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The vasopressin and copeptin response in patients with vasodilatory shock after cardiac surgery: a prospective, controlled study

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Abstract *Objective:* To evaluate arginine vasopressin (AVP) and copeptin plasma concentrations in patients with vasodilatory shock after cardiac surgery. *Design:* Prospective, controlled, clinical study. *Setting:* Surgical intensive care unit and cardiac surgery ward in a tertiary university teaching hospital. *Patients and participants:* Thirty-three critically ill patients with vasodilatory shock after cardiac surgery and ten control patients undergoing uncomplicated aorto-coronary bypass surgery. *Measurements and results:* Hemodynamic, laboratory and clinical data were recorded daily in all patients during the first 7 days after cardiac surgery. At the same time, points blood was withdrawn to determine plasma concentrations of AVP (radioimmunoassay) and copeptin (immunoluminometric assy). Standard tests, a mixed effects model and regression analyses were used for statistical analysis. The course of AVP was significantly different between groups ($P < 0.001$). While AVP concentrations were lower in the study group on the first postoperative day, they were higher than that in the control group from postoperative day 3 on. There was no difference in the postoperative AVP response between study patients with or without chronic angiotensin-converting enzyme inhibitor therapy. Except during continuous veno-venous hemofiltration, AVP and copeptin correlated significantly with each other ($P < 0.001$; $r = 0.749$). *Conclusions:* The AVP response to cardiac surgery is significantly different between patients with vasodilatory shock and patients undergoing uncomplicated aorto-coronary bypass surgery. Although no causative relationship between AVP concentrations and cardiovascular instability can be drawn from these results, our data support the hypothesis that inadequately low AVP plasma levels contribute to the failure to restore vascular tone in vasodilatory shock after cardiac surgery.

Keywords Cardiac surgery · Vasodilatory shock · Plasma levels · Vasopressin · Copeptin

Introduction

Severe postoperative cardiovascular failure occurs in 3–5% of patients undergoing cardiac surgery using cardiopulmonary bypass [1, 2]. While myocardial dysfunction is the major component of cardiovascular failure in some patients, it is lower than expected systemic vascular resistance predominates in others [1–3]. The latter condition has been referred to as vasodilatory postcardiotomy shock and is characterized by decreased vascular tone, tissue hypoperfusion and metabolic acidosis [1, 2, 4]. Since inadequate low-plasma concentrations of the vasoconstrictor hormone arginine vasopressin (AVP) were observed in septic shock patients, it has been suggested that relative AVP insufficiency may also contribute to the failure to restore vascular tone in vasodilatory shock after cardiac surgery [4]. Accordingly, first clinical reports showed beneficial effects of AVP therapy on cardiovascular function in cardiac surgery patients with severe vasodilatory shock [3, 5–8]. So far, knowledge of the endogenous AVP response to cardiac surgery is limited. In a recent study, AVP plasma concentrations in cardiac surgery patients, 24 h after intensive care unit (ICU) admission were higher than that in patients with sepsis or the systemic inflammatory response syndrome [9]. More knowledge about the endogenous AVP response may facilitate understanding and therapy of vasodilatory shock after cardiac surgery.

The aim of this prospective, controlled study was to compare plasma concentrations of AVP and copeptin, a stable precursor of AVP, during the first 7 days after cardiac surgery in 33 vasodilatory shock patients and in 10 patients undergoing uncomplicated aorto-coronary bypass surgery. Our hypothesis was that the postoperative AVP response was more pronounced in patients with vasodilatory shock than in patients undergoing uncomplicated aorto-coronary bypass surgery. Parts of this work were presented as an abstract at the 20th Congress of the European Society of Intensive Care Medicine [10].

