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Vasopressin or norepinephrine in early hyperdynamic septic shock: a randomized clinical trial

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Abstract *Objective:* To compare the effects of arginine-vasopressin (AVP) and norepinephrine (NE) on hemodynamic variables, organ dysfunction, and adverse events in early hyperdynamic septic shock. *Design and setting:* Randomized, controlled, open-label trial. *Patients and participants:* Twenty-three patients with early (12 h) hyperdynamic septic shock in two teaching hospitals. *Interventions:* AVP (0.04–0.20 U min⁻¹, *n* = 13) as a single agent or NE (0.1–2.8 µg kg⁻¹ min⁻¹, *n* = 10) infusion for 48 h to achieve mean arterial pressure at or above 70 mmHg. *Measurements and results:* Hemodynamic parameters and Sequential Organ Failure Assessment (SOFA) score were measured. AVP and NE equally increased mean arterial pressure over 48 h, but NE was required in 36% of AVP patients at 48 h. Compared to baseline, AVP increased systemic vascular resistance, decreased exposure to NE, decreased cardiac output by decreasing heart

rate, increased creatinine clearance, and improved SOFA score. The PrCO₂ – PaCO₂ difference remained stable throughout the study. One AVP patient developed acute coronary syndrome with dose-dependent ECG changes. Three patients in both groups died during their ICU stay. *Conclusion:* In early hyperdynamic septic shock, the administration of high-dose AVP as a single agent fails to increase mean arterial pressure in the first hour but maintains it above 70 mmHg in two-thirds of patients at 48 h. AVP decreases NE exposure, has no effect on the PrCO₂ – PaCO₂ difference, and improves renal function and SOFA score.

Keywords Vasopressin · Norepinephrine · Shock, septic · Sepsis · Kidney failure, acute · Multiple organ failure

Introduction

Severe sepsis is the tenth leading cause of death in the United States [1], with an incidence rate of 3.0 per 1,000 persons/year [2]. The mortality rate remains high (up to 30%) [2] and may reach 55% in septic shock [3].

Fluid management, antibiotics, source control, vasopressors, inotropes, activated protein C, and low-dose corticosteroids in selected patients are the foundations of septic shock treatment. Recently, early goal-directed

therapy [4] has also figured among the most important components of initial septic shock management. However, no particular vasopressor in the early resuscitation phase of septic shock has proven to be superior in improving clinical outcome [5].

The use of exogenous arginine-vasopressin (AVP) infusion in catecholamine-refractory shock has become popular since the description of relative vasopressin depletion in patients with septic shock compared to cardiogenic shock [6]. Subsequently, vasopressin defi-

ciency was shown to occur approx. 36 h after the onset of septic shock [7]. Uncontrolled trials and retrospective cohort studies have provided some understanding of the pharmacological effects of a replacement dose of AVP [8, 9, 10, 11, 12, 13, 14, 15, 16]. AVP has been reported to (a) increase mean arterial pressure [9, 10, 12, 13, 14, 15, 16], (b) slightly decrease [10, 11, 12, 13, 15] or maintain [12, 14] cardiac output, (c) improve short-term urine output [14, 15, 16] and creatinine clearance, (d) enhance gastric-arterial PCO₂ (PrCO₂ – PaCO₂) difference [11, 12], and (e) decrease catecholamine requirements [13, 15, 16]. The catecholamine-sparing properties [17, 18, 19] and possible renoprotective [18] effects of AVP have also been confirmed in small randomized controlled trials [17, 18, 19], although the safety of AVP on cardiac output and splanchnic perfusion remains a matter of debate.

To date, no trial has examined the value of AVP as part of early management of hyperdynamic septic shock. The purpose of this study was therefore to evaluate the effects of AVP on mean arterial pressure, other hemodynamic variables, and organ dysfunction when used to replace norepinephrine (NE) in the early resuscitation phase of hyperdynamic septic shock.

Materials and methods

Patients

The study was performed at the Centre Hospitalier Universitaire de Sherbrooke, Hôpital Fleurimont (Sherbrooke, Canada) and the Centre Hospitalier Universitaire de Nancy, Hôpital Central, Service de Réanimation Médicale (Nancy, France) between August 2000 and June 2004. The second recruiting center experienced temporary inability to recruit because AVP was retired for intravenous use in France. Local institutional ethics committees approved the study, and informed consent was obtained from the next of kin. Patients were eligible if they (a) met criteria for septic shock [20], (b) had at some point a mean arterial pressure of 60 mmHg or less after at least a 1000-ml crystalloid bolus, (c) were on vasopressors for less than 12 h before randomization, (d) had pulmonary artery occlusion pressure of 12 mmHg or higher, and (e) had a cardiac index of 3 l min⁻¹ m⁻² or higher. If informed consent was rapidly obtained, hypotensive patients were randomized prior exposure to any vasoactive drug. Patients younger than 16 years old, receiving chronic dialysis, not expected to survive longer than 48 h, and pregnant patients were excluded.

