; InVent GmbH, Hennigsdorf, Germany) at a 1:5 molar ratio for 20 minutes at 22°C, and the process was stopped by the addition of a 1/5 volume of 50 mmol/L glycine for 10 minutes at 22°C. As described previously, the labeled antibody was diluted in the assay buffer (300 mmol/L K-phosphate, 100 mmol/L NaCl, 10 mmol/L sodium ethylenediaminetetraacetic acid, 5 g/L bovine serum albumin [protease-free],1 g/L each of nonspecific bovine and mouse IgG, 0.9 g/L Na-azide, 20 tablets per liter Protease Inhibitor Cocktail [Roche Diagnostics GmbH, Penzberg, Germany], 10 μmol/L amastatin, 20 μmol/L leupeptin; pH 7.0). Dilutions of the full-length human ADM peptide (American Peptide Company, Sunnyvale, CA) in Calibrator Dilution Buffer (10 mmol/L Tris, 250 mmol/L NaCl, 2 g/L Triton X-100, 50 g/L bovine serum albumin [protease-free], and 20 tablets per liter Protease Inhibitor Cocktail [Roche AG]; pH 7.0) served as calibrators [12].

The immunoassays were performed with 50-μL plasma samples or calibrators and 200 μL of the labeled detection antibody (800 000 relative light units per 200 μL). Both were added to the coated tubes, incubated for 18 hours at 4°C, and washed 5 times with wash solution (1 mL each). Finally, the chemiluminescence was measured for 1 second using an LB953 Multi-Tube Luminometer (Berthold Technologies GmbH & Co KG, Bad Wildbad, Germany). The analytical assay sensitivity was 2 pg/mL.

2.3. Statistical analysis

The values are expressed as the median and interquartile range (IQR) or as the count and percentage as appropriate. Group comparisons of the continuous variables were performed using the Kruskal-Wallis test. The

Table 1
Patient characteristics on admission

Variable	Total population (N = 56)	Control group (n = 14)	Sepsis (n = 8)	Severe sepsis (n = 19)	Septic shock (n = 15)	*P* value
Demographics						
Sex (male), n (%)	37 (66.1)	9 (64.3)	7 (87.5)	13 (68.4)	8 (53.3)	.440
Sex (female), n (%)	19 (33.9)	5 (35.7)	1 (12.5)	6 (31.6)	7 (46.7)	.440
Age (y), median (IQR)	70 (61-77)	69 (63-74)	58 (35-77)	74 (57-79)	73 (65-78)	.380
BMI (kg/m^2), median (IQR)	26.2 (24.2-29.4)	27.1 (24.5-29.1)	26.1 (23.4-29.6)	25.8 (23.9-28.4)	27.0 (23.7-32.0)	.936
Medical history						
Diabetes (yes), n (%)	12 (21.4)	4 (28.6)	0 (0.0)	3 (15.8)	5 (33.3)	.256
Laboratory variables						
Bio-ADM, (pg/mL), median (IQR)	54.8 (20.3-107.6)	16.2 (11.8-20.0)	25.8 (20.3-40.2)	84.2 (42.7-118.5)	119.7 (83.8-172.6)	<.001
PCT (ng/mL), median (IQR)	0.37 (0.14-1.50)	0.07 (0.05-0.16)	0.31 (0.11-0.57)	0.44 (0.25-3.41)	1.62 (0.39-5.72)	<.001
Crea clearance, (mL/min), median (IQR)	87.2 (59.1-99.7)	87.3 (67.2-96.3)	96.9 (92.7-115.7)	85.4 (32.6-100.2)	80.6 (44.6-91.5)	.113
Creatinine, (mg/dL), median (IQR)	0.87 (0.72-1.20)	0.86 (0.71-1.04)	0.79 (0.69-0.86)	0.88 (0.76-2.58)	0.9 (0.73-1.39)	.449
CRP (mg/dL), median (IQR)	92.3 (15.6-201.4)	3.5 (2.1-5.2)	87.3 (58.5-118)	234.3 (92.0-267)	99.7 (88.1-194)	<.001
WBC (10^9 cells/L), median (IQR)	12.2 (9.0-16.0)	11.8 (10.3-14.3)	12.4 (10.4-13.3)	12.5 (10.8-20.0)	11.4 (7.6-13.7)	.354
Platelets (10^9 cells/L), median (IQR)	217 (144-338)	199 (184-219)	169 (104-299)	246 (180-359)	284 (117-375)	.418
Other						
APACHE II score (points), median (IQR)	16 (11-18.3)	10 (7.5-11)	13.5 (9.8-16)	18 (15-19)	18 (15.5-24.5)	<.001
SOFA score (points), median (IQR)	7 (4-9)	5 (3-6)	4 (3.5-5)	7 (6-9)	8 (8-11)	<.001
Length of ICU stay (d), median (IQR)	8 (1-22)	1 (1-1)	14 (8-21)	11 (6-33)	8 (5-24)	<0.001
Length of hospital stay (d), median (IQR)	17 (8-21)	11 (7-18)	19 (15-23)	17 (11-35)	19 (10-21)	.252
28-d mortality (%)	6 (10.7)	0 (0)	1 (12.5)	2 (10.5)	3 (20.0)	.121
90-d mortality (%)	14 (25.0)	1 (7.1)	2 (25.0)	6 (31.6)	5 (33.3)	.388

