Serum vasopressin concentrations in critically ill patients*

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Objective: **To measure arginine vasopressin (AVP) serum concentrations in critically ill patients.**

Design: **Prospective study.**

Setting: **Twelve-bed general and surgical intensive care unit in a tertiary, university teaching hospital.**

Patients: **Two-hundred-thirty-nine mixed critically ill patients and 70 healthy volunteers.**

Interventions: **None.**

Measurements and Main Results: **Demographic data, hemodynamic variables, vasopressor drug requirements, blood gases, AVP serum concentrations within 24 hrs after admission, multiple organ dysfunction score, and outcome were recorded. Twenty-four hours after admission, study patients had significantly higher AVP concentrations (11.9 ± 20.6 pg/mL) than healthy controls (0.92 ± 0.38 pg/mL; $p < .001$). Males had lower AVP concentrations than females (9.7 ± 19.5 vs. 15.1 ± 20.6 pg/mL; $p = .014$). Patients with hemodynamic dysfunction had higher AVP concentrations than patients without hemodynamic dysfunction (14.1 ± 27.1 vs. 8.7 ± 10.8 pg/mL; $p = .042$). Patients after cardiac surgery (n = 96) had significantly higher AVP concentrations when compared to patients admitted for other diagnoses (n = 143; $p < .001$). AVP concentrations were inversely correlated with length of stay in the intensive care unit (correlation coefficient, −0.222; $p = .002$). There was no correlation between serum AVP concentrations and the incidence of shock or specific hemodynamic parameters. Four (1.7%) of the 239 study patients met criteria for an absolute AVP deficiency (AVP, <0.83 pg/mL), and 32 (13.4%) met criteria for a relative AVP deficiency (AVP, <10 pg/mL, and mean arterial pressure, <70 mm Hg). In shock patients, relative AVP deficiency occurred in 22.2% (septic shock), 15.4% (postcardiotomy shock), and 10% (shock due to a severe systemic inflammatory response syndrome) ($p = .316$).**

Conclusions: **AVP serum concentrations 24 hrs after intensive care unit admission were significantly increased in this mixed critically ill patient population. The lack of a correlation between AVP serum concentrations and hemodynamic parameters suggests complex dysfunction of the vasopressinergic system in critical illness. Relative and absolute AVP deficiency may be infrequent entities during acute surgical critical illness, mostly remaining without significant effects on cardiovascular function. (Crit Care Med 2006; 34:293–299)**

KEY WORDS: arginine vasopressin; serum concentrations; critical illness; shock; sepsis; vasopressin deficiency;

In 1997, Landry et al. observed that patients in septic shock had significantly lower arginine vasopressin (AVP) serum concentrations than patients with cardiogenic shock (1). Several subsequent studies showed low AVP concentrations in patients with arterial hypotension due to different advanced shock states (2–4). Therefore, AVP deficiency seems to play an important role in loss of vascular tone in vasodilatory shock (5). It was hypothesized that, comparable to substitution of inadequately low cortisol concentrations in septic shock, substitution of AVP deficiency in shock patients by exogenous AVP infusion might be beneficial (6–8). Although endocrinologic substitution should imply re-establishment of adequate hormone concentrations, adequate AVP concentrations in critically ill patients have not yet been described. In order to correctly interpret AVP serum concentrations in critically ill patients with inadequately low blood pressure, measurement of AVP concentrations in a mixed critically ill patient population is of interest to improve management of vasodilatory shock.

In this prospective study, we examined serum AVP concentrations 24 hrs after admission in 239 mixed critically ill patients over an 11-month period and assessed the incidence of relative and absolute AVP deficiency. Our hypothesis was that endogenous AVP serum concentrations were increased and correlated with cardiocirculatory function in critically ill patients.

MATERIALS AND METHODS

The trial was performed from March 2003 until January 2004 in a 12-bed general and surgical intensive care unit in a tertiary, university teaching hospital. The study protocol was approved by the institutional review board as well as the ethics committee of Innsbruck Medical University. Written informed consent was obtained from the nearest relatives of all patients eligible, before study enrollment.

Patients. All patients admitted to the intensive care unit were included in the study unless written consent was refused or they were <19 yrs old, were pregnant, suffered from central nervous system pathology, were discharged or died within 24 hrs, or had already received an AVP infusion (n = 18).