Twenty-three patients participated in the study, 18 in Canada and 5 in France; 13 received AVP (6 men, 7 women; 51.2 ± 17.2 years old; body mass index 25.7 ± 6.7) and 10 NE (8 men, 2 women; 58.1 ± 17.5 years old, body mass index 25.0 ± 3.8; Table 1). No significant differences were observed be-

Table 1 Baseline characteristics (AVP arginine-vasopressin, NE norepinephrine, APACHE Acute Physiology and Chronic Health Evaluation, SOFA Sequential Organ Failure Assessment)

	AVP (n = 13)	NE (n = 10)	p
Age (years)	51.2 ± 17.2	58.1 ± 17.5	0.35
Gender: M/F	6/7	8/2	0.20
Body mass index	25.7 ± 6.7	25.0 ± 3.8	0.73
Recent surgical history	3	3	1.00
Site of infection			0.80
Lung	7	4	
Abdomen	4	4	
Other	2	2	
Gram staining of bacterial pathogen			0.93
Gram-negative	3	3	
Gram-positive	7	4	
Mixed	2	2	
Unknown	1	1	
APACHE II score	22.8 ± 3.4	23.5 ± 4.2	0.65
Modified SOFA score	8.5 ± 1.4	9.3 ± 1.4	0.17
Chronic corticosteroid use	5 (38%)	2 (20%)	0.41
Relative adrenal insufficiency	3/8 (38%)	6/8 (75%)	0.31
Overall corticosteroid use	8 (62%)	8 (80%)	0.41
Drotrecogin α use	2 (15%)	3 (30%)	0.62
Time from onset of septic shock to baseline measurements (h)	7.4 ± 5.4	8.2 ± 6.2	0.74

tween the study groups at randomization except for higher bilirubin levels in the AVP group, and patients enrolled in Canada and in France were also similar. One patient originally allocated to the NE group did not provide consent; because the next of kin refused to give consent for the insertion of pulmonary arterial catheter, this patient was excluded. No patients required continuous renal replacement therapy throughout the study. Eight patients in each group received corticosteroids. Although not statistically significant, patients in the AVP group (n = 5) than in the NE group (n = 2) were more often receiving chronic corticosteroids for medical reasons before randomization, while patients in the NE group (n = 6) than in the AVP group (n = 3) developed relative adrenal insufficiency within the first 24 h of septic shock. Resuscitation fluid amounts infused prior to inclusion were similar in the two groups (AVP 4.37 l, interquartile range, 2.20–4.54; NE 3.87 l, 3.22–5.72).

Protocol

A computer-generated block randomization list for each center was prepared by a pharmacist not involved in patient recruitment. Randomization was concealed using numbered, opaque sealed envelopes. Patients were allocated to open-label AVP (0.04–0.20 U/min; Ferring, Toronto, Ontario) or NE bitartrate (0.1–2.8 µg kg⁻¹ min⁻¹; Sabex, Boucherville, Quebec), which was infused in

a central venous catheter to maintain a mean arterial pressure above 70 mmHg. Other vasopressive drugs were tapered and weaned as the experimental drug was increased. When maximal dosage of the experimental drug was reached (AVP 0.20 U min⁻¹; NE 2.8 µg kg⁻¹ min⁻¹), administration of the other drug (either NE or AVP) was allowed as rescue therapy if the mean arterial pressure was still below 70 mmHg. Dobutamine was used if cardiac index decreased below 3 l min⁻¹ m⁻² despite adequate volume resuscitation. Either colloids (albumin 25%, Bayer, Toronto, Ontario; pentastarch 10%, Bristol-Myers-Squibb Canada, Montreal, Quebec) or crystalloids were used to maintain pulmonary artery occlusion pressure greater than 12 mmHg. Within 24 h after randomization an ACTH stimulation test was performed in all patients by injecting 250 µg ACTH and by measuring cortisol before and 30 and 60 min after the injection. Relative adrenal insufficiency was defined by a response of 9 µg dl⁻¹ or less. Nonresponders and chronic corticosteroid users were treated with hydrocortisone 50 mg intravenously every 6 h for at least 1 week [21]. Antibiotic use, surgical management of infection, insulin, sedation, analgesia, transfusions, and other supportive treatments were at the discretion of the ICU team.