Materials and methods

From November 2005 to December 2006, this prospective study was performed in a 12-bed general and surgical ICU of a tertiary, university teaching hospital (study group), and in a 30-bed cardiac surgery ward in the same hospital (control group). The study protocol was approved by the Ethics Committee of the Innsbruck Medical University. Written informed consent was obtained from all control patients and from the next family members of the study patients. After recovery, written informed consent was given by study patients.

Patients

The study population consisted of two groups of cardiac surgery patients (study and control group). The inclusion criterion for the study population was development of vasodilatory shock within 24 h after cardiac surgery. Vasodilatory shock was defined as the simultaneous occurrence of a mean arterial blood pressure (MAP) <60 mmHg together with a systemic vascular resistance index <1,200 dyne × s/cm^5 × m^2 resulting in the need for a norepinephrine infusion with dosages >0.1 μg/kg per minute for at least 12 h. Patients with cardiogenic shock defined as a cardiac index <2 L/min per m^2 with a systemic vascular resistance index >2,000 dyne × s/cm^5 × m^2 were excluded from the analysis. The control group consisted of patients who underwent uncomplicated aorto-coronary bypass surgery. Exclusion criteria for both groups were refusal of written informed consent, sepsis as the cause of shock, age <19 years, pregnancy, central nervous system pathology, or treatment with AVP before study entry.

As part of the perioperative routine, all patients were monitored with an arterial, central venous and pulmonary artery catheter. All quantitative determinations of cardiac output were based on pulmonary artery catheter measurements. According to an institutional protocol, which served as a recommendation, the hemodynamic management constituted of the following: volume-resuscitation was guided by the response of filling pressures and/or cardiac/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 per m^2 or mixed venous oxygen saturation <60%, a milrinone and/or epinephrine infusion was started. Norepinephrine was infused to maintain MAP >60 mmHg. If norepinephrine requirements exceeded 0.6 μg/kg per minute, a supplementary AVP infusion (2–4 IU/h) could be installed at the discretion of the attending physician. In these patients, only AVP plasma levels at the time points before start of the AVP infusion were included into the statistical analysis. Intubated patients were analgosedated by continuous infusion of sufentanil, midazolam, and/or morphine. Continuous veno-venous hemofiltration (CVVHF) was employed for renal indications only.

Data collection

In all patients, demographic data, past medical history, chronic intake of angiotensin converting enzyme (ACE) inhibitors, pre-operative ejection fraction, type of surgical intervention, classification of the American Society of Anesthesiologists [11], the aortic cross clamp time and simplified acute physiology score II [12] were documented. Within 36 h after ICU admission, during which

the inclusion criterion had to be fulfilled, 3 mL of arterial EDTA blood were sampled to determine AVP and copeptin plasma concentrations. Blood was taken from an arterial line (study group), a central venous catheter or by puncture of a peripheral vein (control group) once daily at the same time point for 7 days. Blood samples were immediately centrifuged in the central institutional laboratory and the plasma portion was frozen at −80°C.

At the same time points, heart rate, MAP, central venous pressure (CVP), mean pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac and stroke volume index, the cardiac power index (MAP × cardiac index × 0.0022, [13]), systemic vascular resistance index, norepinephrine, epinephrine, and/or milrinone requirements, laboratory parameters (hemoglobin, white blood cell and platelet count, serum osmolarity, colloid osmotic pressure, liver and kidney function parameters, coagulation parameters, electrolytes, C-reactive protein, troponin I, arterial lactate, arterial blood gas analysis), the PaO_2/FiO_2 ratio, body temperature, analgosedative drug requirements, urine output in the past 24 h, injection of diuretics, and the need for CVVHF were recorded in the study group. In the control group, the same parameters were documented at given time points. After withdrawal of the arterial line, systemic blood pressure was measured using either the oscillatory or the auscultation method. CVP, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac/stroke volume index were recorded for the duration a central venous and/or pulmonary artery catheter was in place. Daily urine output was measured until the urinary catheter was removed. Laboratory variables were measured on day 1, 4 and 7 only, since no major variations were expected in this group.