***See also p. 542.**

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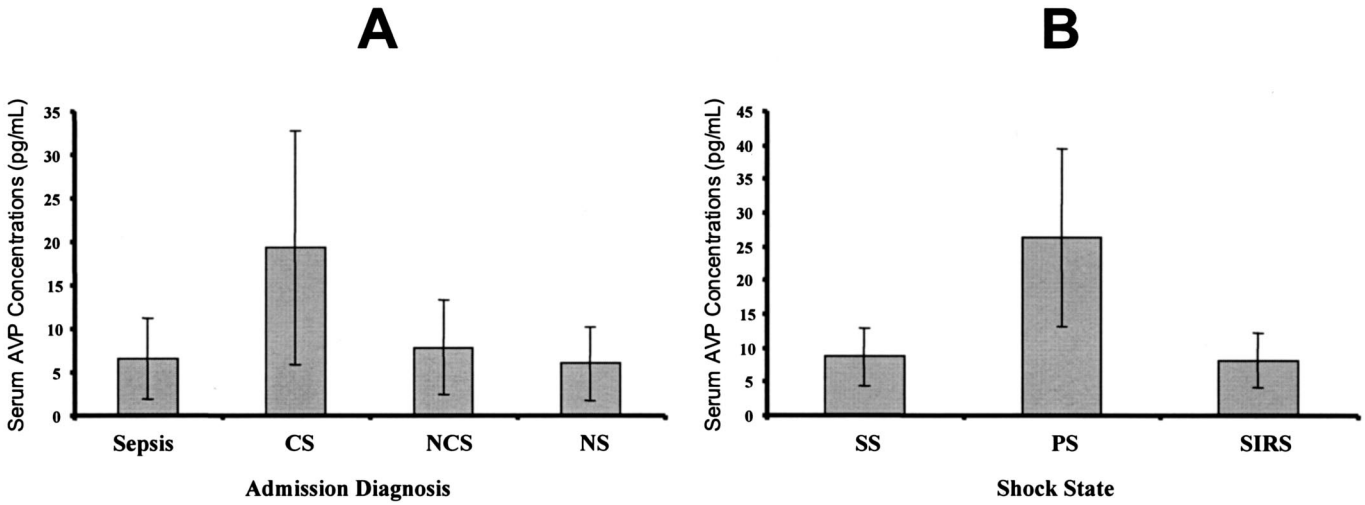

Figure 1. Definitions and grading of organ dysfunction (multiple organ dysfunction syndrome score), modified from (9, 10). *AVP*, arginine vasopressin; *CS*, cardiac surgery; *NCS*, noncardiac surgery; *NS*, nonsurgical diagnosis; *SS*,septic shock; *PS*, postcardiotomy shock; *SIRS*, shock due to systemic inflammatory response syndrome. There was a significant difference between CS and other admission diagnoses ($p < .001$).

All patients were volume-resuscitated according to the response of filling pressures (e.g., central venous pressure up to 12–15 mm Hg) or stroke volume to fluid loading with colloids (Gelofusin, B Braun, Melsungen, Germany). If stroke volume remained <25 mL/min/m^2 or echocardiography revealed a decreased ejection fraction (<50%) despite adequate volume resuscitation, a milrinone and/or epinephrine infusion was started. In order to increase mean arterial pressure >70 mm Hg, phenylephrine infusion (for mild cardiovascular failure) or norepinephrine infusion (for moderate to severe cardiovascular failure) was continuously administered. Phenylephrine was infused in 76 (32%), norepinephrine in 35 (15%), epinephrine in 8 (3%), and milrinone in 56 patients (23%); in total, 144 patients (60%) received a cardiovascular-active drug. Twenty-nine patients (12%) received two or more drugs. Although no patient received exogenous AVP infusion before or during AVP sampling, 22 patients were infused with supplementary AVP (4 IU/hr) because of advanced vasodilatory shock (mean arterial pressure, <70 mm Hg despite norepinephrine dosage of >0.5 μg/kg/min) during the subsequent stay in the intensive care unit.

Intubated patients on mechanical, assisted, or spontaneous breathing (n = 182, 76.2%) were analgosedated by continuous infusion of either sufentanil and midazolam or by single-use morphine with or without haloperidol.

