The vasopressin and copeptin response to infection, severe sepsis, and septic shock

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Objective: **To compare the course of arginine vasopressin (AVP) and copeptin plasma concentrations between patients with infection, severe sepsis, and septic shock.**

Design: **Prospective, closed-cohort study.**

Setting: **Twelve-bed general and surgical intensive care unit and 33-bed internal medicine ward in a university hospital.**

Patients: **Ten patients with infection, 22 with severe sepsis, and 28 with septic shock.**

Interventions: **None.**

Measurements and Main Results: **Hemodynamic, laboratory and clinical data were recorded daily during the first 7 days after intensive care unit or hospital admission. Parallel thereto, blood was withdrawn to determine plasma AVP (radioimmunoassay) and copeptin (immunoluminometric assay) concentrations. Standard tests, a mixed effects model, and a linear regression analysis were used for statistical analysis. The AVP response was different between the three study groups ($p < 0.001$) but did not change over time ($p = 0.12$). Although patients with severe sepsis and septic shock had higher AVP levels than did patients with infection (both $p < 0.001$), no difference in AVP concentrations was seen between severe sepsis and septic shock patients ($p = 0.98$). No difference in AVP was observed between survivors and nonsurvivors at day 28 ($p = 0.87$). In patients with severe sepsis, serum osmolarity ($p < 0.001$), arterial pH ($p = 0.001$), lactate ($p < 0.001$), and Pao_2 ($p = 0.04$) were associated with the course of AVP plasma levels, whereas it was serum osmolarity alone in patients with septic shock ($p = 0.03$). Plasma AVP concentrations correlated with copeptin ($r = .614$, $p < 0.001$), but this correlation was influenced by continuous veno-venous hemofiltration ($p = 0.002$).**

Conclusions: **Severe sepsis induced a stronger AVP response than infection without systemic inflammation. However, the lack of a difference in AVP plasma concentrations between patients with and without shock indicates that the AVP system does not function normally in severe sepsis. Our data support the hypothesis that impaired AVP response is at least partially responsible for the failure to restore vascular tone in septic shock. (Crit Care Med 2009; 37:000–000)**

KEY WORDS: vasopressin; plasma concentrations; infection; severe sepsis; septic shock; copeptin

Septic shock is characterized by hypovolemia and decreased vascular resistance with or without myocardial dysfunction (1). Multiple pathophysiologic mechanisms are responsible for cardiovascular failure in patients with sepsis. Decreased arteriolar tone, which often dominates the clinical picture, has been attributed to a disturbance in the endogenous vasodilatator–vasoconstrictor balance, activation of K_{ATP} channels, quantitative and qualitative downregulation of vasoconstrictor hormone receptors, and relative deficiency of neuroendocrine stress hormones (2).

Both adrenal insufficiency and inadequate plasma concentrations of arginine vasopressin (AVP) have been suggested to contribute to the failure to restore vascular tone (1, 2). Relative AVP deficiency has been reported in one third of patients with septic shock (3). Accordingly, lower AVP plasma levels were observed during septic as compared with cardiogenic shock, in which peripheral vascular tone is typically maintained (4). Exogenous administration of AVP restored hemodynamic variables in septic shock poorly responsive to standard catecholamine therapy (5). A recent multicenter trial evaluating the effects of an adjunct AVP infusion on outcome in septic shock failed to detect an overall benefit of AVP but indicated improved survival rates if AVP was added before norepinephrine dosages exceeded 15 μg/min (6).

It can be expected that infusion of a vasoconstrictor hormone such as AVP increases arterial blood pressure in septic shock (5). However, it is unclear whether such a therapy reverses an endogenous AVP deficiency, causally interferes with pathophysiologic mechanisms of septic shock, or simply constitutes a pharmacologic intervention to increase peripheral vascular tone. Knowledge of the endogenous AVP response to sepsis and septic shock could be helpful in answering this question. Confirmation of the hypothesis of a relative AVP deficiency in septic shock would provide a sound basis for the therapeutic infusion of AVP in patients with sepsis-associated cardiovascular failure.

This prospective, closed-cohort study measured AVP and copeptin plasma concentrations in 50 patients with sepsis or

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septic shock and in ten patients with infection but no systemic inflammation during the first 7 days after intensive care unit (ICU) or hospital admission.

PATIENTS AND METHODS

From November 2005 to November 2006, this prospective study was performed in a 12-bed general and surgical ICU (severe sepsis and septic shock group) and in a 33-bed internal medicine ward (infection group), both in a university teaching hospital. The study protocol was approved by the institutional review board and the Ethics Committee of Innsbruck Medical University (UN2387; 232/4.16). Written informed consent was obtained from all patients in the infection group and from the next of kin of patients in the severe sepsis and septic shock group.