In both study groups, the maximum multiple organ dysfunction syndrome score [14] count, length of ICU stay, need for a supplementary AVP infusion, and mortality were documented upon discharge from the ICU.

Measurement of AVP and copeptin plasma concentrations

After completion of patient recruitment, frozen plasma samples were transferred to the endocrinologic laboratories. All samples were blinded to the laboratory staff. For measurement of AVP, a radioimmunoassay (DRG Diagnostics, Marburg, Germany) was used [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 and inter assay variation is 4.9–6.5% and 6–6.9%, respectively. In case of test results lied significantly out of the clinically expected range (<0.83 or >50 pmol/L), measurements were repeated to reconfirm the results. Copeptin plasma concentrations were determined using a sandwich immunolumino-metric assay (B.R.A.H.M.S. AG; Hennigsdorf, Germany) [16]. The analytical detection limit of the copeptin assay is 1.7 pmol/L, its interlaboratory CV is <20% for values >2.25 pmol/L.

Study objects

The primary object was to compare the course of AVP plasma concentrations between patients with vasodilatory shock after cardiac surgery and patients undergoing uncomplicated aorto-coronary bypass surgery. The secondary study object was to determine associations between AVP plasma concentrations and clinical, hemodynamic and laboratory parameters in vasodilatory shock patients. The tertiary study object was to assess the correlation between AVP and copeptin levels.

Statistical analysis

For statistical analysis, the SPSS software program (Version 12.0.1; SPSS Inc., Illinois, United States of America) was used. To test for normality distribution, variables were visually inspected using normal probability plots. C-reactive protein and arginine vasopressin plasma levels showed deviations from normality and were log-transformed. All other variables were approximately normally distributed. Demographic and clinical parameters were compared between groups using the Student's t or Fisher's exact test, as appropriate. The course of AVP levels was compared between groups using a mixed effects model that considers repeated measurements to be correlated and not independent of each other. In case of statistical significance, AVP levels at single time points were compared using Student's t tests. In order to detect associations between the course of AVP plasma concentrations and hemodynamic, laboratory or clinical parameters during the observation period in vasodilatory shock patients, a bivariate followed by a multivariate regression model were calculated using a mixed effects model. In an explorative approach, all demographic, sequential clinical, hemodynamic and laboratory variables were included into the bivariate analysis. Selection of variables for the multivariate regression analysis was based on previous clinical knowledge and univariate significant ($P < 0.05$) correlations. Only variables showing a significant influence in the multivariate model were kept in the final model. A linear regression model was used to evaluate the correlation between AVP and copeptin plasma levels in all study patients. In order to assess the influence of plasma creatinine levels, creatinine clearance or the need for CVVHF on the correlation between AVP and copeptin, single variables were entered as co-variates into the model.

Statistical significance was assumed if P was <0.05. For comparisons of AVP levels between groups at single time points, Bonferroni corrections were applied and $P < 0.007$ was considered to indicate statistical significance. Data are given as mean values ± SD, if not indicated otherwise.

Results

Thirty-three and ten patients were included in the study and control group, respectively (Table 1). The pre-operative ejection fraction was lower, the American Association of Anesthesiologists classification and the need for CVVHF was higher in study than that in control patients. Aortic cross clamp time and ICU length of stay were longer in the study group. Study patients had a higher simplified acute physiology and multiple organ dysfunction syndrome score count. While all control patients survived, three study group patients succumbed. All three were treated with exogenous AVP infusion after norepinephrine requirements had exceeded 0.6 µg/kg per minute. In these patients, only AVP plasma levels at the time points before start of the AVP infusion were included into the statistical analysis. No other study patient received an AVP infusion. The mean duration of shock was 9.9 ± 6.9 days in study patients (Electronic repository, Fig. 1).

