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Prognostic value of midregional pro-atrial natriuretic peptide in ventilator-associated pneumonia

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Abstract Objective: This study aimed to investigate the correlation of midregional pro-atrial natriuretic peptide (MR-proANP) with severity of septic status in patients with ventilator-associated pneumonia (VAP) and the usefulness of MR-proANP for mortality prediction in VAP.

Design: Prospective observational cohort study. **Setting:** University Hospital. **Patients:** Seventy-one patients consecutively admitted to ICU who developed VAP. Patients were followed for 28 days after diagnosis, when they were considered survivors. There were no interventions. **Results:** MR-proANP levels increased from sepsis to severe sepsis and septic shock on D0 and D4 of VAP (0.002 and 0.02 respectively). Median MR-proANP levels on day 0 and day 4 (pmol/L [interquartile range]) were 149.0 (79.8–480.0) and 249.0 (93.6–571.0) in septic patients, 438.5 (229.3–762.0) and 407.5 (197.8–738.0) in severe sepsis, 519.5 (369.5–1282.3) and 632.0 (476.0–1047.5) in septic shock. On day 0 and day 4, MR-proANP levels were significantly higher in non-survivors

(525.0 [324.0–957.8] and 679.5 [435.0–879.5], respectively) than in survivors (235.0 [102.0–535.0] and 254.0 [110.0–571.0], respectively; $P = 0.004$). Univariate logistic regression model for mortality included age, gender, APACHE II score, creatinine, logarithmic transformed MR-proANP (LnMR-proANP). Mortality was directly related to LnMR-proANP on D0 and D4, with odds ratios (OR) of 2.06 (95% CI 1.21–3.51) and 2.63 (1.33–5.23), respectively. In multivariate logistic regression, only LnMR-proANP D0 with OR = 2.35 (1.05–5.26) and LnMR-proANP D4 with OR = 3.76 (1.39–10.18) remained significant. **Conclusions:** Our data demonstrated that MR-proANP levels increase progressively with the severity of sepsis and are independent predictors of mortality in VAP.

Keywords Midregional pro-atrial natriuretic peptide · Ventilator-associated pneumonia · Sepsis · Septic shock

Introduction

Ventilator-associated pneumonia (VAP) is the leading cause of death from hospital-acquired infections. The estimated prevalence of nosocomial pneumonia in intensive care units ranges from 10 to 65%, with case fatality

rates of 13 to 55% [1]. VAP complicates the course of 8–28% of patients receiving mechanical ventilation [2].

Worsening of respiratory failure, the presence of an ultimately or rapidly fatal underlying condition, the presence of shock, inappropriate antibiotic therapy are the factors that negatively affect the prognosis of VAP [3].

In addition to the clinical evaluation, a novel approach to estimate the presence of an infection and to grade its severity and treatment response is the use of biomarkers.

Atrial natriuretic peptide (ANP), a member of the family of natriuretic peptides, regulates a variety of physiological parameters including diuresis and natriuresis, and reduces systemic blood pressure [4, 5]. It is predominantly produced in the atrium of the heart and comprises 98% of natriuretic peptides in the circulation [5]. Mature ANP is cleaved from carboxylterminal amino acids of the prohormone of ANP. The N-terminal portion of the prohormone is secreted in the same molar ratio as ANP [5–7]. Because of its longer half-life, the N-terminal portion of proANP, particularly the mid region of this molecule (MR-proANP) has been shown to be a more reliable analyte [6, 8].

Plasma MR-proANP concentrations have recently emerged as a valuable tool for individual risk assessment in sepsis patients [7]. ANP levels may reflect the inflammatory cytokine response correlated with the severity of pneumonia, as well as the presence of disease-relevant comorbidities, namely heart failure and renal dysfunction [9–13]. ANP levels seem to be more determined by the intrinsic myocardial depression of sepsis. In addition to sepsis-induced myocardial depression, acute lung injury and an increased afterload placed on the right heart following pulmonary hypertension may contribute to cardiac dilation and a rise in circulating ANP [14].

Previous study observed a significant correlation of circulating pro-ANP levels with serum osmolality and creatinine in septic patients. Non-septic patients with kidney failure revealed mostly normal pro-ANP values, and it is therefore possible that the observed elevation in pro-ANP and creatinine in this study was a result of kidney failure related to sepsis (7).