Definitions. Hemodynamic dysfunction and shock were defined according to a modified Goris multiple organ dysfunction syndrome score (Fig. 1) (9, 10), dividing cardiocirculatory function into three stages: 0, no support necessary; 1 (hemodynamic dysfunction), normal fluid requirements plus 30%, inotropic therapy, phenylephrine, or norepinephrine infusion of up to 0.1 μg/kg/min; and 2 (shock), need for norepinephrine infusion >0.1 μg/kg/min, combination of cardiovascular active drugs, or either intra-aortic balloon counterpulsation or ventricular assist device placement. Systemic inflammatory response syndrome and sepsis were defined in accordance with the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) (11).

In order to determine the normal range of AVP serum concentrations, 70 healthy volunteers (blood donors; mean [SD] age, 40.5 ± 11.8 yrs) were examined. Mean AVP serum concentrations were 0.92 ± 0.38 pg/mL (95% confidence interval, 0.83–1.01 pg/mL). Hence, absolute AVP deficiency in critically ill patients was defined as AVP serum concentrations <0.83 pg/mL. AVP serum concentrations <10 pg/mL despite arterial hypotension (mean arterial pressure, <70 mm Hg) were considered to indicate relative AVP deficiency in critically ill patients. The definition of relative AVP deficiency was chosen in accordance with the physiologic observation that AVP serum concentrations >10 pg/mL induce an increase in vascular tone (12).

Diabetes insipidus was defined as a urine output >3 L during the first 24 hrs after intensive care unit admission without the use of diuretics or of fluid therapy exceeding 50% of basic requirements, together with characteristic urine and serum electrolyte changes (specific weight of urine, <1.005; serum sodium, >145 mmol/L).

Data Collection. For all patients, demographic data, medical history, admission diagnosis, and classification of the American Society of Anesthesiologists (13) were documented at study entry.

!Twenty-four hrs after intensive care unit admission, 3 mL of arterial EDTA blood was sampled in order to determine AVP concentrations. The blood was immediately centrifuged on the intensive care unit and frozen at −80°C. The time point of 24 hrs after intensive care unit admission was chosen in order to prevent inclusion of patients in acute, still untreated shock states. At the same time point, heart rate, mean arterial pressure, central venous pressure, presence of hemodynamic dysfunction or shock, as well as phenylephrine, norepinephrine, epinephrine, and/or milrinone requirements and the incidence of diabetes insipidus, were recorded. In patients with a pulmonary artery catheter, cardiac and stroke volume indices were measured, and systemic vascular resistance index was calculated according to standard formulas. A multiple organ dysfunction syndrome score was calculated from clinical and laboratory data. Upon discharge from the intensive care unit, length of hemodynamic dysfunction and intensive care unit stay, need for an additional AVP infusion due to advanced vasodilatory shock during the remaining intensive care unit stay, and outcomes at 28 days and at discharge from the intensive care unit were documented.

Determination of AVP Serum Concentrations. After completion of patient recruitment, frozen blood samples were transferred to the endocrinology laboratory. For measurement of AVP, 1 mL EDTA serum 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 were assayed by radioimmunoassay (DRG Diagnostics, Marburg, Germany) (14). The AVP assay standard calibration curve ranged from 0.5 to 60 pg/mL, with a minimum limit of quantitation of 0.1 pg/mL. If test results were significantly out of the clinically expected range (<0.83 pg/mL or >50 pg/mL) they were repeated and results were reconfirmed.

Study End Points. The primary end point of this study was to compare serum AVP concentrations in critically ill patients vs. healthy

Table 1. Demography, past medical history, admission diagnoses, hemodynamic variables, and laboratory data of study patients and their correlation to serum arginine vasopressin concentrations