BMI indicates body mass index; Crea, creatinine.

biomarker data were log-transformed. Spearman rank-order correlations were applied to the continuous variables.

All statistical tests were 2-tailed, and a 2-sided *P* value of .05 was taken to indicate significance. The statistical analyses were performed using R version 2.5.1 (http://www.r-project.org, library Design, Hmisc, ROCR) and the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc, Chicago, IL).

3. Results

The median patient age was 70 years (IQR 61-77 years), and 66% of the individuals were male. The median body mass indices did not differ significantly between the groups (Table 1). The length of stay (LOS) in the ICU was 7.5 days (IQR, 1.0-21.8), and the LOS in the hospital was 16.5 days (IQR, 8-21).

Overall mortality after 28 days was 6%. After 90 days, 25% of patients died (Table 1).

The control group exhibited the lowest bio-ADM levels (16.2 pg/mL; IQR, 11.8-20.0). The levels increased significantly with the severity of sepsis ($P < .0001$, Fig. 1). The patients who met the sepsis criteria exhibited a median bio-ADM level of 25.8 pg/mL (IQR, 20.3-40.2). The bio-ADM level of the patients with severe sepsis was 84.2 pg/mL (IQR, 42.7-118.5). The highest bio-ADM level (119.7 pg/mL; IQR, 83.8-172.6)) was observed in the patients with septic shock (Fig. 1).

Higher APACHE II scores and higher SOFA scores corresponded with the severity of disease, and the PCT and CRP levels were also associated with the severity of disease (Table 1).

The median PCT level of the control group was 0.07 ng/mL (IQR, 0.05-0.16), and this level was increased in the patients with septic shock (1.62 ng/mL; IQR, 0.39-5.72). In contrast, the highest CRP was detected in the severe sepsis patients (234.3 mg/dL; IQR, 92.0-267). In the patients with septic shock, the median CRP value was 99.7 mg/dL (IQR, 88.1-194). The control group exhibited a median CRP of 3.5 mg/dL (IQR, 2.1-5.2; Table 1).

No significant differences between the groups were observed in the white blood cells (WBC), platelets, creatinine clearance, or creatinine measurements (Table 1).

Among all of the assessed variables, 90-day survivors showed significantly lower bio-ADM levels on ICU admission (Fig. 2, $P = .019$) and APACHE II scores (Table 2, $P = .044$); PCT, creatinine clearance, creatinine, CRP, WBC, and platelets were not significantly different between survivors and nonsurvivors (Table 2).

During the hospital stays, the 40 patients on vasopressor therapy in ICU exhibited significantly higher bio-ADM levels after 16 hours of sepsis than the 16 patients without any vasopressor therapy ($P = .001$, Fig. 3).