To date, no published information exists about the behavior of ANP in patients with ventilator-associated pneumonia (VAP).

Our study aimed to investigate the correlation of MR-proANP with severity of septic status in patients with VAP and to analyze the usefulness of MR-proANP as a predictor of mortality in VAP.

Materials and methods

The study was conducted in the clinical/surgical 26-bed intensive care unit (ICU) of the Hospital de Clínicas de Porto Alegre (HCPA), a tertiary-care-teaching institution with 744 hospital beds.

All patients, consecutively admitted to the ICU suspected of VAP were eligible for this prospective observational cohort study. Patients at least 18 years old of age were recruited. Exclusion criteria were a previous

diagnosis of AIDS or neutropenia below 1,000 cells/mL. Pneumonia was considered ventilator associated when it occurred after 48 h of mechanical ventilation and was judged to not have been incubating before starting of mechanical ventilation. VAP was considered early-onset when it occurred during the first 4 days of mechanical ventilation and late-onset when it developed 5 or more days later after the initiation of mechanical ventilation [15]. APACHE II [16] was calculated during the first 24 h of admission to ICU. Patients were considered immunosuppressed when they had received chemotherapy within the preceding 45 days, or had neutropenia of less than 1,000/mm³.

Diagnosis of pneumonia was suspected, when a patient developed a new and persistent radiographic infiltrate plus two of the following signs/symptoms: (a) body temperature greater than 38°C or less than 36°C; (b) white blood cells more than 11,000 or less than 4,000/mm³; (c) macroscopically purulent tracheal aspirate [17]. Purulent endotracheal aspirate was defined on inspection by the assistant team. The axillary temperature used was the highest in the previous 24 h, before inclusion into the study.

Chest X-ray, arterial blood gases, complete blood count, creatinine, total bilirubin, and albumin were obtained by the time VAP was suspected (D0) and were repeated on the fourth day of treatment (D4). Quantitative endotracheal aspirate (QEA) was obtained on D0, repeated on the third day after the diagnosis (D3) and then weekly. Sterile endotracheal aspirates were obtained with a suction catheter adapted to a mucus collector without saline instillation, and two samples of hemocultures were collected from different veins with a 15-min interval before starting antimicrobial treatment.

Clinical pulmonary infection score (CPIS) [18], modified as described by Singh and colleagues [19], was calculated on the basis of data on D0 and D3. Patients were assumed to have VAP when the CPIS was 7 points or more. CPIS was calculated with data from D0, adding points for microbiological results and progression of pulmonary infiltrate on a new chest X-ray on D3. To calculate CPIS on D3, data from D3 were used.

For a diagnosis of VAP, there should be no evidence of other medical conditions to which the presenting symptoms, signs or radiological findings could be attributed. A SOFA score was calculated on D0 and D4. QEA was considered positive when values were at least 10⁵ colony-forming units/mL.

All patients with a clinical suspicion of VAP, later confirmed by a CPIS of at least 7 and fulfilling inclusion criteria, were included and they received empirical antimicrobial therapy on D0. The choice of antibiotics and changes rested solely with the critical care team or primary service caring for the patient. Modifications to empirical therapy were based on the results of QEA and hemocultures. Mechanical ventilation, physiotherapy and

airway management were performed in accordance with a standard protocol in all patients.

Patients at the time of VAP diagnosis were classified as those with sepsis, severe sepsis and septic shock, which were defined according to international criteria [20, 21].

Patients' progress was followed until the 28th day (D28) after the diagnosis of VAP. Patients who survived until follow-up were counted as survivors. Patients who died before D28 were non-survivors. Patients discharged from the ICU before D28 were also considered survivors. All patients with VAP were reviewed by one of the investigators to confirm the diagnosis on the basis of predetermined criteria.

