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POSTOPERATIVE VASOPRESSIN AND COPEPTIN LEVELS IN NONCARDIAC SURGERY PATIENTS: A PROSPECTIVE CONTROLLED TRIAL

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ABSTRACT—Further information on the endogenous arginine vasopressin (AVP) response in patients with postoperative systemic inflammatory response syndrome (SIRS) and vasodilatory shock would provide more insight into the pathophysiology of SIRS-associated cardiovascular failure and help indicate AVP therapy. Patients after uncomplicated abdominal surgery without SIRS (n = 10), critically ill patients after noncardiac surgery with SIRS (n = 9), and patients with SIRS plus vasodilatory shock (n = 22) were included in this prospective trial. Plasma AVP (radioimmunoassay) and copeptin (immunoluminometric assay) concentrations together with clinical parameters were documented daily during the first 7 days postoperative. The AVP response significantly differed between the three groups. Patients without SIRS had lower AVP concentrations than SIRS patients with ($P = 0.001$) or without shock ($P = 0.003$). Patients with SIRS and shock had higher AVP levels than patients with SIRS alone ($P < 0.001$). Arginine vasopressin decreased over time ($P = 0.007$) in all groups. At day 28, nonsurvivors had higher AVP levels than did survivors ($P < 0.001$). In SIRS patients without shock, serum osmolarity was indirectly associated with AVP levels, whereas mean arterial blood pressure and serum osmolarity were associated with AVP in SIRS patients with shock. Arginine vasopressin and copeptin correlated significantly with each other ($P < 0.001$; $r = 0.76$). In patients without hemofiltration, copeptin levels predicted 28-day mortality with high sensitivity and specificity. The postoperative AVP response in noncardiac surgery patients seems well maintained. The possibility that AVP plays a contributory role in the failure to restore vascular tone in patients with vasodilatory shock cannot be excluded but seems less important than in septic or postcardiotomy shock.

KEYWORDS—Vasopressin, plasma concentrations, postoperative, SIRS, shock, copeptin

INTRODUCTION

Systemic inflammatory response syndrome (SIRS) refers to the general activation of the immune system by noninfectious stimuli, which may cause cardiovascular failure and subsequent multiple organ dysfunction (1). Comparable to the clinical presentation of septic shock, hemodynamic instability associated with SIRS is characterized by hypovolemia and peripheral vasodilatation with or without myocardial dysfunction (2). Because of their clinical resemblance, similar pathophysiological mechanisms are considered responsible for the development of both septic and SIRS-associated vasodilatory shock. Suggested mechanisms include overproduction of endogenous vasodilators such as NO, adenosine, or adrenomedullin, activation of K_{ATP} channels, downregulation of endogenous vasoconstrictor receptors, as well as relative deficiency of important neuroendocrine stress hormones such as cortisol and arginine vasopressin (AVP) (3). Because the response to exogenous catecholamines is frequently decreased in vasodilatory shock accompanying SIRS, a supplementary AVP infusion has successfully been administered to restore hemodynamic stability in patients with SIRS and shock (4).

To date, little is known about the postoperative AVP response in noncardiac surgery patients. Earlier reports suggest that the AVP system, together with other neuroendocrine stress hormones, is stimulated during the early postoperative period (5–8). However, no data on the course of AVP plasma concentrations in patients presenting with postoperative SIRS have yet been presented. In a recent clinical study, we reported endogenous AVP plasma concentrations of 8.2 ± 4.5 pmol/L in patients being admitted to the intensive care unit (ICU) because of SIRS (9). Further information on the endogenous AVP response in patients with postoperative SIRS and vasodilatory shock would provide better insight into the pathophysiology of cardiovascular failure associated with SIRS, and may also help indicate exogenous AVP therapy.