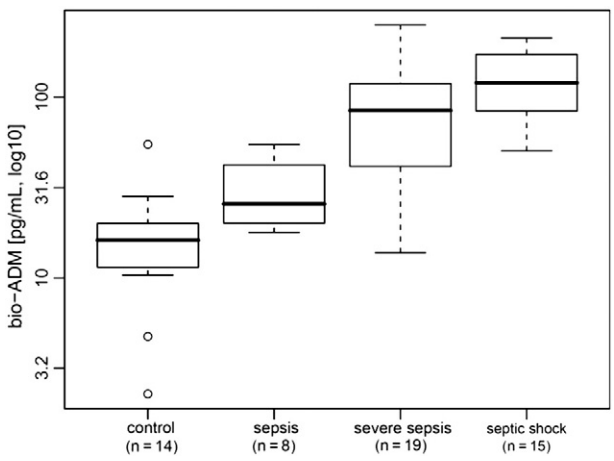

Fig. 1. Plasma bio-ADM levels according to disease severity. Bio-ADM levels in sepsis, severe sepsis, septic shock, and control group ($P \leq .0001$, septic shock group compared with the control and sepsis groups; $P \leq .0001$, severe sepsis group compared with the control group). The data are shown as median and IQR.

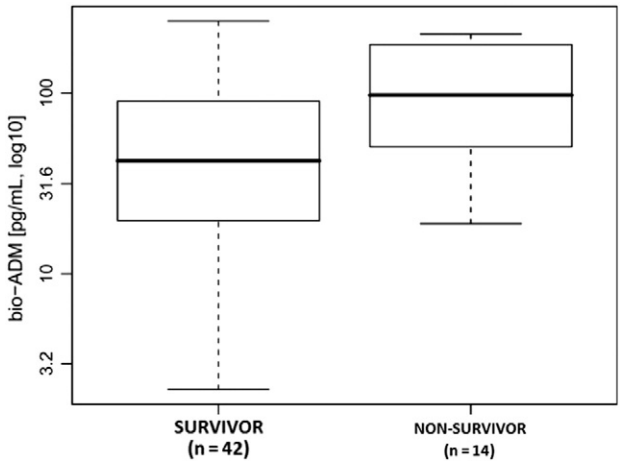

Fig. 2. Plasma bio-ADM levels according to 90-day outcome ($P = .019$). The data are shown as median and IQR.

Noradrenalin is the only vasopressor used in these patients with doses between 0 and 0.12 (mean, 0.016) μg/(kg min) in sepsis, between 0 and 0.83 (mean, 0.098) μg/(kg min) in severe sepsis, between 0.04 and 1.0 (mean, 0.329) μg/(kg min) in septic shock, and between 0 and 0.198 (mean, 0.038) μg/(kg min) in the control group. Four (50%) of 8 patients with sepsis, 74% (14/19) of patients with severe sepsis, and all patients with septic shock (15 patients) received vasopressor therapy, whereas 7 (50%) of 14 patients received vasopressor therapy in the control group.

In sepsis, patients received vasopressor support within the first 28 days for 3.1 ± 0.3 days (mean ± SEM), in severe sepsis for 6.7 ± 1.6 days, in septic shock for 6.0 ± 1.2 days, and in the control group for 0.7 ± 0.3 days.

4. Discussion

This is the first study to investigate plasma bio-ADM in critically ill patients with sepsis after major surgery.

The main findings of this investigation are that the plasma bio-ADM levels of critically ill patients with sepsis on admission after major surgery indicate the severity of disease and are associated with vasopressor use. Furthermore, based on our data, the plasma bio-ADM level can predict 90-day mortality more reliably than CRP or PCT.

Increasing numbers of studies demonstrated the diagnostic and prognostic significance of the ADM levels of medical patients using different assays. A systematic review showed that ADM is an independent predictor of death in patients with heart failure and major cardiovascular events [14]. Another cross-sectional study reported that ADM levels are significantly increased in patients with established heart failure compared with controls [16].

The prognostic value of ADM has also been described in medical patients after acute myocardial infarction. In a study of 983 post–

Table 2
Variables obtained on admission associated with 90-day mortality.