Seventy-one patients enrolled from October 2003 to August 2005 constituted the study population. The research protocol was reviewed and approved by the Human Research Committee from the HCPA, and informed written consent was obtained from patients' representatives before enrollment. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

Trained investigators collected data on D0, D3, D4, and weekly until D28. Recorded data included age, sex, cause of ICU admission, arterial partial pressure of oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$), APACHE II score, SOFA score, CPIS, co-morbidities including chronic obstructive pulmonary disease, whether active smoker, history of congestive heart failure, history of malignancy, immunosuppression, albumin, use of histamine type-2 receptor (H2) antagonist, use of proton pump inhibitor, use of corticosteroids, dialysis, central vein catheterization, urinary tract catheterization, duration of mechanical ventilation, duration of stay in ICU before VAP, cardiopulmonary resuscitation, intubation (oro-tracheal versus nasotracheal), and tracheotomy.

Adequacy of the empirical antimicrobial treatment was recorded on the basis of microbiological results. Adequate antibiotic therapy was defined as coverage of all the pathogens isolated (from QEA culture or from blood), by at least one antimicrobial administered at the onset of VAP, determined by the sensitivity pattern in the antibiogram [22]. Treatment was considered adequate when cultures were negative.

Blood was drawn when a diagnosis of VAP was clinically suspected, before empirical antibiotic treatment was started. Samples of serum were prepared and frozen immediately after blood was drawn, then stored at -80°C in the HCPA research laboratory. Assays were performed in batches at the end of the study period.

MR-proANP measurements were performed using an immunoluminometric sandwich assay (B.R.A.H.M.S MR-proANP LIA; B.R.A.H.M.S AG, Hennigsdorf, Germany) as described in detail elsewhere [6]. As a modification to the published assay, the calibration was changed from a synthetic peptide to native pro-ANP in human serum. This modification to the initial description

increased precision and dynamics (i.e., signal to noise ratio) of the assay. Details on this modification have been published elsewhere [7]. The functional assay sensitivity (defined as lowest value with an interassay CV $<20\%$) is 11 pmol/L. Median MR-proANP in 325 healthy individuals in earlier investigations was 45 pmol/L [6].

Laboratory measurements were performed in a blinded fashion without knowledge of the clinical status of the patient.

Statistical analysis

Continuous baseline data are expressed as mean \pm SD. Categorical variables were compared with the Chi square test. Comparison of MR-proANP levels between survivors and non-survivors was analyzed by Mann-Whitney test. Comparison of MR-proANP levels in different septic status was analyzed by Kruskal-Wallis Test. For these analyses, two-tailed tests and $P \leq 0.05$ were considered statistically significant. Logistic regression analysis was used to determine the relation of risk factors to clinical outcome. We performed logarithmic transformation of MR-proANP values in the regression models, since they have a non-parametric distribution. In multivariate model, we considered significant variables with biological importance. Variables with $P < 0.20$ in univariate logistic regression were entered into the multivariate model. In the multivariate model, we considered as significant those variables with $P < 0.05$. SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Seventy-one patients were included in the study. Forty-five were survivors and 26 non-survivors.

Detailed baseline characteristics of the study population, stratified as survivors or non-survivors, are given in Table 1.

Microbiological identification of VAP is shown in Table 2.

Eight patients were not included in D4 analysis because six patients died before D4, one patient left the ICU before D4 and for one patient MR-proANP measurement was not performed because a serum sample was not available.

Thirty-five of 45 (77.8%) survivors received adequate antimicrobial therapy, compared to 18 out of 26 (69.2%) non-survivors ($P = 0.57$).

Accuracy of MR-proANP to predict mortality in VAP patients on D0 and D4 was assessed by ROC curve analysis. Data are presented in Fig. 1. MR-proANP had a

Table 1 Baseline characteristics of 71 patients who developed ventilator-associated pneumonia

Parameter	Survivors (<i>n</i> = 45)	Non-survivors (<i>n</i> = 26)	Total (<i>n</i> = 71)	<i>P</i>
Age (years) ^a	58 ± 14	64 ± 16	60 ± 15	0.12
APACHE II score ^a	18 ± 6	22 ± 9	19 ± 7	0.06
Albumin level (mg/dL) ^a	2.8 ± 0.6	2.4 ± 0.5	2.7 ± 0.6	0.01
Gender (%)				0.09
Male	66.7	46.2	59.2	
Female	33.3	53.8	40.8	
Origin (%)				0.24
Medical	51.1	65.4	56.3	
Surgical	48.9	34.6	43.7	
Onset (%) ^b				0.93
Early onset	22.2	23.1	22.5	
Late onset	77.8	76.9	77.5	
COPD (%)	17.7	26.9	19.7	0.59
Congestive heart failure (%)	17.8	26.9	21.1	0.36
Malignancy (%)	13.3	15.4	14.1	0.81
H2 antagonist (%)	66.7	57.7	63.4	0.45
Proton pump inhibitor (%)	22.2	34.6	26.8	0.26
Corticosteroids (%)	13.3	19.2	15.5	0.51
Dialysis (%)	11.1	19.2	14.1	0.34
Smoker (%)	37.8	38.5	38.0	0.95
Septic status (%)				0.01
Sepsis	66.7	15.4	47.9	
Severe sepsis	28.9	30.8	29.6	
Septic shock	4.4	53.8	22.5	