Hemodynamic monitoring included radial and pulmonary arterial catheters (Edwards Life Sciences, Irvine Calif., USA). Parameters were measured at 0, 1, 6, 12, 24, and 48 h after protocol initiation. Since all patients were mechanically ventilated, pressures were measured at end-expiration. Cardiac index was obtained by thermodilution. Mean cardiac index was calculated after performing three measurements with 10 ml dextrose water (5%) at room temperature (<22 °C) injected in less than 2 s. Gastric tonometry was performed after insertion of a TRIP catheter (16 F) by nasogastric route (Tonocap, Tonometrics, Datex-Ohmeda, Madison Wisc., USA). Enteral nutrition was not allowed for the first 24 h and was discontinued 8 h prior to the last tonometric measurement at 48 h.

Arterial blood gases, pulmonary artery blood gases, and lactate concentration were obtained for each cardiac index measurement. The PaO₂/FIO₂ ratio, creatinine clearance, bilirubin, platelet count, and modified Sequential Organ Failure Assessment (SOFA) score were measured at 0, 12, 24, and 48 h. Modified SOFA score was determined without considering the neurological component as all patients were sedated. While the cardiovascular component of the SOFA score considers catecholamine (but not AVP) use as a marker of organ dysfunction, additional points were prospectively assigned to AVP patients not on NE to avoid a vasopressor-selection bias (2 points if AVP infusion was at or below 0.04 U/min and 3 points if at or below 0.04 U/min). Creatinine clearance was based on 2-h urine collection.

Adverse reactions such as acute coronary syndromes, arrhythmias, clinically significant gut and skin ischemia were prospectively and systematically recorded in each group by a physician not involved in the study. Acute coronary syndrome was a priori defined as an increase in troponin I level above the normal threshold combined with electrocardiographic (ECG) changes (ST segment elevation or depression of ≥ 1 mV or a T wave inversion of ≥ 2 mV).

Statistical analysis

We respected the intention-to-treat principle by analyzing all patients according to their initial assignment. Data are expressed as mean ± SD or median with interquartile range. Normality was assessed by the Shapiro-Wilks test for each variable. Baseline characteristics were compared using the unpaired Student's *t* test for quantitative variables and Fisher's exact test for categorical variables. Differences within groups were analyzed by one-way analysis of variance for parametric variables. We used the Dunnett's method for comparisons with baseline when time-effect was significant. For nonparametric variables (vasoactive drugs requirements and alanine transaminase levels) we used the Kruskal-Wallis test for comparison within groups and the Mann-Whitney *U* test with Bonferroni's adjustment for comparisons between pairs. Differences between groups were analyzed by linear mixed-effects models to consider death-related dropouts. All comparisons with a *p* value less than 0.05 were considered as statistically significant.

Results

Hemodynamic parameters

Hemodynamic parameters and vasoactive drug requirements were similar at the beginning of drug infusion (Table 2). Central venous pressure, pulmonary artery occlusion pressure, and mean pulmonary artery pressure remained stable over time and were similar in each group. In both groups the mean arterial pressure increased over time and differed significantly at the end of the study compared with baseline (AVP *p* = 0.004, NE *p* = 0.02). No differences were observed between groups (*p* = 0.74). There was a transient decrease in cardiac index vs. baseline among patients receiving AVP, which was significant at 1, 6, and 12 h (*p* = 0.02) and was associated with a sustained increase in systemic vascular resistance (*p* = 0.002; Table 2). In addition, there was a decrease in O₂ delivery at 48 h in the AVP group (*p* = 0.01; Table 3). There was no overall difference in cardiac index, O₂ delivery, or consumption in the NE group. The NE dose was lower in the AVP group at the end of the study compared to

Table 2 Hemodynamic parameters (AVP arginine-vasopressin, NE norepinephrine, MPAP mean pulmonary artery pressure, CVP central venous pressure, PAOP pulmonary artery occlusion pressure, SVRI systemic vascular resistance index, PVRI pulmonary vascular resistance index)