Despite the role of AVP in the pathogenesis, and partly also in the therapy, of shock, serious concerns exist about the methodological reliability of AVP assays (>90% of circulating AVP is bound to platelets, rapid plasma clearance of AVP, low *ex vivo* stability of AVP even at −20°C, only competitive immunoassays can measure AVP because of its small size) (10). Copeptin is a stable fragment of the AVP pre-pro-hormone

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TABLE 1. **Characteristics of the study population**

	Abdominal surgery without SIRS	SIRS	SIRS + shock	*P*
n	10	9	22	
Male sex, n (%)	3 (30)	8 (88.9)	16 (72.7)	0.02*
Age, yrs	62 ± 11	64 ± 15	66 ± 18	0.99
BMI, kg/m^2	27 ± 2	26 ± 3	26 ± 6	0.78
Chronic ACEI therapy, n (%)	2 (20)	0 (0)	8 (36.4)	0.1
ASA Classification	2.1 ± 0.3	3.6 ± 0.5	3.8 ± 0.4	<0.001*
Type of surgery, n (%)				0.1
Abdominal	10 (100)	4 (44.4)	9 (40.9)	
Vascular	0 (0)	2 (22.2)	4 (18.2)	
Orthopedic	0 (0)	1 (11.1)	4 (18.2)	
Other	0 (0)	2 (22.2)	5 (22.7)	
SAPS II, points	n.a.	45 ± 19	51 ± 18	0.39
Mechanical ventilation, n (%)	0 (0)	8 (80)	18 (81.8)	<0.001*
RRT, n (%)	0 (0)	1 (11.1)	4 (18.2)	0.34
Goris MODS score, points	2.2 ± 1	8.3 ± 2.6	10.1 ± 1.9	<0.001*
ICU length of stay, days	n.a.	17 ± 17	15 ± 15	0.76
28-day mortality, n (%)	0 (0)	2 (22.2)	7 (31.8)	0.13

Data are given as mean ± SD, if not indicated otherwise.
*Significant difference between groups.
ACEI–angiotensin-converting enzyme inhibitor; ASA–American Society of Anesthesiologists; BMI–body mass index; MODS–multiple organ dysfunction syndrome; n.a.–not applicable; RRT–renal replacement therapy; SAPS–Simplified Acute Physiology Score.

and has recently been introduced as an indirect parameter to assess AVP secretion (10). Measuring copeptin holds several advantages over AVP determination (only small plasma amounts [50 μL] required, no preanalytical procedures necessary, measurable with an immunoluminometric assay having high precision and sensitivity, results within a few hours) of which the high *ex vivo* stability of AVP (up to 7 days at room temperature and up to 14 days at 4°C) is the most important (10).

This prospective study evaluated plasma AVP and copeptin response during the first 7 days after noncardiac surgery in patients developing postoperative SIRS with or without vasodilatory shock and in patients after scheduled abdominal surgery and not developing systemic inflammation. Our hypothesis was that the postoperative AVP response does not differ between the three study groups.

PATIENTS AND METHODS

This prospective study was performed in a 12-bed general and surgical ICU of a university teaching hospital (SIRS and SIRS plus shock group), and in a 110-bed general surgery unit at the same hospital (scheduled abdominal surgery group without SIRS) from November 2005 until December 2006. The study protocol was approved by the institutional review board and the ethics committee of Innsbruck Medical University.Written informed consent was obtained from all patients in the scheduled abdominal surgery group without SIRS, and from the next of kin of patients in the SIRS and SIRS plus shock group.

Patients and study groups

The study population consisted of three groups each including patients after noncardiac surgery. The inclusion criterion for the SIRS and SIRS plus shock group was ICU admission because of postoperative SIRS defined according to the American College of Chest Physicians and the Society of Critical Care Medicine criteria (11). In the SIRS plus shock group, vasodilatory shock was defined as hypotension (MAP, <60 mmHg) despite normovolemia (assessed as a central venous pressure [CVP] >10 mmHg, adequacy of peripheral perfusion, and/or echocardiography) and sufficient systemic blood flow (assessed by pulmonary artery catheter measurements [n = 13] showing a cardiac index >2 L/min per square meter and systemic vascular resistance index <1,200 dyne*s/cm^5 per square meter, echocardiography, central or mixed venous oxygen saturation >65%, and/or adequacy of peripheral perfusion) subsequently resulting in the need for a norepinephrine infusion with dosages exceeding 0.1 μg/kg per minute for at least 12 h. Patients with postoperative SIRS and cardiogenic shock (e.g., perioperative myocardial infarction) with sustained or increased systemic vascular resistance index (>2,000 dyne*s/cm^5 per square meter) or shock states of other origin (e.g., sepsis, hemorrhage, anaphylaxis) were excluded. The study group without SIRS consisted of patients who had undergone scheduled abdominal surgery and had no more than one sign of systemic inflammation during the postoperative period. Exclusion criteria for all study groups were cardiac surgery using cardiopulmonary bypass, discharge alive before ICU (SIRS and SIRS plus shock group) or before hospital day 7 (abdominal surgery group without SIRS), central nervous system pathology, known or suspected pathology of the AVP system, treatment with AVP before or during the observation period, age younger than 19 years, pregnancy, or refusal to grant written consent. Data sets of patients who died before ICU day 7 were retained in the statistical analysis.