APACHE II Acute physiology and chronic health evaluation, COPD chronic obstructive pulmonary disease

^a Results are mean ± SD

^b Early onset is defined as occurring during the first 4 days of mechanical ventilation, and late onset as occurring 5 or more days after mechanical ventilation

Table 2 Microbiological identification in 71 ventilator-associated pneumonia patients and mortality

Microorganisms	Survivors ^a <i>n</i> = 56 ^b	Non-survivors ^a <i>n</i> = 31 ^b	Total ^a <i>n</i> = 87 ^b
<i>Pseudomonas aeruginosa</i>	9 (16.1)	6 (19.4)	15 (17.2)
<i>Staphylococcus aureus</i> OR	8 (14.3)	5 (16.1)	13 (14.9)
<i>Staphylococcus aureus</i> OS	7 (12.5)	1 (3.2)	8 (9.2)
<i>Stenotrophomonas maltophilia</i>	3 (5.4)	3 (9.7)	6 (6.9)
<i>Acinetobacter</i> sp	4 (7.1)	1 (3.2)	5 (5.7)
<i>Klebsiella pneumoniae</i>	2 (3.6)	3 (9.7)	5 (5.7)
<i>Enterobacter</i> sp	4 (7.1)	0	4 (4.6)
<i>Haemophilus</i> sp	4 (7.1)	0	4 (4.6)
<i>Escherichia coli</i>	0	2 (6.5)	2 (2.3)
<i>Citrobacter koseri</i>	2 (3.6)	0	2 (2.3)
<i>Proteus mirabilis</i>	2 (3.6)	0	2 (2.3)
Other	5 (8.9)	1 (3.2)	6 (6.9)
Non-identified	6 (10.7)	9 (29.0)	15 (17.2)

OR Oxacillin resistant, OS oxacillin sensitive

^a Frequency (%)

^b We identified more than one microorganism in 11 patients who survived and in 5 patients who died. In total 16 patients had more than one microorganism identified

Positive quantitative endotracheal aspirate when $\geq 10^5$ CFU/mL

Not all percentages add up to 100 because of rounding

slightly higher accuracy on D4 compared to D0. The AUC for MR-proANP on D0 was 0.71 (SD 0.06; $P = 0.004$). For a threshold of 489.0 pmol/L (minimal

false negative and false positive results), sensitivity was 0.65 and specificity was 0.76. The AUC for MR-proANP on D4 was 0.73 (SD 0.06; $P = 0.004$). Using a cut-off level of 465.5 pmol/L, sensitivity was 0.75 and specificity was 0.72.

MR-proANP levels were lower in survivors compared to non-survivors on D0 ($P = 0.004$) and D4 ($P = 0.004$). Data are shown in Table 3.

MR-proANP levels at different clinical conditions are shown in Table 4. Patients with late-onset VAP had higher levels than those with early-onset ($P = 0.03$). The presence of congestive heart failure resulted in higher MR-proANP levels ($P = 0.001$), but there was no difference in survival between the groups ($P = 0.36$).

We found correlation between creatinine and septic status ($P = 0.04$), creatinine and MR-proANP levels ($P = 0.0001$), and between creatinine and mortality ($P = 0.03$).

The influence of septic status on MR-proANP levels is shown in Table 5. MR-proANP levels increased from sepsis to severe sepsis and septic shock on D0 and D4 ($P = 0.002$ on D0 and 0.02 on D4).

Logistic regression analysis was used to determine the relation of risk factors to mortality.