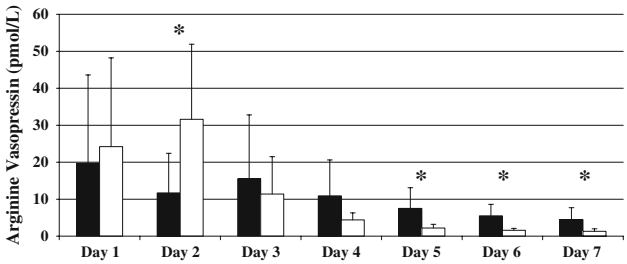

Fig. 1 Course of arginine vasopressin plasma concentrations in patients with vasodilatory shock after cardiac surgery (*black bars*) and patients after uncomplicated cardiac surgery (*white bars*). *Significant difference between groups ($P < 0.007$)

The course of AVP plasma concentrations significantly differed between study and control patients ($P < 0.001$) (Fig. 1). In vasodilatory shock patients, the type of the cardiac surgical procedure did not influence the postoperative AVP response ($P = 0.25$). If only vasodilatory shock patients undergoing aorto-coronary bypass grafting ($n = 15$) were analyzed, their AVP levels resembled those of the entire study group and significantly differed from control patients (Electronic repository Fig. 2). AVP levels decreased before initiation of AVP therapy in all three patients who developed advanced vasodilatory shock, required AVP infusion and subsequently died (Table 2). There was no difference in MAP ($P = 0.12$), norepinephrine requirements ($P = 0.43$), and the postoperative AVP response (Fig. 2)

Table 1 Characteristics of patient groups at baseline

	Vasodilatory shock	Uncomplicated CS	*P* value
n	33	10	
Age (years)	68 ± 8	70 ± 7	0.58
Male (%)	17 (51.5)	7 (70)	0.47
BMI (kg/m^2)	27 ± 5	26 ± 4	0.63
Chronic ACE-I therapy *n* (%)	19 (57.6)	8 (80)	0.29
Pre-operative EF (%)	48 ± 15	62 ± 11	0.01*
ASA classification *n* (%)			<0.001*
III	8 (24.2)	10 (100)	
IV	25 (75.8)	0	
Surgical intervention *n* (%)			0.05
CABG	15 (45.5)	10 (100)	
Valvular surgery	10 (30.3)	0	
CABG and valvular surgery	3 (9.1)	0	
Others	5 (15.1)	0	
Aortic cross clamp time (min)	117 ± 68	60 ± 15	<0.001*
SAPS II (pts)	37 ± 9	26 ± 9	0.004*
MODS score (pts)	9.6 ± 1.4	3.6 ± 1.8	<0.001*
CVVHF *n* (%)	11 (33.3)	0	0.04*
ICU length of stay (days)	14 ± 10	2 ± 0.4	<0.001*
Survival at ICU Discharge *n* (%)	30 (90.9)	10 (100)	1

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

CS Cardiac surgery, *BMI* body mass index, *ACE-I* angiotensin converting enzyme inhibitor, *EF* ejection fraction, *ASA* American Society of Anesthesiologists, *CABG* coronary artery bypass grafting, *SAPS* simplified acute physiology score, *MODS* multiple organ dysfunction syndrome, *CVVHF* continuous veno-venous hemofiltration, *ICU* intensive care unit

* Significant differences between groups

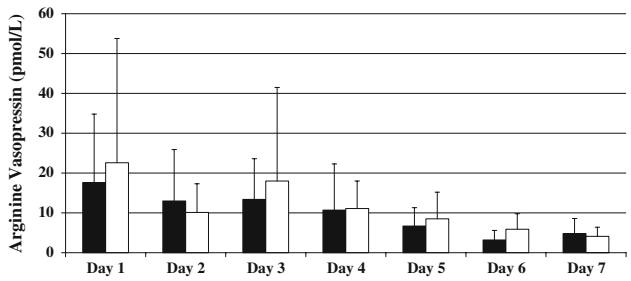

Fig. 2 Course of arginine vasopressin plasma concentrations in vasodilatory shock patients with (*black bars*, $n = 14$) and without (*white bars*, $n = 19$) chronic angiotensin converting enzyme inhibitor therapy

between the study patients with or without chronic ACE inhibitor intake.