Critically ill patients on mechanical, assisted, or spontaneous breathing were analgosedated by continuous infusion of either sufentanil and midazolam or morphine alone, as clinically indicated. Continuous venovenous hemofiltration (CVVHF) was used for postoperative acute renal failure only (filtration rates, 35–40 mL/min; used filter, Aquamax H07; Edwards Lifesciences, Unterschleissheim, Germany; average pore size inner layer, 5 nm; middle layer, 100 nm; outer layer, 10 nm; filtered solutes <30 kd).

To exclude sepsis, repeated microbiological cultures were performed in all study patients. If microbiological cultures turned out to be positive and sepsis was diagnosed, the patient was retrospectively excluded from the study protocol. Perioperative antibiotic prophylaxis was performed in most study patients. Except for major vascular surgery (48 h), antibiotic prophylaxis was discontinued at the latest 24 h after surgery.

Data collection

In all study patients, demographic data, medical history, chronic intake of angiotensin-converting enzyme inhibitors, and the preoperatively

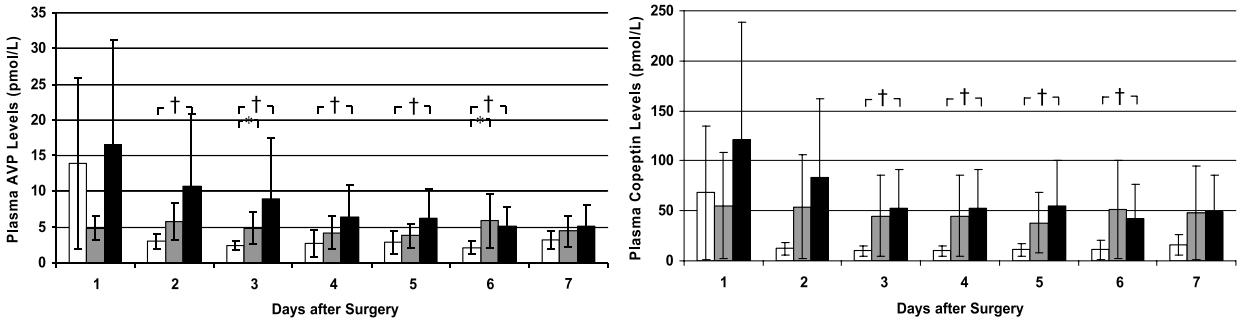

FIG. 1. **Course of plasma AVP and copeptin levels in postoperative patients without SIRS (n = 10, white bars), patients with SIRS (n = 9, gray bars), and patients with SIRS plus vasodilatory shock (n = 22, black bars)**. *Significant difference ($P < 0.017$) between postoperative patients without SIRS and patients with SIRS; †Significant difference ($P < 0.017$) between postoperative patients without SIRS and patients with postoperative SIRS plus vasodilatory shock.

evaluated classification according to the American Society of Anesthesiologists (12) were documented at study entry. Twenty-four hours after ICU admission, the Simplified Acute Physiology Score II (13) was calculated from worst laboratory and clinical parameters. Within 36 h after ICU admission, 3 mL of EDTA blood was drawn to determine AVP and copeptin plasma concentrations. Blood was taken from an arterial line (SIRS and SIRS plus shock group) or by puncture of a peripheral vein (abdominal surgery group) once daily at the same time point each day during the first 7 postoperative days. Blood samples were immediately centrifuged in the central institutional laboratory, and the supernatant plasma portion was frozen at −80°C.