Variables included in univariate logistic regression analysis for mortality were age, gender, APACHE II, Creatinine, LnMR-proANP D0 and LnMR-proANP D4. In univariate analysis, LnMR-proANP on D0 [(odds ratio

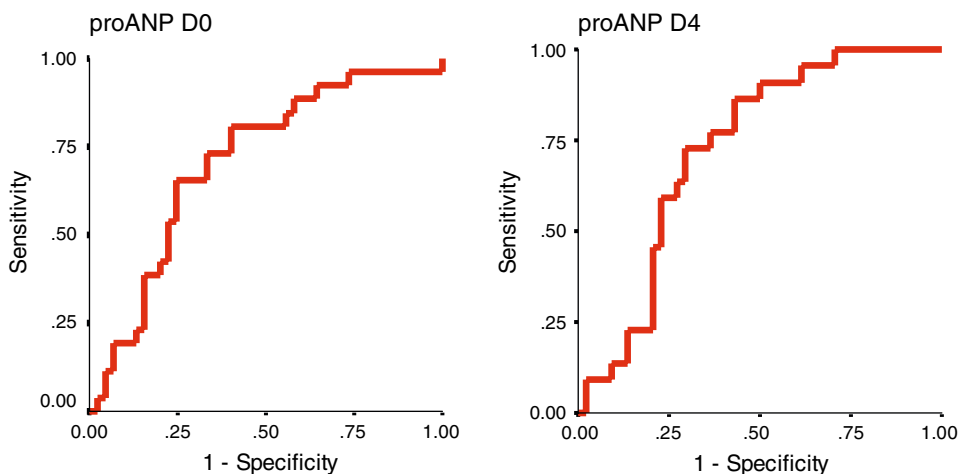


Fig. 1 Receiver operating characteristic (ROC) analysis of pro-ANP with respect to mortality prediction in patients with VAP. Data on the day of diagnosis of VAP (D0 left panel) and on day 4 (D4 right panel) are shown. MR-proANP had a slightly higher accuracy on D4 compared to D0. The AUC for MR-proANP on D0

was 0.71 (SD 0.06; $P = 0.004$). For a threshold of 489.0 pmol/L, sensitivity was 0.65 and specificity was 0.76. The AUC for MR-proANP on D4 was 0.73 (SD 0.06; $P = 0.004$). Using the cut-off level of 465.5 pmol/L, sensitivity was 0.75 and specificity was 0.72

Table 3 Comparison of MR-proANP levels between survivors and non-survivors, Mann–Whitney Test

Variable		Median pmol/L	IQR pmol/L	P
MR-proANP D0	Survivor	235.0	102.0–535.0	0.004
	Non-survivor	525.0	324.0–957.8	
MR-proANP D4	Survivor	254.0	110.0–571.0	0.004
	Non-survivor	679.5	435.0–879.5	

MR-proANP Midregional pro-atrial natriuretic peptide, *IQR* interquartile range

[OR] = 2.06) $P = 0.03$] and LnMR-proANP on D4 [(OR = 2.63) $P = 0.006$] were predictors of mortality. There was a trend to significance for age, gender, APACHE II and creatinine.

Multivariate logistic regression model for mortality included the variables from the univariate analysis. The only variables that remained as independent predictors of death were LnMR-proANP D0 with an OR = 2.35 [(95% confidence interval 1.05–5.26), $P = 0.04$], and LnMR-proANP D4 with an OR = 3.76 [(95% confidence interval 1.39–10.18), $P = 0.01$], (Table 6).

Discussion

The current study demonstrated that MR-proANP levels are significantly higher in VAP patients dying within 28 days when compared to survivors. In multivariate logistic regression models of predictors of death including age, sex, APACHE II, creatinine and LnMR-proANP on

Table 4 Comparison of MR-proANP levels on D0 between different clinical variables of 71 patients who developed ventilator-associated pneumonia, Mann–Whitney Test

Parameter	MR-proANP	IQR	n	P
Gender				
Male	287.0	132.8–603.0	42	0.14
Female	498.0	153.0–1075	29	
Origin				
Medical	302.0	104.8–696.8	40	0.12
Surgical	431.0	225.0–954.0	31	
Onset				
Early onset	190.0	119.0–395.8	16	0.03
Late onset	431.0	179.0–954.0	55	
COPD				
Yes	610.5	288.5–853.5	14	0.06
No	314.0	128.5–815.0	57	
Congestive heart failure				
Yes	832.0	480.0–1270.0	15	0.001
No	265.5	124.3–543.3	56	
Malignancy				
Yes	533.5	224.5–1360.0	10	0.18
No	371.0	140.5–774.0	61	