		Standardized β-Coefficient[a]	*p* Value
n	239		
Arginine vasopressin, pg/mL	11.9 ± 20.6		
Age	61.4 ± 15.1	0.132	0.065
Male sex	162/239 (67.8%)[b]	−0.161	0.014
Past medical history			
Chronic obstructive pulmonary disease	86/239 (35.9%)	−0.097	0.174
Coronary heart disease	92/239 (38.5%)	0.029	0.689
Congestive heart failure	40/239 (16.7%)	0.085	0.235
Arterial hypertension	103/239 (43.1%)	0.033	0.641
Renal insufficiency	72/239 (30.1%)	−0.093	0.193
Liver cirrhosis	12/239 (5%)	−0.160	0.074
Diabetes mellitus	33/239 (13.8%)	−0.049	0.495
Carcinoma	46/239 (19.2%)	−0.026	0.717
Admission diagnoses			
Sepsis	25/239 (10.5%)	−0.09	0.169
Cardiac surgery	96/239 (40.2%)[b]	0.379	<0.001
Non-cardiac surgery	67/239 (28%)[b]	−0.148	0.023
Non-surgical	51/239 (21.3%)[b]	−0.226	0.001
ASA	3.5± 0.7	−0.051	0.446
Heart rate, beats/min	85 ± 17	0.086	0.191
Mean arterial blood pressure, mm Hg	81 ± 14	0.032	0.624
SVRI, dynes/sec/cm^5/m^2	1900 ± 632	−0.013	0.905
Central venous pressure, mm Hg	9.5 ± 5.7	0.060	0.626
Cardiac index, L/min/m^2	3.1 ± 0.9	−0.078	0.461
Stroke volume index, mL/beat/m^2	37 ± 10	−0.204	0.100
Phenylephrine, μg/kg/min, n = 76	1.01 ± 1.07	0.172	0.140
Norepinephrine, μg/kg/min, n = 35	0.3 ± 0.5	0.105	0.549
Epinephrine, μg/kg/min, n = 8	0.13 ± 0.23	0.276	0.509
Milrinone, μg/kg/min, n = 56	0.38 ± 0.19	0.255	0.060
Hemodynamic dysfunction	122/239 (51%)[b]	0.133	0.042
Shock	62/239 (25.9%)	0.063	0.334
Duration of hemodynamic dysfunction, days	4.8 ± 6.1	−0.118	0.106
Arginine vasopressin during ICU stay	22/239 (9.4%)	0.046	0.520
Multiple organ dysfunction syndrome score (patients)	4.2 ± 2.4	0.026	0.690
Length of ICU stay, days	11.6 ± 10.8[b]	−0.222	0.002
28-day mortality	11/239 (4.6%)	0.080	0.717
ICU mortality	17/239 (7.1%)	0.083	0.243

ASA, American Society of Anesthesiologists Classification; SVRI, systemic vascular resistance index; ICU, intensive care unit.

[a]Calculated from bivariate regression analyses; [b]significant correlation with arginine vasopressin concentrations. Data are given as mean ± SD, if not indicated otherwise.

volunteers and to search for a possible correlation between AVP serum concentrations and demographic, hemodynamic, or clinical data. The secondary study end point was to compare AVP serum concentrations in patients with different admission diagnoses and shock states. The tertiary study end point was to evaluate the incidence of absolute or relative AVP deficiency in critically ill patients.

Statistical Analysis. For statistical analysis, a software program (12.0.1 [Nov 2003], SPSS, Chicago, IL) was used. Kolomogorov-Smirnov tests were applied to check for normality distribution of the study parameters. Normality assumption was approximately fulfilled in all variables except for AVP serum concentrations, which were log-transformed. Demographic, hemodynamic, and clinical data were entered into bivariate linear regression models in order to detect possible correlations between AVP serum concentrations and the study variables. For comparison of AVP serum concentrations between critically ill patients and healthy volunteers and comparisons of hemodynamic data between patients with an absolute or relative AVP deficiency and patients without AVP deficiency, independent-sample Student's *t*-tests were performed. Categorical data were compared with the chi-square test. Statistical significance was assumed if p was <.05. Data are given as mean values ± SD, if not indicated otherwise.

RESULTS

During the observation period, 384 patients were admitted to the intensive care unit. One hundred forty-five patients were excluded from study enrollment because of an intensive care unit stay shorter than 24 hrs (n = 96), central nervous system pathology (n = 25), supplementary AVP infusion due to advanced vasodilatory shock within 24 hrs after intensive care unit admission (n = 18), age <19 yrs (n = 3), or death within 24 hrs after intensive care unit admission (n = 3). Two hundred thirty-nine patients were eligible for study inclusion. Mean AVP serum concentrations at 24 hrs after admission were 11.9 ± 20.6 pg/mL. AVP serum concentrations in critically ill patients were significantly higher than in the healthy control group (0.92 ± 0.38 pg/mL; $p < .001$).