At the same time each day, MAP, CVP, pulmonary capillary wedge pressure (where available), norepinephrine requirements, serum osmolarity, arterial pH, and partial arterial oxygen tension (PaO_2), as well as daily sufentanil and morphine dosages were recorded in the SIRS and SIRS plus shock group. A multiple organ dysfunction syndrome score (14) was calculated from the most aberrant clinical and laboratory data. At ICU discharge, the need for CVVHF and the length of ICU stay were documented. In the abdominal surgery group without SIRS, the same parameters as in the two SIRS groups were recorded wherever available and measurable at given times. In these patients, arterial blood pressure was measured using either the oscillatory or the auscultation method. In all study patients, mortality was registered 28 days after surgery.

Measurement of AVP and copeptin plasma concentrations

After completing patient recruitment, frozen plasma samples were transferred to the endocrinologic laboratories. All samples were blinded to assure that laboratory staff could not differentiate between the three study groups. 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 of extract. Subsequently, 0.4 mL of extract was assayed using a radioimmunoassay (DRG Diagnostics, Marburg, Germany) (15). The AVP assay standard calibration curve ranges from 0.5 to 60 pmol/L with a minimum limit of quantitation of 0.1 pmol/L. The intra-assay and interassay variation is 4.9% to 6.5% and 6% to 6.9%, respectively. In the event that test results were located significantly outside the clinically expected range (<0.83 or >50 pmol/L), measurements were repeated to confirm the results.

Copeptin (39-amino acid glycopeptide, 4,021 d) plasma concentrations were determined using a sandwich immunoluminometric assay (B.R.A.H.M.S. LUMItest CT-proAVP, B.R.A.H.M.S. A.G., Hennigsdorf/Berlin, Germany) as previously described in detail (10). Since this initial publication, the assay was modified as follows: the capture antibody was replaced with a murine monoclonal antibody directed to amino acids 137–144 (GPAGAL) of pro-AVP. This modification improved assay sensitivity. The lower detection limit is 0.4 pmol/L, and the functional assay sensitivity (<20% interassay coefficient of variation) is less than 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 plasma AVP response during the first 7 postoperative days between patients without SIRS, with SIRS, and with SIRS plus vasodilatory 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 study groups. The tertiary study end point was to evaluate the correlation between AVP and copeptin plasma concentrations in all patients.

Statistical analysis

The SPSS software (Version 12.0.1; SPSS Inc, Chicago, Ill) was used. Kolmogorov-Smirnov tests were applied to check for normality distribution of study parameters. Demographic and clinical parameters were compared between study groups using the Student *t* test 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 (16). In case of statistical significance, AVP levels at individual time points were compared between the three study groups using the Student *t* test. To test for a possible association between AVP levels and parameters physiologically known to influence AVP release (MAP, CVP, pulmonary capillary wedge pressure, norepinephrine requirements, serum osmolarity, arterial pH, PaO_2 daily sufentanil and morphine dosage), a mixed effects model was used. A nonparametric Spearman rank correlation was used to evaluate the correlation between AVP and copeptin plasma concentrations in all study patients.

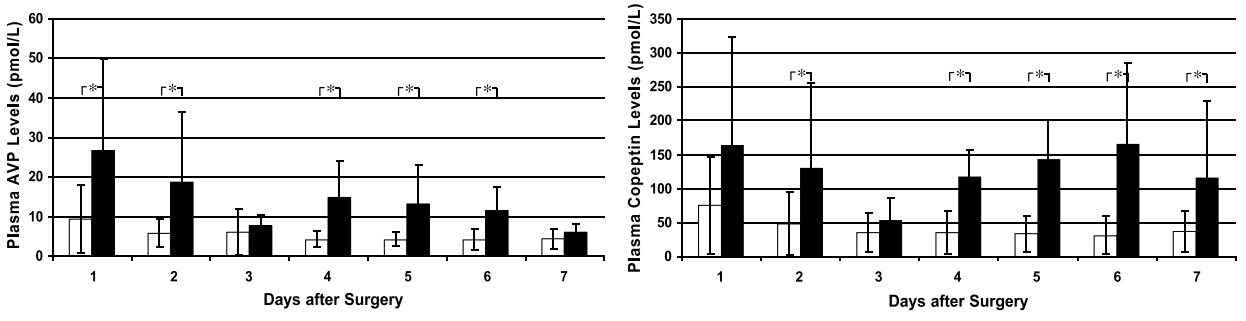

FIG. 2. **Course of plasma AVP and copeptin levels during the first 7 days after surgery in survivors (n = 32, white bars) and nonsurvivors (n = 9, black bars) at postoperative day 28**. *Significant difference ($P < 0.05$) between survivors and nonsurvivors.