Table 3 presents hemodynamic, clinical, and laboratory parameters in study and control patients. The course of milrinone requirements ($P < 0.001$), serum sodium concentrations ($P < 0.001$), and the need for CVVHF ($P < 0.001$) were the parameters correlated most significantly with AVP in the explorative bivariate regression analysis. There was no detectable correlation between AVP levels and hemodynamic parameters. In the multivariate analysis, need for CVVHF was independently associated with lower AVP plasma levels ($F = 16.753$, $P = 0.005$).

In the linear regression model, AVP and copeptin plasma concentrations correlated significantly with each other ($P < 0.001$; $r = 0.749$) (Fig. 3). This correlation was neither influenced by plasma creatinine concentrations ($P = 0.29$) nor the creatinine clearance ($P = 0.13$), but by the need for CVVHF ($P = 0.001$). While patients without CVVHF exhibited a correlation coefficient of $r = 0.803$, it was $r = 0.385$ in patients on CVVHF. Except for a missing plasma peak on the first postoperative day in the control group, the postoperative copeptin response was comparable to that of AVP (Electronic repository Fig. 3).

Discussion

In patients with vasodilatory shock after cardiac surgery, the endogenous AVP response to cardiac surgery significantly differed from patients undergoing uncomplicated aorto-coronary bypass grafting. While vasodilatory shock patients failed to exhibit a postoperative peak, their AVP levels remained moderately elevated during the first 7 postoperative days. AVP plasma concentrations were

Table 2 Hemodynamic parameters and AVP plasma levels in the three patients who reveived on AVP infusion and died

Sex	Age (years)	Parameter (unit)	Postop day 1	Postop day 2	Postop day 3	Postop day 4	Postop day 5	Postop day 6	Postop day 7
Pat 1									
Male	85	AVP levels (pmol/L)	11.2	9.4	5.5	745	[a]		
		AVP infusion (IU/h)	0	0	0	4			
		Heart rate (beats/min)	82	103	96	124			
		MAP (mmHg)	67	61	69	42			
		CVP (mmHg)	12	12	11	12			
		NE dosage (μg/kg per minute)	0.19	0.32	0.49	2.64			
Pat 2									
Male	74	AVP levels (pmol/L)	7.6	82.6	67.5	58.2	16.5	3.7	68.4
		AVP infusion (IU/h)	0	2	2	2	0	0	2
		Heart rate (beats/min)	100	97	114	103	101	105	101
		MAP (mmHg)	70	65	64	60	58	60	53
		CVP (mmHg)	16	17	11	19	16	17	18
		NE dosage (μg/kg per minute)	0.42	1.41	1.41	0.79	1.53	2.26	0.79
Pat 3									
Male	78	AVP levels (pmol/L)	59.8	1.3	154	[a]			
		AVP infusion (IU/h)	0	0	4				
		Heart rate (beats/min)	89	93	90				
		MAP (mmHg)	93	69	56				
		CVP (mmHg)	15	13	16				
		NE dosage (μg/kg per minute)	0.43	0.92	1.39				

At all time points, the three patients fulfilled the systemic inflammatory response syndrome criteria

AVP Arginine vasopressin, *MAP* mean arterial blood pressure, *CVP* central venous pressure, *NE* norepinephrine

[a] Day of death

Table 3 Hemodynamic, clinical, and laboratory parameters in study and control patients during the observation period