Male sex, cardiac surgery, noncardiac surgery, and nonsurgical diseases as admission diagnoses, incidence of hemodynamic dysfunction, and duration of the intensive care unit stay were significantly related to serum AVP concentrations. There were no detectable correlations between serum AVP concentrations and age, medical history, classification of the American Society of Anesthesiologists, incidence of shock, specific hemodynamic parameters (heart rate, mean arterial pressure, central venous pressure, systemic vascular resistance index, cardiac and stroke volume index, vasopressor or inotropic requirements), multiple organ dysfunction syndrome score, and 28-day or intensive care unit mortality (Table 1). Male patients had lower AVP concentrations than females (9.7 ± 19.5 vs. 15.1 ± 20.6 pg/mL; $p = .014$). Patients with hemodynamic dysfunction had higher serum AVP concentrations than patients without hemodynamic dysfunction (14.1 ± 26 vs. 8.7 ± 10.8 pg/mL; $p = .042$). AVP serum concentrations on the first day after admission were inversely related to length of stay in the intensive care unit ($r = −0.222$; $p = .002$).

Figure 2 presents AVP serum concentrations of patients with different admission diagnoses and different shock states. Patients after cardiac surgery (n = 96; 19.5 ± 30.4 pg/mL) had significantly higher AVP serum concentrations than patients with sepsis (n = 25; 6.5 ± 4.3 pg/mL), patients after noncardiac surgery (n = 67; 7.6 ± 6.5 pg/mL), or patients admitted for nonsurgical diseases (n = 51; 6.5 ± 4.3 pg/mL; $p < .001$). However, there was no significant difference in AVP serum concentrations between patients with different shock states ($p = .126$). Mean AVP serum concentrations were as follows: patients with septic shock, 8.7 ±

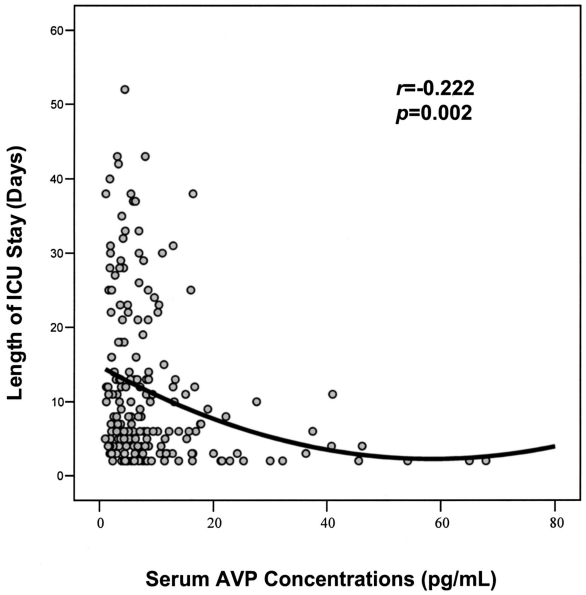

Figure 2. Relationship between arginine vasopressin (*AVP*) serum concentrations and length of intensive care unit (*ICU*) stay.

4.3 pg/mL; patients with postcardiotomy shock, 26.3 ± 39.5 pg/mL; and patients with shock due to systemic inflammatory response syndrome, 8.1 ± 9.4 pg/mL.

Four of 239 patients (1.7%) met the criteria for absolute AVP deficiency, and 32 of 239 patients (13.4%) met the criteria for relative AVP deficiency. Patients with an absolute AVP deficiency had significantly higher mean arterial blood pressure ($p = .013$) and lower multiple organ dysfunction syndrome score than patients without AVP deficiency ($p = .007$). In accordance with the definition of relative AVP deficiency, mean arterial blood pressure was significantly lower in patients with relative AVP deficiency than in patients without AVP deficiency ($p < .001$). There was no difference in heart rate, central venous pressure, cardiac and stroke volume index, or vasopressor or inotropic drug requirements between patients with relative or absolute AVP deficiency vs. no AVP deficiency (Table 2). Among patients with shock, relative AVP deficiency was found in 22.2% of septic shock patients, 15.4% of postcardiotomy shock patients, and 10% of patients with shock due to severe systemic inflammatory response syndrome. There was no difference in the incidence of relative AVP deficiency between patients with different shock states ($p = .316$). No patient in shock fulfilled the criteria for absolute AVP deficiency. No study patient had clinical signs of diabetes insipidus.