TABLE 2. **Parameters physiologically known to influence AVP release in postoperative patients without SIRS, with SIRS, and with SIRS plus shock**

		ICU day 1	ICU day 2	ICU day 3	ICU day 4	ICU day 5	ICU day 6	ICU day 7
MAP, mmHg	Without SIRS	95 ± 6	88 ± 13	101 ± 12	97 ± 12	100 ± 11	97 ± 12	98 ± 9
	SIRS	79 ± 10	74 ± 6	80 ± 12	80 ± 13	90 ± 18	90 ± 11	83 ± 20
	SIRS + shock	73 ± 12	73 ± 8	76 ± 11	80 ± 10	84 ± 14	82 ± 15	94 ± 17
CVP, mmHg	Without SIRS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	SIRS	11 ± 2	10 ± 2	9 ± 2	9 ± 2	8 ± 3	7 ± 4	8 ± 3
	SIRS + shock	12 ± 5	11 ± 3	11 ± 4	10 ± 3	10 ± 4	10 ± 3	8 ± 4
PCWP, mmHg	Without SIRS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	SIRS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	SIRS + shock	13 ± 3	15 ± 3	14 ± 4	13 ± 4	16 ± 4	15 ± 3	14 ± 4
NE dosage, μg/kg per min	Without SIRS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	SIRS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	SIRS + shock	0.33 ± 0.27	0.2 ± 0.12	0.18 ± 0.13	0.13 ± 0.06	0.12 ± 0.11	0.25 ± 0.35	0.18 ± 0.21
Serum osmolarity	Without SIRS	286 ± 20	290 ± 14	291 ± 13	293 ± 11	292 ± 15	290 ± 9	291 ± 11
	SIRS	308 ± 15	312 ± 16	310 ± 13	310 ± 14	313 ± 13	314 ± 16	314 ± 16
	SIRS + shock	307 ± 17	312 ± 15	310 ± 13	311 ± 16	315 ± 20	317 ± 27	307 ± 12
Arterial pH	Without SIRS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	SIRS	7.4 ± 0.1	7.39 ± 0.08	7.41 ± 0.04	7.43 ± 0.03	7.44 ± 0.05	7.46 ± 0.05	7.45 ± 0.07
	SIRS + shock	7.34 ± 0.09	7.38 ± 0.07	7.41 ± 0.07	7.45 ± 0.06	7.44 ± 0.05	7.42 ± 0.06	7.44 ± 0.07
PaO_2, mmHg	Without SIRS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	SIRS	106 ± 28	90 ± 14	100 ± 20	94 ± 16	92 ± 13	95 ± 11	98 ± 14
	SIRS + shock	103 ± 33	98 ± 20	96 ± 14	98 ± 17	101 ± 19	91 ± 20	88 ± 15
Sufentanil, mg/d	Without SIRS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	SIRS (n = 3)	0.5 ± 0.3	0.5 ± 0.4	0.6 ± 0.5	0.1 ± 0.1	n.a.	n.a.	n.a.
	SIRS + shock (n = 8)	2 ± 1.8	1.1 ± 1.4	1.2 ± 1.2	0.9 ± 1.2	1.4 ± 1.3	0.9 ± 1.2	0.7 ± 1.1
Morphine, mg/d	Without SIRS	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	SIRS (n = 5)	42 ± 11	34 ± 16	20 ± 14	12 ± 9	21 ± 26	28 ± 13	47 ± 33
	SIRS + shock (n = 12)	30 ± 14	24 ± 10	24 ± 12	19 ± 13	23 ± 15	23 ± 9	17 ± 8

Data are given as mean ± SD.
n.a.–not available/applicable; NE–norepinephrine; PCWP–pulmonary capillary wedge pressure.

Statistical significance was assumed if the $P < 0.05$. For multiple comparisons between the three study groups, Bonferroni corrections were applied and a $P = 0.017$ was considered to indicate statistical significance. Data are given as mean values ± SD, if not otherwise indicated.