Patients. The study population consisted of three groups to which patients were assigned based on their clinical course during the first 36 hours after ICU or hospital admission. The inclusion criterion for the severe sepsis or septic shock group was ICU admission because of severe sepsis or septic shock, respectively. Severe sepsis and septic shock were defined according to the ACCP/SCCM criteria (7). The infection group consisted of patients who were admitted to the hospital because of an infection but did not show more than one sign of systemic inflammation. Exclusion criteria were discharged alive from the ICU (severe sepsis and septic shock group) or from hospital (infection group) before day 7, central nervous system pathology, known pathology of the AVP system, treatment with AVP before or during the study period, age <19 years, pregnancy, or refusal to give written informed consent.

All severe sepsis and septic shock patients were volume resuscitated according to the response of filling pressures [e.g., central venous pressure (central venous pressure), pulmonary capillary wedge pressure], and/or stroke volume index to fluid loading using gelatin-based colloids (Gelofusin; B Braun, Melsungen, Germany). If hemodynamic instability persisted and stroke volume index remained <25 mL/min/m^2 or mixed venous oxygen saturation remained <60% despite adequate volume resuscitation, a milrinone and/or an epinephrine infusion was started. After ensuring adequate systemic blood flow using volume and inotropic therapy, norepinephrine was continuously infused to increase mean arterial blood pressure (MAP) >60 mm Hg. Intubated patients on mechanical, assisted, or spontaneous breathing were analgosedated by continuous infusion of either sufentanil and midazolam or morphine alone. Continuous venovenous hemofiltration (CVVHF) was used for renal indications only. With the exception of milrinone therapy and activated protein C administration, causative and supportive sepsis therapy was performed according to recommended guidelines (8). Hydrocortisone was infused in addition to norepinephrine in 15 patients with septic shock (53.6%).

Data Collection. In all study patients, demographic data, medical history, chronic intake of angiotensin-converting enzyme inhibitors, classification of the American Society of Anesthesiologists (9), and the source of infection were documented at study entry. Twenty-four hours after ICU admission, the Simplified Acute Physiology Score II (10) was calculated from worst laboratory and clinical parameters in severe sepsis and septic shock patients. Within 36 hours after ICU admission, 3 mL of arterial EDTA blood were sampled to determine AVP and copeptin plasma concentrations. Blood was taken from an arterial line (sepsis and septic shock group) or by puncturing a peripheral vein (infection group) once daily at the same time for 7 days. Blood samples were immediately centrifuged at the central institutional laboratory and the supernatant plasma portion frozen at −80°C.

At the same time, MAP, central venous pressure, pulmonary artery occlusion pressure, norepinephrine requirements, serum osmolarity, arterial pH, lactate levels and partial oxygen pressure (Pa_{O_2}), and daily sufentanil and morphine dosages were recorded in the severe sepsis and septic shock group. A multiple organ dysfunction syndrome score (11) was calculated from worst clinical and laboratory data. At ICU discharge, the length of ICU stay was documented. In the infection group, the same parameters as in the two sepsis groups were recorded whenever available and measurable at the given times. In all patients, mortality was registered 28 days after admission to the ICU (severe sepsis and septic shock group) or to the hospital (infection group).

Measurement of AVP and Copeptin Plasma Concentrations. After completing patient recruitment, blinded frozen plasma samples were transferred to the endocrinologic laboratories. For measurement of AVP, 1 mL EDTA plasma was extracted with 4 mL ethanol, evaporated, and then reconstituted in 1 mL assay buffer and 0.3 mL extract. Subsequently, 0.4-mL extract was assayed using a radioimmunoassay (DRG Diagnostics, Marburg, Germany) (12). The AVP assay standard calibration curve ranges from 0.5 to 60 pmol/L with a minimum quantitation limit of 0.1 pmol/L. The intra- and interassay variation is 4.9% to 6.5% and 6% to 6.9%, respectively. Only when test results lay outside the clinically expected range (<0.83 or >50 pmol/L) were measurements repeated to confirm the results. All other measurements were performed once.

Copeptin plasma concentrations were determined once using a sandwich immunoluminometric assay (B.R.A.H.M.S. LUMItest CT-proAVP, B.R.A.H.M.S AG, Hennigsdorf/Berlin, Germany) as described in detail before (13). Since this initial publication, the assay was modified as follows: the capture antibody was replaced with a murine monoclonal antibody directed against amino acids 137–144 (GPAGAL) of proAVP. This modification improved the sensitivity of the assay. The lower detection limit is 0.4 pmol/L and the functional assay sensitivity (<20% interassay CV) is <1 pmol/L. Median copeptin levels in 200 healthy individuals were 3.7 pmol/L and the 97.5 percentile was 16.4 pmol/L.

Study End Points. The primary end point was to compare the course of AVP plasma concentrations between patients with infection, severe sepsis, and septic shock. The secondary study end point was to test for an association between the course of AVP plasma concentrations and parameters physiologically known to influence AVP release in any of the groups. The tertiary study end point was to evaluate the correlation between AVP and copeptin plasma concentrations.