DISCUSSION

In this mixed critically ill patient population, AVP serum concentrations 24 hrs after admission were 12-fold higher than in a healthy control group. Repeated hypotensive, hypoxic, hyperosmolar, or acidotic stimuli, together with increased sympathetic tone, are known to increase AVP concentrations in animals and humans (15–17), and this may explain the significantly increased AVP concentrations in this study population.

The results of this study are in line with the serum AVP concentrations observed in critically ill patients by other authors (18–21). Whereas one report described lower AVP concentrations (3.1 ± 0.4 pg/mL) in patients with advanced vasodilatory septic shock (1) and another noted their occurrence in hemodynamically unstable organ donors (2.9 ± 0.8 pg/mL) (22), higher AVP serum concentrations (41.6 pg/mL) so far have been observed only during meningococcal septic shock in children (23).

AVP serum concentrations were significantly related to male sex, admission diagnosis, incidence of hemodynamic dysfunction, and length of intensive care unit stay but surprisingly not to the incidence of shock or other specific hemodynamic parameters. Although endogenous AVP concentrations >10 pg/mL were shown to increase vascular tone (12), the lack of a correlation between AVP serum concentrations and hemodynamic parameters as well as requirements of cardiovascular active drugs suggests that endogenous AVP concentrations had no obvious impact on cardiovascular function in this critically ill patient population. This finding is in agreement with the observations of Boldt and colleagues, who reported a lack of association between circulating vasoactive substances, such as AVP, and hemodynamic variables (24). However, therapeutic infusion of AVP, resulting in AVP serum concentrations as high as 150–250 pg/mL (1, 2, 19, 20), has been shown repeatedly to significantly improve cardiocirculatory function in advanced vasodilatory shock states (1, 25, 26). The vasoconstrictive response to low AVP concentrations in healthy subjects but lack of blood pressure response to supraphysiologic AVP concentrations in critically ill patients and the rapid blood pressure response to AVP concentrations ~150–200 times normal in critically ill patients with vasodilatory shock suggest a right-shifted curve of blood pressure response vs. AVP serum concentrations in severe illness.

Corresponding to findings on catecholamines, reduced effects of endogenous AVP on cardiovascular function strongly suggest peripheral-AVP-receptor hyposensitivity in critically ill patients. Accordingly, experimental studies showed that at the molecular level, the vasoconstrictive response to AVP was markedly reduced in shock states (27, 28). This possibly nitric oxide–mediated AVP hyposensitivity in critically ill patients includes quantitative and qualitative receptor downregulation (29) and impairment of the postreceptor inositol lipid metabolism (30), as well as perturbation of transmembrane signaling pathways (31).

Since physiologically AVP concentrations are mainly regulated by hemodynamic stimuli, dysfunction of AVP release may explain the lack of a correlation between AVP serum concentrations and hemodynamic parameters in critically ill patients. Although in patients with hemodynamic dysfunction there was still a detectable correlation between AVP serum concentration and cardiovascular function ($p = .042$), in patients in shock such a correlation was completely lost ($p = .334$). This might indicate that the physiologic association between hemodynamic parameters and AVP serum con-

Table 2. Hemodynamic and clinical data of patients with relative or absolute arginine vasopressin deficiency when compared with patients without arginine vasopressin deficiency

	Relative AVP Deficiency	Absolute AVP Deficiency	No AVP Deficiency
No. (%)	32/239 (13.4)	4/239 (1.7)	203/239 (84.9)
Heart rate, beats/min	81 ± 15	92 ± 6	85 ± 17
MAP, mm Hg	64 ± 4[a]	98 ± 4[b]	81 ± 14
CVP, mm Hg	8.8 ± 3	4 ± 3.7	9.7 ± 6
Cardiac index, L/min/m^2	3 ± 0.7	3.1 ± 0	3.1 ± 0.9
SVI, mL/beat/m^2	39 ± 16	35 ± 0	36 ± 10
Phenylephrine, μg/kg/min	1.08 ± 0.72	Not applied	1.01 ± 1.15
Norepinephrine, μg/kg/min	0.2 ± 0.2	Not applied	0.3 ± 0.5
Epinephrine, μg/kg/min	0.03 ± 0	Not applied	0.13 ± 0.23
Milrinone, μg/kg/min	0.45 ± 0.13	Not applied	0.39 ± 0.18
HD (%)	19/39 (59.4)	0/4 (0)	102/203 (50.2)
Shock (%)	4/39 (12.5)	0/4 (0)	58/203 (28.6)
DHD, days	4.8 ± 4.7	1.2 ± 0.9	4.9 ± 6.9
MODS, patients	4.9 ± 2.7	1 ± 1.4[b]	4.2 ± 2.4
ICU stay, days	12.9 ± 11.6	17 ± 15.7	11.5 ± 10.7
Mortality (%)	4/32 (12.5)	0/4 (0)	16/203 (7.9)