Variable	Died within 90 d (n = 14)	Survived 90 d (n = 42)	*P* value
Bio-ADM (pg/mL), median (IQR)	97.5 (52.2-179.0)	42.6 (19.8–89.6)	.019
PCT (ng/mL), median (IQR)	0.38 (0.19-5.27)	0.37 (0.13-1.11)	.359
CRP (mg/dL), median (IQR)	114.8 (69.7-265.9)	88.4 (5.6-185.8)	.064
WBC (10^9 cells/L), median (IQR)	12.4 (8.1-18.3)	12.2 (9.3-15.5)	.940
Platelets (10^9 cells/L), median (IQR)	245 (130-348)	210 (159-338)	.817
APACHE II score (points), median (IQR)	17 (15-20)	14 (10-18)	.044
SOFA (points), median (IQR)	8.0 (6-11)	6.5 (4-8)	.180

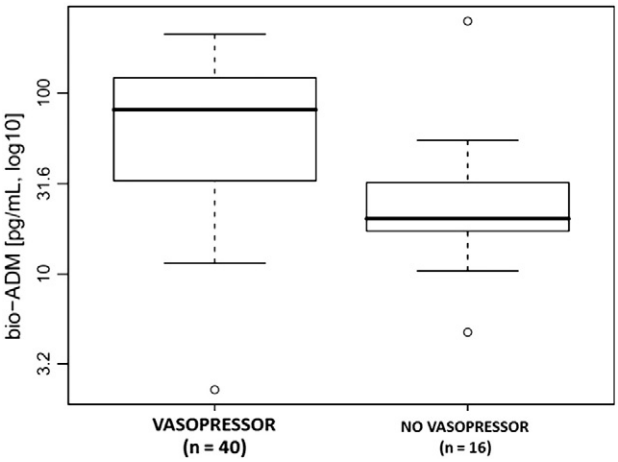

Fig. 3. Levels of plasma bio-ADM according to vasopressor use during the hospital stay (any vasopressor use vs no vasopressor use during the hospital stay, $P \leq .001$). The data are shown as median and IQR.

myocardial infarction patients, ADM was found to be an independent predictor of death [17]. Even in critically ill children, Jordan and colleagues [18] demonstrated that ADM was superior to PCT and CRP in predicting the severity of disease.

Recently, Marino and colleagues [12] obtained the plasma bio-ADM levels of 101 consecutive patients with suspected sepsis on admission to the emergency department and daily for the next 4 days. They found associations of bio-ADM with the disease severity and 28-day mortality which are comparable to our results. In our investigation, we found a significant difference in the bio-ADM levels on admission between patients who did and did not survive for 90 days. Patients who receive vasopressor therapy exhibit higher bio-ADM levels and can be discriminated from the patients who do not require vasopressors. Furthermore, Marino et al [12] demonstrated in their investigation of septic patients in the emergency department that the admission ADM levels were negatively correlated with the mean arterial pressure ($r = -0.39$, $P < .0001$). This finding is comparable to the significantly different bio-ADM levels between the patients who did and did not require vasopressors in our study. Despite the differences between the medical patients who have been assessed in other studies [12,14] and the surgical patients in our investigation, our results underline the reliability of bio-ADM as a prognostic biomarker of sepsis in surgical patients. To have the opportunity to know if a patient would need a vasopressor therapy during their hospital stay would give us an additional tool in risk stratification. In times of restricted resources in intensive care medicine, we have to weigh which patient needs a further intensive care treatment and who is not already in the emergency department [19].

Nishio and colleagues [20] described the effect of ADM on human blood vessels. These authors found a correlation between the ADM plasma levels and the vascular tone of patients with septic shock. This finding may provide a good explanation of the correlation of the bio-ADM plasma levels with the need for vasopressors in septic patients. In contrast, from animal experiments, it appears that a relevant action of ADM is decreasing capillary leakage and hyperpermeability during septic shock [6,7].