Statistical Analysis. For statistical analysis, the SPSS software program (Version 12.0.1; SPSS, Chicago, IL) was used. Kolmogorov-Smirnov tests were applied to check for normality distribution of study variables. In case variables were not normally distributed (AVP, copeptin, body mass index, MAP, serum osmolarity, and arterial lactate), *ln*-transformation was performed to attain a Gaussian distribution. Demographic and clinical variables were compared between groups using a one-way analysis of variance, the Student's *t*, or the Chi-square test, as appropriate. The course of AVP plasma concentrations over time and differences between groups were analyzed using a linear mixed effects model that considers repeated measurements to be correlated and not independent of each other (14). In case of statistical significance, AVP levels at single time points were compared between the three groups using Student's *t* tests. To test for a possible association between AVP plasma levels and parameters known to influence AVP release, a mixed effects model was used as well. Because copeptin was not normally distributed, a nonparametric Spearman's rank correlation was used to evaluate the correlation between AVP and copeptin plasma concentrations in all patients. Statistical significance was assumed if p was <0.05; in the case of multiple comparisons, Bonferroni corrections were applied. Data are given as mean ± SD, if not indicated otherwise.

RESULTS

During the observation period, 79 patients with sepsis (n = 42) and septic shock (n = 37) were admitted to the ICU. Twenty-six patients were discharged alive before ICU day 7, and written informed consent could not be obtained in three patients. Twenty-two patients with severe sepsis and 28 patients with septic shock were included in the study protocol. Six patients who presented with severe sepsis during the first 36 hours developed shock during the observation period. The mean duration of cardiovascular dysfunc-

tion was 9.3 ± 10.1 days in the septic shock group. No study patient received a supplementary AVP infusion. During the same time, ten patients with infection treated at the internal medicine ward were enrolled in the study protocol. None of these patients exhibited two or more signs of prolonged systemic inflammation (>24 hours) during the observation period.

Table 1 presents demographic and clinical characteristics of the study population. The American Society of Anesthesiologists' classification differed significantly between the three groups. The Simplified Acute Physiology Score II and multiple organ dysfunction syndrome score were higher, and the length of ICU stay was longer in patients with septic shock than in those with severe sepsis. The time between ICU or hospital admission and study inclusion was 8.7 ± 7.1, 10.3 ± 7.3, and 8.8 ± 9.2 hours in the infection, severe sepsis, and septic shock group, respectively ($p = 0.79$).

The AVP response differed significantly between the three groups ($p < 0.001$), but did not change over time ($p = 0.12$). Although patients with severe sepsis and septic shock had significantly higher AVP levels than did patients with infection (both $p < 0.001$), there was no difference in the course of plasma AVP concentrations between patients with severe sepsis and those with septic shock ($p = 0.98$) (Fig. 1). No difference was observed in AVP plasma concentrations between survivors and nonsurvivors ($p = 0.87$) (Fig. 2). Plasma AVP levels in severe sepsis patients who developed shock during the observation period are shown in Table 2. Infusion of hydrocortisone did not significantly influence the course of plasma AVP levels in patients with septic shock ($p = 0.08$).

Variables known to influence the release of AVP and arterial lactate levels are presented for each of the three groups in Table 3. No correlation between any of these variables and the course of AVP plasma levels was detected in the infection group (Table 4). In patients with severe sepsis, serum osmolarity and arterial lactate levels were directly and arterial pH and Pao_2 were inversely associated with the course of AVP plasma levels, whereas in patients with septic shock only serum osmolarity was directly correlated. Although the number of measurements at MAP levels <60 mm Hg was small (n = 7), hypotensive septic shock patients had significantly higher plasma

Table 1. Characteristics of the study population

	Infection	Severe Sepsis	Septic Shock	*p*
n	10	22	28	
Male, n (%)	6 (60)	15 (68.2)	21 (75)	0.66
Age (yrs)	59 ± 16	57 ± 17	63 ± 15	0.44
BMI (kg/m^2)	29 ± 6	26 ± 6	26 ± 5	0.41
Chronic ACEI therapy, n (%)	2 (20)	3 (13.6)	6 (21.4)	0.75
ASA classification	2.4 ± 0.5	3.6 ± 0.6	3.6 ± 0.5	<0.001[a]
Source of infection, n (%)				
Lungs	6 (60)	6 (27.3)	6 (21.4)	0.29
Abdomen	1 (10)	9 (40.9)	14 (50)	
Urinary tract	1 (10)	1 (4.5)	2 (7.1)	
Others	2 (20)	6 (27.3)	6 (21.4)	
SAPS II (points)	n.a.	38 ± 13	49 ± 16	<0.001[b]
Mechanical ventilation, n (%)	n.a.	18 (81.8)	25 (89.3)	0.68
RRT, n (%)	n.a.	2 (9.1)	6 (21.4)	0.24
Goris MODS Score (points)	n.a.	7.6 ± 1.8	9.5 ± 1.8	<0.001[b]
ICU length of stay (days)	n.a.	14 ± 9	20 ± 13	<0.001[b]
28-Day mortality, n (%)	1 (10)	1 (4.5)	6 (21.4)	0.21

BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ASA, American Society of Anesthesiologists; SAPS, Simplified Acute Physiology Score; RRT, renal replacement therapy; MODS, multiple organ dysfunction syndrome; ICU, intensive care unit.