AVP, arginine vasopressin; MAP, mean arterial pressure; CVP, central venous pressure; SVI, stroke volume index; HD, hemodynamic dysfunction; DHD, duration of hemodynamic dysfunction; MODS, multiple organ dysfunction syndrome score; ICU, intensive care unit.

[a]Significant difference between patients with relative AVP deficiency and patients without AVP deficiency; [b]significant difference between patients with absolute AVP deficiency and patients without AVP deficiency. Data are given as mean ± SD, if not indicated otherwise.

centrations is substantially altered in critically ill patients with hemodynamic dysfunction and completely lost in patients with shock. Autonomic dysfunction with loss of baroreceptor function (32), decreased endogenous AVP production (33), and exhausted AVP stores (18) may account for this clinically observed dysfunction of the vasopressinergic system in critically ill patients.

Patients after cardiac surgery had significantly higher AVP serum concentrations than patients who were admitted for other diagnoses. Although patients with postcardiotomy shock had higher AVP serum concentrations than patients with septic shock or shock due to overwhelming systemic inflammatory response syndrome (Fig. 2), this difference did not reach statistical significance because of the low number of patients in shock (n = 62) and high standard deviations. At our institution, mean arterial blood pressure during cardiopulmonary bypass is usually targeted at 50 mm Hg and might thus pose a significant hypotensive stimulus for AVP release in these usually preoperatively noncritically ill patients (34, 35). Since dysfunction of the vasopressinergic system during cardiac surgery might not yet be as complex and pronounced as in critically ill patients, hypotension during cardiopulmonary bypass together with other perioperative stimuli may have resulted in a significant release of AVP. Other authors have reported similar AVP concentrations in patients after cardiac surgery (36) or after left ventricular assist device placement (16.2 ± 12.8 pg/mL) (37). Whereas Argenziano et al. found that patients with postcardiotomy shock who had a cardiac index >2.5 L/min/m^2 had lower AVP serum concentrations than patients with a cardiac index <2.5 L/min/m^2 (12 ± 6.6 pg/mL vs. 29.3 ± 15) (36), we could not observe a relationship between serum AVP concentrations and cardiac index in the present study (entire study population, $p = .461$; cardiac surgery patients, $p = .819$; postcardiotomy shock patients, $p = .264$).

Although serum AVP concentrations were associated with neither the severity of multiple organ dysfunction nor 28-day and intensive care unit mortality in this study population, AVP concentrations 24 hrs after admission were inversely correlated with the length of stay in the intensive care unit. However, these values seem to be insufficient to predict the duration of intensive care unit stay correctly, since a cohort of patients with low initial AVP serum concentrations was discharged within only 10 days. However, it is interesting that not a single patient with an initially elevated AVP serum concentration (>18 pg/mL) stayed longer than 11 days in the intensive care unit; this circumstance suggests that an adequate initial endogenous stress response may correlate with rapid recovery or even subsequent survival. This may be similar to elevated AVP serum concentrations in patients undergoing cardiac resuscitation, when AVP concentrations >120 pmol/L indicated substantially improved survival (38).

In this study, male patients had lower AVP serum concentrations than females. Accordingly, Wang et al. reported that the effects of AVP were dependent on gender; in their study, male rats exhibited a significantly greater antidiuretic response than female rats (39). Although not significant, there was a trend toward a correlation between AVP serum concentrations and age. Older patients tended to have higher AVP concentrations than younger patients. This observation is in contrast to other endocrine dysfunctions, where high age is usually associated with lower hormone serum concentrations.