	Postop day 1	Postop day 2	Postop day 3	Postop day 4	Postop day 5	Postop day 6	Postop day 7
Heart rate (bpm)							
Vasodilatory shock	98 ± 12	92 ± 14	88 ± 13	87 ± 15	88 ± 14	89 ± 12	87 ± 12
Uncomplicated CS	81 ± 14	87 ± 10	87 ± 13	84 ± 9	79 ± 15	73 ± 8	70 ± 6
MAP (mmHg)							
Vasodilatory shock	73 ± 13	73 ± 10	76 ± 11	79 ± 15	82 ± 14	82 ± 14	84 ± 18
Uncomplicated CS	79 ± 10	84 ± 12	82 ± 11	90 ± 9	85 ± 11	89 ± 10	91 ± 14
CVP (mmHg)							
Vasodilatory shock	12 ± 3	13 ± 3	12 ± 3	12 ± 2	12 ± 3	11 ± 3	11 ± 5
Uncomplicated CS	9 ± 3	8 ± 3	7 ± 3	9 ± 3	NA	NA	NA
Cardiac index (L/min per m^2)							
Vasodilatory shock	2.5 ± 0.6	3 ± 0.5	3 ± 0.6	2.9 ± 0.5	3.1 ± 0.8	3.1 ± 0.7	3 ± 0.7
Uncomplicated CS	2.5 ± 0.6	NA	NA	NA	NA	NA	NA
Cardiac power index (Watt/m^2)							
Vasodilatory shock	0.41 ± 0.12	0.48 ± 0.1	0.5 ± 0.13	0.51 ± 0.13	0.53 ± 0.15	0.54 ± 0.16	0.53 ± 0.21
Uncomplicated CS	0.44 ± 0.14	NA	NA	NA	NA	NA	NA
SVRI (dyne × s/cm^5 × m^2)							
Vasodilatory shock	1935 ± 571	1634 ± 377	1740 ± 467	1873 ± 449	1849 ± 605	1759 ± 447	1781 ± 442
Uncomplicated CS	2375 ± 473	NA	NA	NA	NA	NA	NA
PCWP (mmHg)							
Vasodilatory shock	15 ± 3	16 ± 4	14 ± 3	16 ± 4	15 ± 4	15 ± 5	15 ± 5
Uncomplicated CS	11 ± 4	NA	NA	NA	NA	NA	NA
NE dosage (µg/kg per min)							
Vasodilatory shock	0.16 ± 0.35	0.25 ± 0.26	0.29 ± 0.39	0.32 ± 0.7	0.33 ± 0.5	0.48 ± 0.83	0.29 ± 0.24
Uncomplicated CS	NA	NA	NA	NA	NA	NA	NA
Mil dosage (µg/kg per min)							
Vasodilatory shock	0.48 ± 0.18	0.42 ± 0.19	0.38 ± 0.22	0.33 ± 0.2	0.34 ± 0.17	0.3 ± 0.18	0.31 ± 0.16
Uncomplicated CS	NA	NA	NA	NA	NA	NA	NA
Fluid balance (mL/day)							
Vasodilatory shock	1734 ± 1013	1142 ± 1359	504 ± 1016	370 ± 795	380 ± 773	78 ± 1065	−312 ± 1080
Uncomplicated CS	1157 ± 1105	1201 ± 956	304 ± 1109	663 ± 984	−294 ± 714	NA	NA
S Sodium (mmol/L)							
Vasodilatory shock	145 ± 5	146 ± 4	147 ± 6	146 ± 7	146 ± 7	143 ± 6	145 ± 6
Uncomplicated CS	142 ± 2	144 ± 3	143 ± 3	142 ± 2	141 ± 4	139 ± 2	139 ± 2
S Osmolartiy (mosmol/L)							
Vasodilatory shock	312 ± 11	312 ± 13	316 ± 14	317 ± 16	317 ± 19	316 ± 16	309 ± 14
Uncomplicated CS	299 ± 4	297 ± 6	298 ± 5	301 ± 7	300 ± 8	298 ± 3	300 ± 4
pH							
Vasodilatory shock	7.4 ± 0.07	7.4 ± 0.07	7.43 ± 0.09	7.45 ± 0.07	7.46 ± 0.05	7.45 ± 0.05	7.47 ± 0.04
Uncomplicated CS	7.39 ± 0.06	7.37 ± 0.03	NA	NA	NA	NA	NA
Lactate (mmol/L)							
Vasodilatory shock	37 ± 39	19 ± 12	20 ± 39	16 ± 22	12 ± 4	17 ± 23	15 ± 23
Uncomplicated CS	11 ± 3	15 ± 6	NA	NA	NA	NA	NA
Need for CVVHF *n* (%)							
Vasodilatory shock	4/33 (12.1)	7/33 (21.2)	11/33 (33.3)	10/32 (31.3)	10/31 (32.3)	10/31 (32.3)	10/31 (32.3)
Uncomplicated CS	NA	NA	NA	NA	NA	NA	NA