A more recently published study focused on the correlation between ADM plasma levels and mortality in surgical patients. Schoe and colleagues [13] analyzed 800 thoracic surgery patients undergoing elective cardiac surgery. These authors examined a set of biomarkers that included ADM and the APACHE IV score. The ADM level and the APACHE IV score were independent predictors of mortality, but ADM was found to be a better predictor of hospital mortality than the APACHE IV score. Furthermore, the data from this study demonstrated that ADM was also superior to PCT, CT-pro–endothelin-1, CT-pro-arginine vasopressin, and MR-pro–atrial natriuretic peptide in the prediction of mortality [13].

Several studies in recent years have demonstrated the prognostic value of ADM in various clinical settings [21]. Debiane and colleagues examined a group of 114 critically ill patients with cancer and fever and found that ADM was superior to CRP and equal to PCT in the prediction of infection. Receiver operating analysis revealed that ADM and PCT performed better in predicting mortality within 2 months after fever onset than CRP. However, in this study, only increased ADM plasma levels could detect nonresponders to antimicrobial therapy, whereas PCT and CRP could not [22].

Christ-Crain and colleagues [10] evaluated the prognostic value of midregional proadrenomedullin (MR-proADM) in a mixed population of critically ill patients. Comparable to our results, these authors found that, among 53 patients with sepsis, severe sepsis, or septic shock, the MR-proADM plasma levels on admission were significantly higher in nonsurvivors than in survivors. The prognostic value of MR-proADM for survival was similar to that of the IL-6 level, APACHE II score, and Simplified Acute Physiology Score II [10]. Another study investigated the prognostic value of ADM in medical septic patients in the emergency department. Chen and colleagues [23] found significant differences in the ADM plasma levels of patients with sepsis, severe sepsis, and septic shock, and that ADM predicted survival better than PCT and the Mortality in Emergency Department Sepsis score.

Furthermore, MR-proADM was found to have prognostic value in septic shock, especially when combined with the APACHE II score, in a cohort study of 246 medical patients who were admitted to the ICU [21]. In critically ill surgical patients, important factors in therapy are the abilities to predict the severity of disease and assess the patients' prognoses. In our study, higher ADM levels upon ICU admission were found to be an indicator of the severity of sepsis and were associated with worse 90-day outcomes. In addition, higher ADM plasma levels were associated with the need for vasopressor therapy in the postoperative course.

However, there are some limitations of our study. First, we performed a pilot study with a limited number of patients in only 1 hospital. However, this study will allow us to perform a multicenter study based on the results of this investigation. Second, we did not collect extended hemodynamic parameters, which could have provided more information on the reason for vasopressor need. Third, we only determined single bio-ADM values. Repeated measurements of bio-ADM may provide useful additional information.

Our results might obtain different results when considering the new Sepsis-3 definition, which was created to recognize and manage sepsis patients earlier [24].

5. Conclusions

This is the first study investigating bio-ADM levels of patients with sepsis after major surgery. Based on our data, bio-ADM plasma levels on admission are associated with vasopressor need and 90-day mortality. Thus, bio-ADM may be a useful additional parameter in surgical patients with suspected sepsis.

Acknowledgments

This study was funded by Sphingotec GmbH (Hennigsdorf, Germany) for the measurement of bio-ADM only.

References

[1] Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546–54.
[2] Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC case mix programme database. Crit Care 2006;10:R42.