MR-proANP midregional pro-atrial natriuretic peptide, *IQR* interquartile range, *COPD* chronic obstructive pulmonary disease

the day of diagnosis of VAP (D0) and on day 4 (D4), LnMR-proANP turned out to be the only parameter that remained as an independent predictor.

Several studies investigated biomarkers to identify patients at high risk for death in respiratory tract infections. Early identification of patients at high risk may provide an opportunity to change the treatment strategy to improve the outcome.

Procalcitonin and C-reactive protein kinetics were assessed as prognostic markers during VAP, with different

Table 5 Comparison of MR-proANP levels between different septic status, Kruskal–Wallis Test

Variable	Median (pmol/L)	IQR (pmol/L)	<i>P</i>
MR-proANP D0			
Sepsis	149.0	79.8–480.0	0.002
Severe sepsis	438.5	229.3–762.0	
Septic shock	519.5	369.5–1282.3	
MR-proANP D4			
Sepsis	249.0	93.6–571.0	0.02
Severe sepsis	407.5	197.8–738.0	
Septic shock	632.0	476.0–1047.5	

MR-proANP midregional pro-atrial natriuretic peptide, IQR interquartile range

outcomes. Increasing procalcitonin values were associated with negative outcomes [23] and decreasing values of procalcitonin and C-reactive protein were associated with survival [24].

Recent studies assessed MR-proANP levels as prognostic biomarker in patients with community acquired pneumonia.

Muller et al. [25] analyzed MR-proANP levels in patients with lower respiratory tract infections to evaluate its prognostic use for the severity of disease and outcome. MR-proANP levels were significantly higher in patients with lower respiratory tract infections when compared with controls, with highest levels in patients with community-acquired pneumonia (CAP). MR-proANP, but not C-reactive protein (CRP) levels, gradually increased with increasing severity of CAP. For survival prediction in patients with CAP, MR-proANP was similar when compared with the PSI, and better when compared with other biomarkers, that is, procalcitonin, CRP and leucocyte count.

Masia and colleagues [26] conducted a prospective observational study of patients with CAP to assess severity of disease. Biomarkers, carboxy-terminal pro-vasopressin (CT-proAVP; copeptin) and midregional proatrial natriuretic peptide (MR-proANP) were measured in 173 patients. They found a positive correlation between pneumonia severity index (PSI) and MR-proANP and between PSI and CT-proAVP. Non-survivors had significantly higher MR-proANP and CT-proAVP

than survivors. In multivariate analyses to identify potential predictors of mortality including PSI, procalcitonin, C-reactive protein, lipopolysaccharidebinding protein, CT-proAVP, and MR-proANP concentrations in serum samples obtained at diagnosis, only CT-proAVP remained an independent predictor of death.

Prat and colleagues [27] evaluated the use of midregional pro-atrial natriuretic peptide (MR-proANP) measurement in the stratification of severity in community-acquired pneumonia. Three hundred patients admitted to Emergency Department with CAP were included. Patients were stratified by the pneumonia severity index (PSI), CURB-65 score and by the development of complications. Serum samples were obtained at the moment of admission and prior to antibiotic therapy. MR-proANP increased with the severity of pneumonia, according to PSI score and CURB-65 score. Median MR-proANP levels were significantly higher in patients with high PSI risk class (IVeV) than in those with low PSI risk class (IeIII). MR-proANP levels were also significantly higher in those patients who developed complications or died. There was no association between MR-proANP and etiology of pneumonia and the radiographic extent.

Kruger and colleagues [28] enrolled 589 patients with proven CAP and MR-proANP, CT-proAVP, C-reactive protein (CRP), procalcitonin (PCT) and CURB-65 score were determined on admission. MR-proANP and CT-proAVP were the strongest predictors of mortality. They are significantly lower in CAP survivors and correlate with the severity of the disease measured by CURB-65 score.