Another interesting finding of this study was that at 24 hrs after intensive care unit admission, relative and absolute AVP deficiencies were rather infrequent entities, occurring in 13.4% and 1.7% of critically ill patients, respectively. Neither absolute nor relative AVP deficiency had a significant influence on cardiocirculatory function in this study. Patients with absolute AVP deficiency even exhibited more stable hemodynamics than patients with normal or elevated serum AVP concentrations. In light of the fact that patients with absolute AVP deficiency had a significantly lower multiple organ dysfunction syndrome score and thus a lower severity of disease, it may be speculated that endogenous stimuli for AVP release were too low to trigger AVP secretion. According to the results of a recent study that repeatedly examined AVP serum concentrations in septic shock (21), however, it must be considered that the incidence of AVP deficiency may vary considerably in relation to the time point of measurement. Nonetheless, Sharshar et al. found that also in late septic shock, relative AVP deficiency can be found in only one third of patients (21). According to these new insights into AVP homeostasis in critically ill patients, it seems that the primary pathophysiology of AVP homeostasis in such patients is more likely to be complex dysfunction of the vasopressinergic system rather than absolute or relative AVP deficiency alone.

When interpreting the results of this study, one must consider some limitations. First, since AVP serum concentrations can substantially vary with time

Relative and absolute arginine vasopressin deficiencies may be infrequent during acute surgical critical illness, mostly remaining without significant effects on cardiovascular function.

during the intensive care unit stay (21) and AVP was determined only once (24 hrs after intensive care unit admission) in this study protocol, the data cannot be extrapolated to a period >24 hrs after admission to the intensive care unit. Second, the heterogeneous patient population, including patients with surgical and nonsurgical diagnoses, might have caused us to miss differences in AVP serum concentrations between single admission diagnoses. Third, the fact that 18 patients were excluded from study inclusion because of advanced vasodilatory shock treated with a supplementary AVP infusion during the first 24 hrs after intensive care unit admission might have caused underestimation of the incidence of AVP deficiency in this study population.

In conclusion, AVP serum concentrations in this mixed critically ill patient population 24 hrs after intensive care unit admission were significantly increased in comparison with a healthy control group. The lack of a correlation between AVP serum concentrations and hemodynamic parameters suggests a complex dysfunction of the vasopressinergic system in critical illness. Relative and absolute AVP deficiency may be infrequent entities during acute surgical critical illness, mostly remaining without significant effects on cardiovascular function.

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APPENDIX

Definitions and grading of organ dysfunction (Multiple Organ Dysfunction Syndrome score)[a]

Function	0	1	2
Pulmonary	Pao_2/Fio_2 ≥300	Pao_2/Fio_2 ≥250	Pao_2/Fio_2 <250
Renal	Creatinine ≤2.0 mg%	Creatinine >2.0 mg%; doubling of creatinine in patients with previous compensated renal failure	Acute hemofiltration
Hepatic	Bilirubin <2 mg%; ASAT/ALAT within normal range	Bilirubin 2–5 mg%; ASAT/ALAT ≤3 times normal value	Bilirubin >5 mg%; ASAT/ALAT >3 times normal value
Hematologic	Thrombocytes within normal range; normal coagulation	Thrombocyte decrease ≥25%; abnormal PT/aPTT with and without bleeding	Hemorrhagic diathesis; massive transfusion 5 blood products/hr or >10 blood products/24 hrs
Cardiovascular	Normal blood pressure; no cardiovascular active drugs necessary	Fluid resuscitation >50% of normal need, inotropic support, phenylephrine, norepinephrine <0.1 μg/kg/min	Norepinephrine >0.1 μg/kg/min, combined inotropic and vasopressor therapy, supplementary AVP infusion, IABP, VAD
Gastrointestinal	Normal gastrointestinal function, no bleeding	Ileus >7 days or bleeding requiring ≤6 blood products/24 hrs	Massive bleeding requiring >6 blood products/24 hrs
Central nervous system, GCS	≥12	11–9	≤8

ASAT, aspartate-aminotransferase; ALAT, alanine-aminotransferase; PT, prothrombin time; aPTT, activated thromboplastin time; AVP, arginine vasopressin; IABP, intra-aortic balloon pump; VAD, ventricular assist device; GCS, Glasgow Coma Scale.

[a]Modified from Goris et al. 9, 10.