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

Postop Postoperative, *MAP* mean arterial blood pressure, *CVP* central venous pressure, *SVRI* systemic vascular resistance index, *PCWP* pulmonary capillary wedge pressure, *NE* norepinephrine, *Mil* milrinone, *CVVHF* continuous veno-venous hemofiltration, *NA* not applicable/available

directly correlated with copeptin and indirectly with the need for CVVHF.

Arterial hypotension during cardiopulmonary bypass is known to stimulate AVP release [17] and could explain the observed postoperative AVP peak in control patients. Since the AVP system rapidly responds to cardiovascular stimuli [18], ongoing postoperative stimulation of AVP release by inflammatory mediators [19, 20] may have contributed to elevated AVP plasma levels until postoperative day 2. Thus, the AVP response to cardiac surgery resembles the postoperative course of other stress hormones [21]. The AVP levels measured in this study are comparable to those observed in cardiac surgery patients, 24 h after ICU admission in a recent investigation [9]. So far, higher AVP levels have only been reported during cardiopulmonary resuscitation [22] or in multiple trauma patients [23].

Since AVP is a potent vasoconstrictor hormone and stimulated by arterial hypotension, higher AVP plasma concentrations would have been expected in patients with vasodilatory shock than in patients after uncomplicated cardiac surgery. However, in our study, contrary results

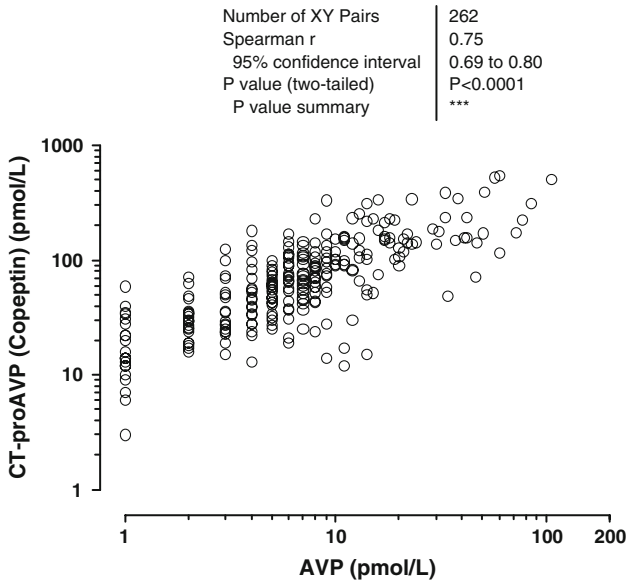

Fig. 3 Correlation between plasma arginine vasopressin and copeptin plasma concentrations in all study patients ($n = 43$)

were observed. So far, several pathophysiologic mechanisms were suggested to explain an inadequate AVP response during critical illness. Autonomic dysfunction is known to hamper physiologic reflex pathways [24] and is likely to involve AVP releasing reflexes, too. Nitric oxide-related impairment of AVP production in hypothalamic neurons [25] together with vigorous stimulation of AVP release from the neurohypophysis could explain depletion of endogenous AVP stores. The latter observation was impressively shown in patients with septic shock [26] and dogs after sustained hemorrhage [4]. Both alpha adrenergic [27, 28] and analgosedative drugs [29], which were administered to all study but none of the control patients may have also modulated the postoperative AVP response. Furthermore, it is possible that determination of AVP and clinical parameters at single time points may have omitted a dynamic relationship between AVP levels and hemodynamic variables.