Haviv and colleagues [4] performed a study to determine ANP plasma levels in 28 children with pneumonia, compared to levels in 25 children without pneumonia. ANP levels in the pneumonia group (mean \pm SD, 16.02 \pm 11.69 pg/mL) increased significantly ($P < 0.01$) when compared to the levels in the control group (mean \pm SD, 7.44 \pm 9.29 pg/mL), but there was no correlation between ANP plasma levels and severity of pneumonia in their sample.

In contrast, our results showed a significant influence of septic status on MR-proANP levels. MR-proANP levels increased from sepsis to severe sepsis and septic

Table 6 Odds Ratios for Mortality in 71 VAP Patients, LnMR-proANP D0 and D4, univariate and multivariate logistic regression analysis

Parameter	Univariate OR (95%CI)	<i>P</i>	Multivariate OR (95%CI)	<i>P</i>
Age	1.03 (0.99–1.06)	0.12	1.00 (0.96–1.04)	0.89
Gender, female	2.33 (0.87–6.28)	0.09	1.80 (0.62–5.26)	0.28
APACHE II	1.07 (1.00–1.15)	0.06	1.06 (0.98–1.15)	0.13
Creatinine	1.51 (0.88–2.59)	0.14	0.73 (0.33–1.64)	0.45
LnMR-proANP D0	2.06 (1.21–3.51)	0.03	2.35 (1.05–5.26)	0.04
LnMR-proANP D4	2.63 (1.33–5.23)	0.01	3.76 (1.39–10.18)	0.01

APACHE II acute physiology and chronic health evaluation, LnMR-proANP logarithmic transformed midregional pro-atrial natriuretic peptide, OR odds ratio, CI confidence interval

shock both on the day of diagnosis of pneumonia and on the fourth day of treatment. ($P = 0.002$ and $P = 0.02$, respectively). We found higher levels of MR-proANP than Haviv et al. We may suppose that our cohort of adults were more severely dysfunctional.

Even though our study involved a different group, ventilated patients with pneumonia acquired in ICU (VAP), our results show great similarity to data presented in the previous studies in CAP patients [25–28]. Our non-survivors group had significantly higher levels of MR-proANP and they gradually increased with increasing severity of VAP.

Morgenthaler et al. [7] studied a cohort of medical intensive care unit patients to compare the prognostic value of MR-proANP levels with those of other biomarkers and physiological scores in 101 consecutive critically ill patients. The prognostic value of pro-ANP levels was compared with that of the APACHE II score and with those of C-reactive protein, IL-6 and procalcitonin. The median MR-proANP value in the survivors

was significantly lower than that in the non-survivors. On the day of admission, MR-proANP levels, but not levels of other biomarkers, were significantly higher in non-surviving than in surviving sepsis patients ($P = 0.001$).

In the present study, we are unable to compare the prognostic reliability of the MR-proANP with other markers, such as PCT or CRP, and therefore we cannot draw any conclusion regarding which one would be the best prognostic marker.

Our cohort was composed of septic, severely septic or shocked septic patients. It was expected to find high levels of MR-proANP in a group of patients with multiple organ dysfunctions. What we found valuable was the increasing levels of MR-proANP according to the severity of sepsis and the prognostic accuracy for mortality in a group of VAP patients.