Data are given as mean ± SD, if not otherwise indicated.

[a]Significant difference between patients with infection, severe sepsis, and septic shock; [b]significant difference between patients with severe sepsis and septic shock.

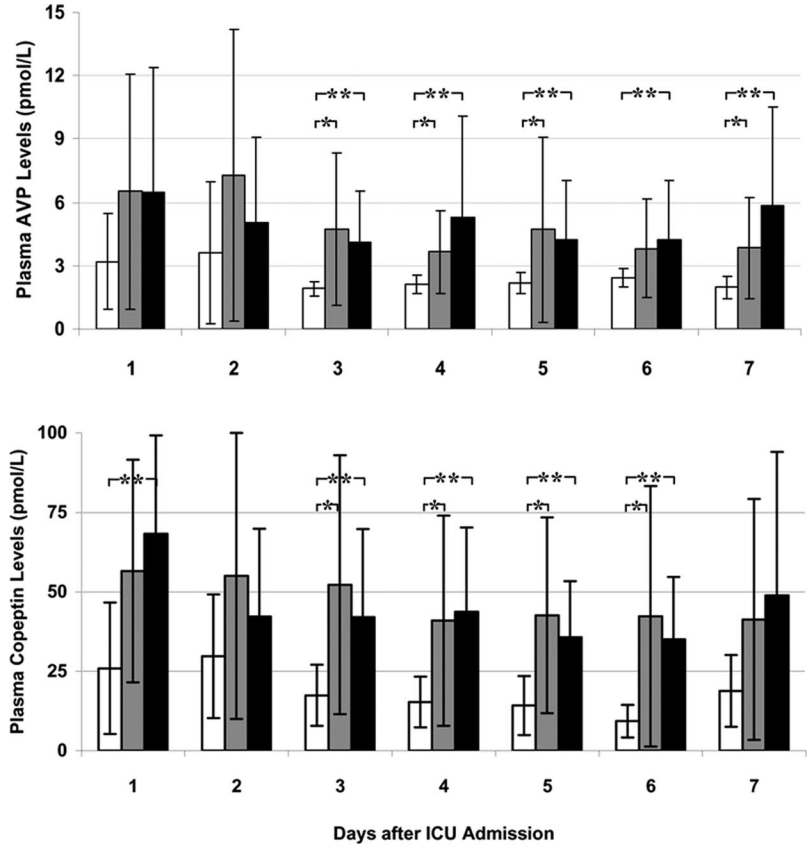

Figure 1. Course of plasma arginine vasopressin (*AVP*) and copeptin concentrations in patients with infection (*white bars*), severe sepsis (*gray bars*), and septic shock (*black bars*). *ICU*, intensive care unit.