RESULTS

During the study period, 36 patients were enrolled in the study protocol. Five patients were retrospectively excluded because they were discharged alive before ICU day 7 (n = 4) or had sepsis (n = 1). Another four patients had positive sputum cultures, but this was not the reason for systemic inflammation in any of these patients. Finally, 31 patients with SIRS after major noncardiac surgery and 10 patients after scheduled abdominal surgery without postoperative SIRS were analyzed. Of the 31 patients with postoperative SIRS, 22 developed vasodilatory shock during the first 36 h after ICU admission and required norepinephrine for 8.5 ± 5.4 days (Table 1). One patient received dopamine therapy (2 μg/kg per minute), and three patients received an additional epinephrine infusion. None of the patients with postoperative SIRS alone developed shock during the observation period. There was a significant sex difference between groups. Patients in the SIRS groups had a higher American Society of Anesthesiologists classification and multiple organ dysfunction syndrome score, and required mechanical ventilation more frequently than did patients without postoperative SIRS. The time between surgery and study inclusion was 6.9 ± 5.4 h (scheduled abdominal surgery), 9 ± 10.6 h (SIRS), and 11.2 ± 11.7 h (SIRS plus shock; $P > 0.05$).

The postoperative AVP response differed significantly between the three study groups (Fig. 1). Patients without postoperative SIRS presented with lower AVP plasma concentrations than did SIRS patients with ($P = 0.001$) or without shock ($P = 0.003$). Patients with postoperative SIRS and vasodilatory shock had higher plasma AVP concentrations than did patients with postoperative SIRS alone ($P < 0.001$). With no significant difference between groups, AVP plasma concentrations decreased over time ($P = 0.007$).

At day 28, nonsurvivors had a higher postoperative AVP response than did survivors ($P < 0.001$; Fig. 2). Whereas AVP plasma concentrations did not decrease in nonsurvivors ($P =$

TABLE 3. **Association between AVP plasma concentrations and parameters physiologically known to influence AVP release**

	Without SIRS (n = 10)		SIRS (n = 9)		SIRS + shock (n = 22)	
	F	*P*	F	*P*	F	*P*
MAP	0.255	0.62	0.904	0.35	5.786	0.02*
CVP	n.a.		1.459	0.24	0.49	0.14
PCWP	n.a.		n.a.		3.274	0.51
NE Dosage	n.a.		n.a.		3.274	0.09
Serum osmolarity	0.402	0.54	29.751	<0.001*	14.611	<0.001*
Arterial pH	0.788	0.47	0.216	0.65	0.068	0.8
PaO_2	0.297	0.6	0.412	0.53	2.972	0.09
Sufentanil dosage	n.a.		n.a.		0.308	0.59
Morphine dosage	n.a.		0.211	0.66	0.133	0.72

*Significant association between AVP plasma concentrations and the parameter.
n.a.–not available/applicable; NE–norepinephrine; PaO_2–partial arterial oxygen tension; PCWP–pulmonary capillary wedge pressure.

0.09), they did in survivors ($P = 0.02$). Nonsurvivors had a significantly longer prothrombin time ($P < 0.001$) and lower platelet counts ($P < 0.001$) than did survivors. No coagulation parameter, however, correlated with AVP or copeptin plasma levels.

No correlation between parameters physiologically known to influence the release of AVP (Table 2) and the course of AVP plasma levels could be detected in postoperative patients without SIRS (Table 3). In patients with SIRS but no shock, serum osmolarity was indirectly associated with the course of AVP plasma levels, whereas MAP and serum osmolarity were associated with AVP plasma levels in patients with SIRS and shock (Tables 2 and 3). Similarly, copeptin plasma concentrations were indirectly associated with serum osmolarity in patients with SIRS (F = 4.271; $P = 0.045$) and