Our analysis cannot elucidate whether there was a causative relationship between inadequately high AVP plasma concentrations and the failure to restore vascular tone in patients with vasodilatory shock after cardiac surgery. However, AVP plasma concentrations in the three patients who presented with the highest norepinephrine requirements and subsequently received exogenous AVP infusion were very low for the degree of hypotension. The explorative regression analysis suggests that AVP plasma levels and CVVHF are indirectly associated with each other. This could indicate that more AVP is removed during CVVHF (sieving coefficient, 0.85 ± 0.11 [30]) than that hypothalamic nuclei can produce. On the other hand, need for CVVHF may also represent a marker of severe disease in which the AVP system is even more disturbed and AVP stores are largely depleted.

Although chronic ACE inhibitor therapy is an independent risk factor for the development of vasodilatory shock after cardiac surgery [31], preoperative ACE inhibitor intake did not influence the postoperative AVP response in our study. Considering these results, it may be speculated that other mechanisms than impaired AVP release account for the high incidence of intra- and postoperative hypotension in cardiovascular surgery patients chronically taking ACE inhibitors [32]. Nonetheless, since no power analysis was performed, the number of patients with vasodilatory shock after cardiac surgery ($n = 33$) may have been too small to uncover a significant difference in AVP levels between the two groups.

Copeptin is a stable fragment of the AVP precursor pre-pro-vasopressin and is released together with AVP in a 1:1 stochiometric pattern [16]. In contrast to AVP, copeptin exhibits an advantageous ex vivo profile, permitting rapid and reliable laboratory testing [16]. Elevated copeptin plasma concentrations were found in critically ill patients with multiple traumas [23], sepsis, postcardiotomy shock, and systemic inflammatory response syndrome [33]. In accordance with results of earlier studies, a good correlation between AVP and copeptin plasma levels was also observed in this analysis. Despite that, copeptin measurements missed the AVP plasma peak that occurred in control patients on postoperative day 2. Given the possible contributory role of inadequately low AVP plasma concentrations to the failure to restore vascular tone in vasodilatory shock after cardiac surgery, copeptin may be used as a surrogate parameter to indicate and guide AVP therapy in these patients. However, future trials are needed to test this hypothesis. Furthermore, the influence of CVVHF on the correlation of the two parameters deserves further investigation. Since AVP and copeptin have different molecular weights (1,084 vs. 4,021 daltons [16, 30]), it is conceivable that CVVHF removes diverse amounts of the two proteins from the plasma.

When interpreting the results of our study, certain limitations must be considered. First, even though all study patients suffered from vasodilatory shock >24 h, the duration of hemodynamic failure was heterogeneous. This may have affected the overall course of postoperative AVP levels. Second, the control group exclusively consisted of patients undergoing uncomplicated aorto-coronary bypass grafting, while study patients underwent also other cardiac surgery procedures. However, given the finding that the surgical procedure did not influence the postoperative AVP response in study patients, it is unlikely that this has relevantly influenced our results.

In conclusion, the AVP response to cardiac surgery is significantly different between patients with vasodilatory shock and patients undergoing uncomplicated aorto-

coronary bypass surgery. Although no causative relationship between AVP concentrations and cardiovascular instability can be drawn from these results, our data support the hypothesis that inadequately low AVP plasma levels contribute to the failure to restore vascular tone in vasodilatory shock after cardiac surgery.

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