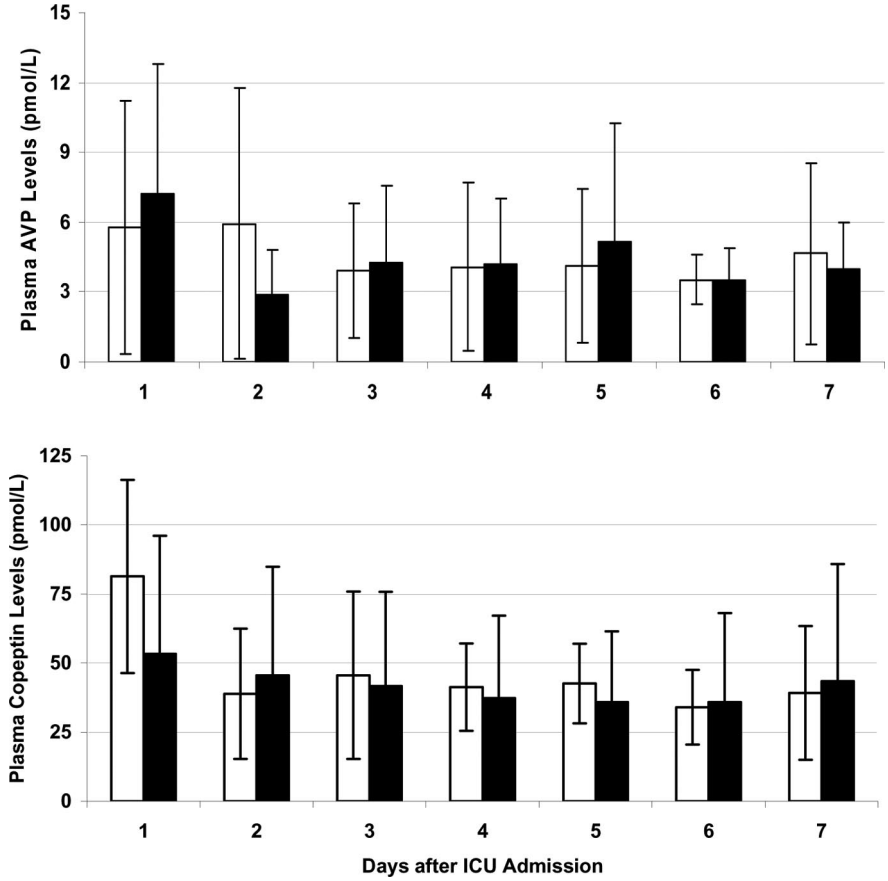

Figure 2. Course of plasma arginine vasopressin (*AVP*) and copeptin concentrations in survivors (*white bars*) and nonsurvivors (*black bars*). *ICU,* intensive care unit.

Table 2. Arginine vasopressin plasma levels (pmol/L) in severe sepsis patients who developed shock during the observation period

Patient	ICU Day 1	ICU Day 2	ICU Day 3	ICU Day 4	ICU Day 5	ICU Day 6	ICU Day 7
1	9.1	22.9[a]	8.6	5.4	5.8[b]	4	4.9
2	2.3	1.6[a]	6	1.8	0.6	2	2.8[b]
3	6.1	3.9	3.5[a]	3.9	2.7	5.7[b]	6.6
4	0.7	0.5	0.9[a]	0.7	3.7[b]	9	0.5
5	1.4	4.4	17.1	2.2	8.1[a]	1.7	1
6	3.2	21.6	1.8	1.3	1.3	3.2	4.7[a]

ICU, intensive care unit.
[a]Start of vasopressor therapy; [b]withdrawal of vasopressor therapy.

AVP levels than did patients with a MAP >60 mm Hg (4.8 ± 4 vs. 8 ± 4.6, $p = 0.04$). Neither in patients with severe sepsis ($p = 0.12$) nor in patients with septic shock ($p = 0.37$) were the degree of multiple organ dysfunction and AVP plasma levels correlated. Similarly, copeptin plasma concentrations were directly associated with serum osmolarity and inversely associated with arterial pH in patients with severe sepsis (serum osmolarity, F value, 38.348; $p < 0.001$; arterial pH, F value, 7.169; $p = 0.007$) and septic shock (serum osmolarity, F value, 7.938; $p = 0.007$; arterial pH, F value, 5.596; $p = 0.03$). Pa_{O_2} was not associated with copeptin in either group ($p > 0.05$).

In the linear regression model, the AVP and copeptin plasma concentrations of the entire study population correlated significantly with each other ($p < 0.001$; $r = .614$) (Fig. 3). This correlation was influenced neither by plasma creatinine concentrations ($p = 0.05$) nor by creatinine clearance ($p = 0.06$), but by the need for CVVHF ($p = 0.002$). Although patients without CVVHF exhibited a correlation coefficient of $r = .672$ ($p < 0.001$), it was $r = .217$ ($p = 0.06$) in patients who required renal replacement therapy. The graphic course of copeptin plasma concentrations resembles that of AVP and shows comparable differences between patients with infection, severe sepsis, and septic shock as well as between survivors and nonsurvivors (Figs. 1 and 2).

DISCUSSION

In this prospective, closed-cohort study, plasma AVP concentrations were higher in patients suffering from sepsis than in patients presenting with infection but no systemic inflammation. However, the AVP response did not differ between severe sepsis patients with and those without shock or between survivors and nonsurvivors. The course of plasma AVP concentrations was associated with serum osmolarity, arterial pH, P_{AO_2}, and arterial lactate in patients with severe sepsis and with serum osmolarity alone in patients with septic shock. Plasma AVP and copeptin concentrations significantly correlated with each other.

It is certainly difficult to form homogeneous groups of patients with severe sepsis or with septic shock who typically have a dynamic disease course. Accordingly, in our study six patients who presented to the ICU with severe sepsis developed shock during the observation period. Although this heterogeneity reflects the clinical situation well, it may limit evaluation and comparability of hormone levels between groups. However, given the relatively small patient population in our trial, alternative patient grouping would have resulted in additional shortcomings such as more and smaller groups requiring more intergroup comparisons.