[3] Schuerholz T, Marx G. Management of sepsis. Minerva Anestesiol 2008;74:181–95.
[4] Kitamura K, Kangawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, et al. Adrenomedullin: a novel hypotensive peptide isolated from human pheochromocytoma. Biochem Biophys Res Commun 1993;192:553–60.
[5] Temmesfeld-Wollbruck B, Hocke AC, Suttorp N, Hippenstiel S. Adrenomedullin and endothelial barrier function. Thromb Haemost 2007;98:944–51.
[6] Temmesfeld-Wollbruck B, Brell B, David I, Dorenberg M, Adolphs J, Schmeck B, et al. Adrenomedullin reduces vascular hyperpermeability and improves survival in rat septic shock. Intensive Care Med 2007;33:703–10.
[7] Hippenstiel S, Witzenrath M, Schmeck B, Hocke A, Krisp M, Krull M, et al. Adrenomedullin reduces endothelial hyperpermeability. Circ Res 2002;91:618–25.
[8] Ueda S, Nishio K, Minamino N, Kubo A, Akai Y, Kangawa K, et al. Increased plasma levels of adrenomedullin in patients with systemic inflammatory response syndrome. Am J Respir Crit Care Med 1999;160:132–6.
[9] Christ-Crain M, Morgenthaler NG, Stolz D, Muller C, Bingisser R, Harbarth S, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia [ISRCTN04176397]. Crit Care 2006;10:R96.
[10] Christ-Crain M, Morgenthaler NG, Struck J, Harbarth S, Bergmann A, Muller B. Mid-regional pro-adrenomedullin as a prognostic marker in sepsis: an observational study. Crit Care 2005;9:R816–24.
[11] Guignant C, Voirin N, Venet F, Poitevin F, Malcus C, Bohe J, et al. Assessment of pro-vasopressin and pro-adrenomedullin as predictors of 28-day mortality in septic shock patients. Intensive Care Med 2009;35:1859–67.
[12] Marino R, Struck J, Maisel AS, Magrini L, Bergmann A, Di Somma S. Plasma adrenomedullin is associated with short-term mortality and vasopressor requirement in patients admitted with sepsis. Crit Care 2014;18:R34.
[13] Schoe A, Schippers EF, Struck J, Ebmeyer S, Klautz RJ, de Jonge E, et al. Postoperative pro-adrenomedullin levels predict mortality in thoracic surgery patients: comparison with acute physiology and chronic health evaluation IV score*. Crit Care Med 2015;43:373–81.
[14] Yuyun MF, Narayan HK, Ng LL. Prognostic significance of adrenomedullin in patients with heart failure and with myocardial infarction. Am J Cardiol 2015;115:986–91.
[15] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. Sccm/Esicm/Accp/Ats/sis. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 2003;31:1250–6.
[16] Adlbrecht C, Hulsmann M, Strunk G, Berger R, Mortl D, Struck J, et al. Prognostic value of plasma midregional pro-adrenomedullin and C-terminal-pro-endothelin-1 in chronic heart failure outpatients. Eur J Heart Fail 2009;11:361–6.
[17] Khan SQ, O'Brien RJ, Struck J, Quinn P, Morgenthaler N, Squire I, et al. Prognostic value of midregional pro-adrenomedullin in patients with acute myocardial infarction: the LAMP (Leicester acute myocardial infarction peptide) study. J Am Coll Cardiol 2007;49:1525–32.
[18] Jordan I, Corniero P, Balaguer M, Ortiz J, Vila D, Velasco J, et al. Adrenomedullin is a useful biomarker for the prognosis of critically ill septic children. Biomark Med 2014;8:1065–72.
[19] Schuetz P, Hausfater P, Amin D, Amin A, Haubitz S, Faessler L, et al. Biomarkers from distinct biological pathways improve early risk stratification in medical emergency patients: the multinational, prospective, observational TRIAGE study. Crit Care 2015;19:377.
[20] Nishio K, Akai Y, Murao Y, Doi N, Ueda S, Tabuse H, et al. Increased plasma concentrations of adrenomedullin correlate with relaxation of vascular tone in patients with septic shock. Crit Care Med 1997;25:953–7.
[21] Enguix-Armada A, Escobar-Conesa R, La Torre AG, De La Torre-Prados MV. Usefulness of several biomarkers in the management of septic patients: C-reactive protein, procalcitonin, presepsin and mid-regional pro-adrenomedullin. Clin Chem Lab Med 2015.
[22] Debiane L, Hachem RY, Al Wohoush I, Shomali W, Bahu RR, Jiang Y, et al. The utility of proadrenomedullin and procalcitonin in comparison to C-reactive protein as predictors of sepsis and bloodstream infections in critically ill patients with cancer*. Crit Care Med 2014;42:2500–7.
[23] Chen YX, Li CS. Prognostic value of adrenomedullin in septic patients in the ED. Am J Emerg Med 2013;31:1017–21.
[24] Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:775–87.