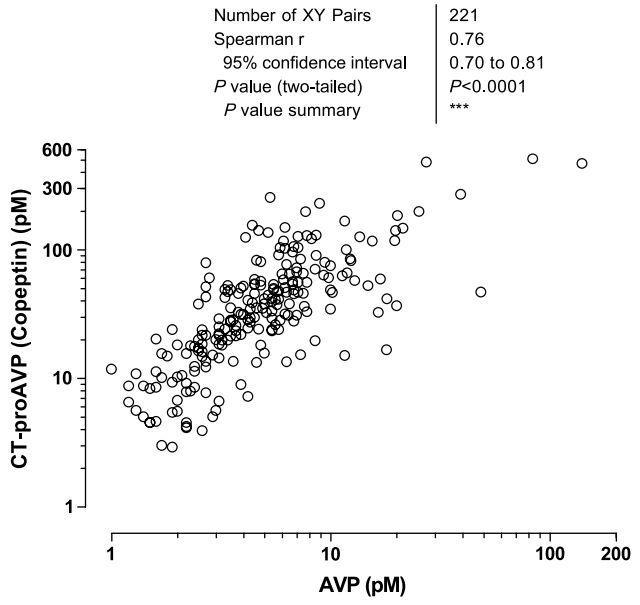

FIG. 3. **Correlation between plasma AVP and copeptin concentrations in all study patients (n = 41)**.

TABLE 4. **Cutoff values for copeptin plasma levels to predict 28-day mortality in patients without CVVHF (n = 36)**

Postoperative day	Copeptin*, pmol/L	Sensitivity, %	Specificity, %	Positive likelihood ratio
1	60	71.4	63	0.5
2	53	75	66.7	0.4
3	66	100	95.2	2
4	64	100	90.5	1
5	80	100	94.7	2
6	73	100	94.5	0.5
7	48	100	85	0.4

*Point of the receiver as the greatest sum of sensitivity plus specificity. The positive likelihood ratio was calculated as the percent of true positives divided by the percent of false positives.

patients with SIRS plus vasodilatory shock (F = 19.027; $P < 0.001$) but not MAP ($P > 0.05$ in both groups).

Arginine vasopressin and copeptin plasma concentrations correlated significantly with each other ($P < 0.001$; $r = 0.76$; Fig. 3). This correlation was influenced neither by plasma creatinine concentrations ($P = 0.69$) nor by creatinine clearance ($P = 0.08$), but by the need for CVVHF ($P = 0.03$). Whereas patients without CVVHF exhibited a correlation coefficient of $r = 0.837$ ($P < 0.001$), this coefficient was $r = 0.242$ ($P = 0.09$) in patients requiring renal replacement therapy. The graphic course of the copeptin plasma concentrations resembled that of AVP and showed comparable differences between postoperative patients without SIRS, with SIRS, and with SIRS plus shock, as well as between survivors and nonsurvivors (Figs. 1 and 2). The sensitivity and specificity of individual plasma copeptin concentrations to predict death within 28 days after surgery in patients without CVVHF as assessed by a receiver operating characteristic analysis are displayed in Table 4.

DISCUSSION

In this prospective study, the postoperative AVP response differed significantly between patients with and without SIRS. The most pronounced AVP response was observed in SIRS patients who developed vasodilatory shock and those succumbing by postoperative day 28. The course of plasma AVP concentrations was indirectly associated with serum osmolarity in postoperative patients with SIRS, as well as MAP and serum osmolarity in patients with SIRS plus vasodilatory shock. Plasma AVP and copeptin concentrations significantly correlated with each other.

Our data indicate a good association between the postoperative AVP and copeptin response and the severity of systemic inflammation and cardiovascular failure. Nonsurvivors with more severe organ dysfunction than survivors (multiple organ dysfunction syndrome score, 11.6 ± 1.4 vs. 6.8 ± 3.6 points, $P < 0.001$) also exhibited higher AVP plasma concentrations. Moreover, persistently increased AVP plasma concentrations in nonsurvivors indicate an ongoing stimulation of AVP secretion, whereas decreasing AVP levels in survivors most probably reflect an improved hemodynamic and clinical condition. These findings agree with physiological observations that hemodynamic instability (17), as well as

inflammation (18, 19), perioperative stress (5–8), and other factors such as hypoxia (20) or acidosis (21), stimulates AVP secretion. In contrast to patients with septic (unpublished data, Jochberger S, MD; Dünser M, MD, 2008) or postcardiotomy shock (22), the AVP response seems to be maintained in noncardiac surgery patients with SIRS and vasodilatory shock. This is underlined by the finding that arterial blood pressure and serum osmolarity were indirectly associated with AVP levels in patients with SIRS and shock. Because postoperative patients with and without SIRS were hemodynamically stable, no association between arterial blood pressure and AVP was detected in those groups.