Although infection itself did not relevantly seem to trigger AVP secretion in this study population, the presence of systemic inflammation did. Animal data proving that inflammatory mediators such as interleukin 1 or tumor necrosis factor alpha stimulate AVP release (15, 16) support this observation. Furthermore, AVP secretion can be induced by several other factors such as acidosis, pain, hypoxia, or neuroendocrine stress (17), all of which are more likely to occur in patients with severe sepsis than in those with infection but no systemic inflammation. However, when comparing the AVP response to severe sepsis or sep-

Table 3. Parameters known to influence arginine vasopressin release and arterial lactate levels in patients with infection, severe sepsis, and septic shock during the observation period

	ICU Day 1	ICU Day 2	ICU Day 3	ICU Day 4	ICU Day 5	ICU Day 6	ICU Day 7
MAP (mm Hg)							
Infection	86 ± 14	88 ± 17	87 ± 14	91 ± 13	97 ± 12	93 ± 6	93 ± 12
Severe sepsis	80 ± 13	76 ± 11	87 ± 16	87 ± 17	87 ± 20	90 ± 13	88 ± 15
Septic shock	75 ± 12	78 ± 12	82 ± 11	83 ± 10	82 ± 13	84 ± 11	86 ± 13
CVP (mm Hg)							
Infection	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Severe sepsis	10 ± 4	9 ± 3	10 ± 3	8 ± 3	8 ± 4	7 ± 4	7 ± 3
Septic shock	12 ± 5	11 ± 3	10 ± 4	10 ± 3	10 ± 2	9 ± 4	8 ± 3
Pulmonary artery occlusion pressure (mm Hg)							
Infection	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Severe sepsis	15 ± 2	13 ± 1	15 ± 4	11 ± 4	n.a.	n.a.	n.a.
Septic shock	18 ± 5	19 ± 5	16 ± 3	14 ± 4	19 ± 6	13 ± 4	14 ± 5
NE dosage (μg/kg/min)							
Infection	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Severe sepsis	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Septic shock	0.23 ± 0.12	0.36 ± 0.73	0.16 ± 0.18	0.08 ± 0.06	0.06 ± 0.04	0.1 ± 0.1	0.05 ± 0.03
Serum osmolarity (mosmol/L)							
Infection	298 ± 8	296 ± 10	287 ± 9	293 ± 6	290 ± 12	289 ± 14	282 ± 19
Severe sepsis	307 ± 12	312 ± 13	311 ± 23	318 ± 19	317 ± 19	314 ± 20	307 ± 19
Septic shock	311 ± 24	313 ± 20	310 ± 21	312 ± 19	313 ± 14	316 ± 17	313 ± 20
Arterial pH							
Infection	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Severe sepsis	7.39 ± 0.09	7.43 ± 0.05	7.44 ± 0.07	7.46 ± 0.05	7.47 ± 0.05	7.47 ± 0.05	7.48 ± 0.06
Septic shock	7.38 ± 0.08	7.39 ± 0.09	7.4 ± 0.09	7.44 ± 0.05	7.47 ± 0.07	7.46 ± 0.05	7.47 ± 0.04
Pa_{O_2} (mm Hg)							
Infection	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Severe sepsis	307 ± 12	312 ± 13	311 ± 23	318 ± 19	317 ± 19	314 ± 20	307 ± 19
Septic shock	311 ± 24	313 ± 20	310 ± 16	313 ± 19	313 ± 14	316 ± 17	313 ± 20
Sufentanil (mg/day)							
Infection	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Severe sepsis	0.6 ± 0.5	0.6 ± 0.4	0.6 ± 0.5	0.6 ± 0.6	0.9 ± 0.6	0.5 ± 0.6	0.9 ± 0.9
Septic shock	0.7 ± 0.4	0.5 ± 0.4	0.5 ± 0.5	0.9 ± 0.7	0.7 ± 0.6	0.6 ± 0.5	0.7 ± 0.6
Morphine (mg/day)							
Infection	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Severe sepsis	20 ± 14	19 ± 14	20 ± 15	20 ± 17	20 ± 16	20 ± 18	20 ± 17
Septic shock	26 ± 17	27 ± 17	22 ± 15	19 ± 15	19 ± 14	18 ± 15	19 ± 16
Arterial lactate (mg/dL)							
Infection	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Severe sepsis	21 ± 15	17 ± 22	12 ± 5	13 ± 6	13 ± 4	12 ± 4	11 ± 3
Septic shock	25 ± 14	23 ± 34	15 ± 7	14 ± 7	15 ± 8	16 ± 8	16 ± 7

ICU, intensive care unit; MAP, mean arterial blood pressure; CVP, central venous pressure; NE, norepinephrine; Pa_{O_2}, partial arterial oxygen tension; n.a., not available/applicable.

Data are given as mean values ± SD.