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References

- Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia (2005) *Am J Respir Crit Care Med* 171:388–416
- Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. *Am J Respir Crit Care Med* 165:867–903
- Torres A, Aznar R, Gatell JM, Jimenez P, Gonzalez J, Ferrer A, Celis R, Rodriguez-Roisin R (1990) Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis* 142:523–528
- Haviv M, Haver E, Lichtstein D, Hurvitz H, Klar A (2005) Atrial natriuretic peptide in children with pneumonia. *Pediatr Pulmonol* 40:306–309
- Vesely DL (2002) Atrial natriuretic peptide prohormone gene expression: hormones and diseases that upregulate its expression. *IUBMB Life* 53:153–159
- Morgenthaler NG, Struck J, Thomas B, Bergmann A (2004) Immunoluminometric assay for the midregion of pro-atrial natriuretic peptide in human plasma. *Clin Chem* 50:234–236
- Morgenthaler NG, Struck J, Christ-Crain M, Bergmann A, Muller B (2005) Pro-atrial natriuretic peptide is a prognostic marker in sepsis, similar to the APACHE II score: an observational study. *Crit Care* 9:R37–R45
- Ala-Kopsala M, Magga J, Peuhkurinen K, Leipala J, Ruskoaho H, Leppaluoto J, Vuolteenaho O (2004) Molecular heterogeneity has a major impact on the measurement of circulating N-terminal fragments of A- and B-type natriuretic peptides. *Clin Chem* 50:1576–1588
- Aiura K, Ueda M, Endo M, Kitajima M (1995) Circulating concentrations and physiologic role of atrial natriuretic peptide during endotoxic shock in the rat. *Crit Care Med* 23:1898–1906
- Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Sutton GC (1997) Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 350:1349–1353
- Lubbesmeyer HJ, Woodson L, Traber LD, Flynn JT, Herndon DN, Traber DL (1988) Immunoreactive atrial natriuretic factor is increased in ovine model of endotoxemia. *Am J Physiol* 254:R567–R571
- McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, Tunstall-Pedoe H, McMurray JJ, Dargie HJ (1998) Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 351:9–13
- Ruskoaho H (2003) Cardiac hormones as diagnostic tools in heart failure. *Endocr Rev* 24:341–356
- Hartemink KJ, Groeneveld AB, de Groot MC, Strack van Schijndel RJ, van Kamp G, Thijs LG (2001) Alpha-atrial natriuretic peptide, cyclic guanosine monophosphate, and endothelin in plasma as markers of myocardial depression in human septic shock. *Crit Care Med* 29:80–87
- Langer M, Cigada M, Mandelli M, Mosconi P, Tognoni G (1987) Early onset pneumonia: a multicenter study in intensive care units. *Intensive Care Med* 13:342–346
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. *Crit Care Med* 13:818–829
- Fabregas N, Ewig S, Torres A, El Ebiary M, Ramirez J, de la Bellacasa JP, Bauer T, Cabello H (1999) Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. *Thorax* 54:867–873
- Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM (1991) Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic “blind” bronchoalveolar lavage fluid. *Am Rev Respir Dis* 143:1121–1129

-
19. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL (2000) Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 162:505–511
 20. American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis (1992) *Crit Care Med* 20:864–874
 21. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/ Society of Critical Care Medicine. *Chest* 101:1644–1655
 22. Luna CM, Blanzaco D, Niederman MS, Matarucco W, Baredes NC, Desmery P, Palizas F, Menga G, Rios F, Apezteguia C (2003) Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. *Crit Care Med* 31:676–682
 23. Luyt CE, Guerin V, Combes A, Trouillet JL, Ayed SB, Bernard M, Gibert C, Chastre J (2005) Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 171:48–53
 24. Seligman R, Meisner M, Lisboa TC, Hertz FT, Filippin TB, Fachel JM, Teixeira PJ (2006) Decreases in procalcitonin and C-reactive protein are strong predictors of survival in ventilator-associated pneumonia. *Crit Care* 10:R125
 25. Muller B, Suess E, Schuetz P, Muller C, Bingisser R, Bergmann A, Stolz D, Tamm M, Morgenthaler NG, Christ-Crain M (2006) Circulating levels of pro-atrial natriuretic peptide in lower respiratory tract infections. *J Intern Med* 260:568–576
 26. Masia M, Papassotiriou J, Morgenthaler NG, Hernandez I, Shum C, Gutierrez F (2007) Midregional pro-atrial natriuretic peptide and carboxy-terminal pro-vasopressin may predict prognosis in community-acquired pneumonia. *Clin Chem* 53:2193–2201
 27. Prat C, Lacoma A, Dominguez J, Papassotiriou J, Morgenthaler NG, Andreo F, Tudela P, Ruiz-Manzano J, Ausina V (2007) Midregional pro-atrial natriuretic peptide as a prognostic marker in pneumonia. *J Infect* 55:400–407
 28. Kruger S, Papassotiriou J, Marre R, Richter K, Schumann C, von Baum H, Morgenthaler NG, Suttrop N, Welte T (2007) Pro-atrial natriuretic peptide and pro-vasopressin to predict severity and prognosis in community-acquired pneumonia : results from the German competence network CAPNETZ. *Intensive Care Med* 33:2069–2078