The present data are in accordance with previous observations made in noncardiac surgery patients. In a mixed general surgical ICU population, patients with postoperative SIRS presented with comparably high AVP plasma concentrations of 8.2 ± 4.5 pmol/L during the first 36 h after surgery (9). Similarly, the initial postoperative AVP response in abdominal surgery patients without SIRS was similar to that reported after abdominal surgery by other authors (23–25). Even though these patients showed neither systemic immune activation nor disturbances in osmotic or cardiovascular homeostasis, their AVP plasma levels were still relevantly increased. Earlier data (5–8), together with the observation that AVP levels rapidly normalized until postoperative day 2 or 3, point to an important role of the neuroendocrine stress response in the perioperative and postoperative secretion of AVP. Accordingly, two studies have shown that the peak intraoperative AVP response occurs shortly after skin incision (5, 6).

Although the different number of patients in each study group may limit the interpretation of our data, the significant results and their correspondence to earlier data and physiological knowledge make a chance finding unlikely. Because critically ill male patients exhibited lower AVP plasma concentrations than did females (9.7 ± 19.5 vs. 15.1 ± 20.6 pg/mL, $P = 0.014$) (9), the baseline difference in sex between abdominal surgery patients and ICU patients with SIRS may have relevantly influenced AVP levels in our work. Because most of the critically ill patients with SIRS in the present study were male, this may have resulted in lower AVP levels than a similar sex-matched population, for example, the abdominal surgery group without postoperative SIRS would have displayed. Nonetheless, the postoperative AVP response was more pronounced in critically ill patients with SIRS than in abdominal surgery patients without SIRS. Thus, dissimilarities in sex are more likely to have underestimated than overestimated differences in the postoperative AVP response between the three study groups. Although cultures were routinely taken to detect sepsis as the cause of systemic inflammation and/or vasodilatory shock, we cannot exclude the possibility that perioperative antibiotic prophylaxis prevented microbiological specimen from turning positive. Furthermore, AVP and copeptin plasma levels as observed in this study population must be interpreted in the light of the hemodynamic protocol applied.

An obviously well functioning AVP system in patients with postoperative SIRS and vasodilatory shock makes a causative relation between AVP plasma concentrations and the failure to restore vascular tone unlikely. Nevertheless, it cannot be concluded from our data whether the postoperative AVP response seen in SIRS patients with vasodilatory shock was adequate, given the duration and severity of cardiovascular failure. However, when comparing the present data with those from patients with postcardiotomy (22) or septic shock (unpublished data) who presented with an impaired or comparable AVP response, it seems that the possible contributory role of AVP to the vasodilatory shock associated with SIRS is less important. Even though a large cohort study observed no differences in hemodynamic response to AVP infusion in patients with advanced vasodilatory shock due to SIRS, sepsis, or after cardiac surgery (26), future clinical studies must evaluate the effects of AVP on patient outcome in these three groups.

Copeptin, a stable fragment of the AVP pre-pro-hormone, possesses an advantageous biochemical profile for laboratory testing (10) and has recently been suggested as a surrogate marker of the AVP system activity in acutely (27) and critically ill patients (28). As also reported in an earlier study (28), the correlation between AVP and copeptin plasma concentrations was excellent in the present study. Similar to findings in patients after cardiac surgery (22) and in patients with sepsis (unpublished data), however, the need for CVVHF relevantly influenced the correlation between AVP and copeptin in this postoperative study population. The observation that CVVHF worsened the correlation between AVP and copeptin indicates that different sieving coefficients may result in diverse amounts of filtered hormone levels during CVVHF. Nonetheless, in patients without renal replacement therapy, determination of copeptin plasma concentrations could help indirectly assess the AVP system in critically ill noncardiac surgery patients. Using cutoff values as shown in Table 4, copeptin might even be used to predict 28-day mortality in the postoperative ICU setting. Nonetheless, the comparably low positive likelihood ratios of individual copeptin values suggest that even high copeptin plasma levels cannot specifically predict death.

In conclusion, the postoperative AVP response in noncardiac surgery patients seems well maintained with elevated AVP plasma concentrations in patients with SIRS and highest AVP levels in nonsurvivors and patients with SIRS and vasodilatory shock. The possibility that AVP plays a contributory role in the failure to restore vascular tone in noncardiac surgery patients with postoperative SIRS and vasodilatory shock cannot be excluded, but seems less important than in septic or postcardiotomy shock.

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