Table 4. Association between arginine vasopressin plasma concentrations and parameters physiologically known to influence arginine vasopressin release

	Infection (n = 10)		Severe Sepsis (n = 22)		Septic Shock (n = 28)	
	F	p	F	p	F	p
MAP	0.602	0.45	0.568	0.45	0.106	0.75
CVP	n.a.	n.a.	0.026	0.87	0.15	0.7
PCWP	n.a.	n.a.	n.a.	n.a.	29.644	0.13
NE dosage	n.a.	n.a.	n.a.	n.a.	0.07	0.793
Serum osmolarity	1.345	0.27	17.874	<0.001[a]	5.571	0.03[a]
Arterial pH	n.a.	n.a.	12.371	0.001[a]	2.405	0.13
Pa_{O_2}	n.a.	n.a.	4.055	0.04[a]	3.782	0.06
Sufentanil dosage	n.a.	n.a.	2.417	0.14	1.414	0.24
Morphine dosage	n.a.	n.a.	0.097	0.76	0.166	0.69
Arterial lactate	n.a.	n.a.	26.633	<0.001[a]	3.891	0.11

MAP, mean arterial blood pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; NE, norepinephrine; Pa_{O_2}, partial arterial oxygen tension; n.a., not available/applicable.

[a]Significant association between AVP plasma concentrations and the parameter.

tic shock with that following cardiac arrest (88–122 pg/mL ~82–114 pmol/L [18]), multiple trauma (43.2 ± 84.9 pmol/L [19]), or vasodilatory shock after cardiac surgery (19.7 ± 24 pmol/L [20]), the plasma AVP concentrations in our study are only moderately increased. AVP plasma levels comparable to the present analysis were observed in a recent multicenter study before starting AVP infusion in septic shock patients (3.2 [interquartile range 1.7–4.9 pmol/L] [6]), and previously by other authors (septic shock, 3.1 ± 0.4 pg/mL ~ 2.9 ± 0.4 pmol/L [4]; septic shock, 7.3 ± 8.5 pg/mL ~ 6.7 ± 7.8 pmol/L [21]), and our own study group (advanced vasodilatory shock, 8.7 ± 5.7 pmol/L [22]; sepsis, 6.3 ± 5.9 pmol/L [23]; septic shock, 8.7 ± 4.3 pmol/L [23]).

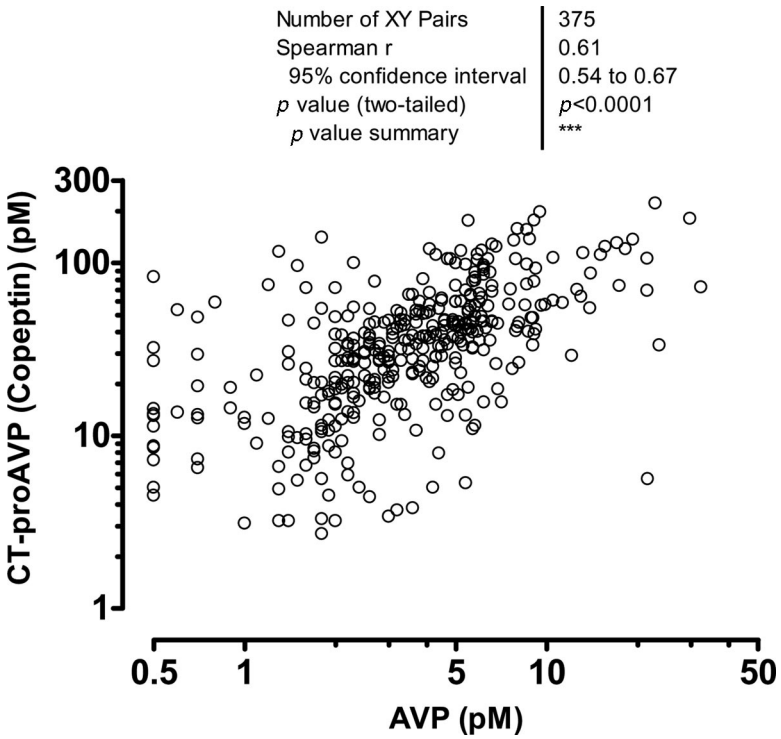

Figure 3. Correlation between plasma arginine vasopressin (*AVP*) and copeptin plasma concentrations in all study patients (n = 60).

Sharshar et al (3) observed a negative correlation between AVP plasma concentrations and the time after shock onset. Almost all of their patients (16 of 18) presented with elevated AVP plasma concentrations during the first 36 hours of septic shock. Interestingly, the AVP response in our study patients with severe sepsis and septic shock did not change over time, as suggested by animal data (17) or a recent clinical trial (3). Although copeptin plasma levels were higher on ICU day 1 in patients with septic shock, this was not statistically significant, but may reflect increased AVP and copeptin secretion at disease onset. Because blood sampling was performed in our study population within 10 hours of ICU or hospital admission, an initial AVP peak might have been missed. It is also conceivable that AVP and copeptin plasma levels would have shown a significant change over time, had more study patients been included.

Although the endogenous AVP system was more activated in patients with severe sepsis than in those with infection, our data suggest that the AVP system was at least somewhat dysfunctional during severe sepsis and particularly during septic shock. Because reduced venous filling and arterial hypotension both stimulate AVP release, higher AVP plasma concentrations would have been physiologically expected in patients with septic shock (24). Although fluid resuscitation and a mean central venous pressure of 10 ± 4 mm Hg may have abolished stimulation of AVP secretion through stretch receptors in the low-pressure circulation, a mean MAP of 75 ± 12 mm Hg should have physiologically continued to stimulate AVP release (25). Mechanisms proposed for a possible sepsis-associated dysfunction of the AVP system include autonomic dysfunction of the afferent pathways and inadequate AVP production with consequent depletion of neurohypophyseal stores (26). Furthermore, inhibitory effects of high catecholamine plasma concentrations (27) and analgosedative drugs (28) on AVP secretion have been observed.

The results of the correlation analysis between AVP plasma concentrations and variables physiologically known to stimulate AVP release support the hypothesis that the severe sepsis and septic shock AVP system does not function normally. Although no correlation with hemodynamic variables could be detected in patients with or without shock, patients with severe sepsis still showed a maintained relationship between AVP plasma levels and serum osmolarity, arterial pH, lactate, and oxygen tension. In contrast, AVP plasma concentrations in septic shock patients were only moderately associated with serum osmolarity. However, it needs to be considered that when sampling hemodynamic variables and AVP plasma concentrations at selected times, a dynamic association over time might not have been detectable. At first glance, it is similarly astonishing that a correlation between MAP or serum osmolarity and AVP plasma concentrations could not be identified in patients with infection. Because these patients did not show pathologic variations in any of these variables, it may have been difficult to detect an association with AVP plasma levels.

Although comparable AVP plasma concentrations in sepsis patients with or without shock cannot prove a causative relationship, it seems plausible that a relative deficiency in AVP at least contributes to the failure to restore vascular tone in patients with septic shock (2). Although there is little convincing scientific evidence to prove this hypothesis, it is supported by findings made by Landry et al (4) who detected lower AVP plasma concentrations in septic shock patients (3.1 ± 0.4 pg/mL ~ 2.9 ± 0.4 pmol/L) than in cardiogenic shock patients with increased arteriolar tone (22.7 ± 2.2 pg/mL ~ 21 ± 2 pmoL/L, $p < 0.001$). Sharshar et al (3) also suggested a relative AVP deficiency in approximately one third of patients with septic shock 36 hours after onset of cardiovascular failure. Similarly, our study group observed a relative AVP deficiency in 22% of patients with septic shock (23). Even though the diagnosis of relative AVP deficiency strongly depends on its definition and cannot establish a causative relationship, it shows a disturbed AVP system in severe sepsis and septic shock. However, compared with the international average, the mortality rate observed in our septic shock population was low. Because only three patients who met the inclusion criteria during the observation period could not be enrolled, it is unlikely that a relevant selection bias occurred and predominantly patients with a mild or moderate disease severity were included. In contrast, the mean multiple organ dysfunction syndrome score of 7.6 and 9.5 points in severe sepsis and septic shock patients corresponds to an average number of 3.8 and 4.8 failing organs, respectively. Although plasma AVP levels did not correlate with the degree of multiple organ dysfunction in our study, we cannot extrapolate the course

of AVP levels in patients with an even more severe course of septic shock from the present data.

Copeptin, a stable fragment of the AVP *prepro*-hormone, exhibits an advantageous biochemical profile over AVP for laboratory testing and has recently been suggested as a surrogate marker for assessing AVP system activity in acutely (29) and critically ill patients (30). In agreement with our results, significantly elevated copeptin plasma concentrations have been observed in clinical sepsis (31) and septic shock (32). Whereas an excellent correlation between copeptin and AVP plasma concentrations was observed in multiple trauma (19) and cardiac surgery (20) patients ($r > 0.7$), the correlation of the two hormones is less convincing in the current study ($r = 0.614$). The finding that the need for CVVHF further worsened the correlation between AVP and copeptin suggests that different sieving coefficients may result in diverse amounts of filtered hormone levels during CVVHF. A previous study (30) showed the ratio of AVP to copeptin to correlate with plasma concentrations of the C-reactive protein suggesting that inflammation may interfere with the association between AVP and copeptin.

CONCLUSION

Severe sepsis induced a stronger AVP response than infection without systemic inflammation. However, the lack of a difference in AVP plasma concentrations between patients with and without shock indicates that the AVP system does not function normally in severe sepsis. Our data support the hypothesis that impaired AVP response is at least partially responsible for the failure to restore vascular tone in septic shock.

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