	Baseline	1 h	6 h	12 h	24 h	48 h	<i>p</i> over time	<i>p</i> between groups
MAP (mmHg)								0.74
AVP	72 ± 7	74 ± 8	75 ± 7	74 ± 12	81 ± 11*	78 ± 12*	0.004	
NE	68 ± 10	72 ± 5	72 ± 8	73 ± 6	77 ± 6	81 ± 9*	0.02	
Heart rate (beats/min)								0.47
AVP	118 ± 16	105 ± 16	100 ± 15*	97 ± 17*	96 ± 20*	93 ± 21*	0.009	
NE	109 ± 23	108 ± 22	104 ± 22	105 ± 20	101 ± 19*	96 ± 18*	0.79	
MPAP (mmHg)								0.24
AVP	30 ± 5	28 ± 6	26 ± 7	27 ± 7	28 ± 5	27 ± 8	0.71	
NE	30 ± 11	29 ± 8	27 ± 8	30 ± 8	26 ± 6	34 ± 5	0.52	
Cardiac index (ml min ⁻¹ m ⁻²)								0.13
AVP	4.6 ± 1.0	3.6 ± 1.1*	3.7 ± 0.7*	3.7 ± 0.5*	4.2 ± 0.8	3.7 ± 0.9	0.02	
NE	4.4 ± 1.4	4.3 ± 1.4	4.3 ± 1.7	4.4 ± 1.8	4.5 ± 1.8	3.7 ± 1.6	0.96	
Stroke volume index, (ml/beat/m ²)								0.39
AVP	39.9 ± 9.7	34.9 ± 10.8	38.1 ± 12.0	38.9 ± 9.2	44.7 ± 9.0	41.8 ± 13.3	0.35	
NE	40.8 ± 11.5	40.1 ± 12.9	41.3 ± 14.5	41.6 ± 13.8	44.3 ± 12.8	41.3 ± 13.7	0.99	
CVP (mmHg)								0.11
AVP	10 ± 4	12 ± 5	12 ± 6	12 ± 5	10 ± 4	12 ± 5	0.87	
NE	13 ± 7	12 ± 5	12 ± 6	12 ± 3	13 ± 4	15 ± 3	0.91	
PAOP (mmHg)								0.40
AVP	13 ± 5	15 ± 4	16 ± 6	14 ± 5	13 ± 5	14 ± 4	0.66	
NE	14 ± 5	14 ± 5	14 ± 5	14 ± 4	15 ± 5	17 ± 2	0.84	
SVRI (dyne·s·cm ⁻⁵ m ⁻²)								0.32
AVP	985 ± 227	1414 ± 397*	1409 ± 316*	1369 ± 306*	1384 ± 246*	1501 ± 361*	0.002	
NE	1108 ± 392	1225 ± 380	1256 ± 399	1258 ± 453	1255 ± 342	1576 ± 396	0.39	
PVRI (dyne·s·cm ⁻⁵ m ⁻²)								0.42
AVP	310 ± 142	304 ± 144	236 ± 166	291 ± 125	305 ± 106	320 ± 233	0.79	
NE	306 ± 159	309 ± 181	307 ± 250	364 ± 298	223 ± 126	416 ± 221	0.62	

* *p* < 0.05 vs. baseline

baseline (*p* = 0.04; Table 4), but 85% of AVP-infused patients received NE at some point because their mean arterial pressure was less than 70 mmHg despite maximal dose of AVP (0.2 U/min). No patients in the NE group received rescue AVP therapy. Three patients in both groups required dobutamine.

Organ dysfunction

Organ dysfunction measurements are shown in Table 3. AVP patients exhibited a lower modified SOFA score at the end of the experiment than NE patients (*p* = 0.04). This was associated with an improvement in creatinine clearance at 24 h in the AVP group (*p* = 0.04) that was not observed in the NE group (*p* = 0.46). Baseline bilirubin levels was higher in the AVP group than the NE group (*p* = 0.03), but this gap remained unchanged throughout the study and was not associated with a difference in alanine transaminase levels. No difference was observed

either between or within groups in terms of PrCO₂ – PaCO₂ difference or platelet count.

Adverse events

Overall three patients in both groups died during ICU stay (ICU mortality rate: AVP group 23.1%, NE group 30%; *p* = 1.00, Fisher's exact test). Three patients died during the study protocol: two in the AVP group and one in the NE group. In each case death was attributed to refractory shock. In one instance, a marked increase in PrCO₂ – PaCO₂ difference was observed while the patient was receiving AVP at 0.2 U/min. However, an autopsy limited to the abdomen and performed by a pathologist unaware of group assignment reported neither macroscopic nor microscopic evidence of mesenteric ischemia. No such event occurred among the other patients. No cutaneous ischemia was observed in either group.

One case of acute coronary syndrome occurred during the protocol in each group, with a maximal troponin I

Table 3 Organ dysfunction (AVP arginine-vasopressin, NE norepinephrine, IQR interquartile range)

	Baseline	12 h	24 h	48 h	<i>p</i> over time	<i>p</i> between groups
Lactate (mmol l ⁻¹)						0.27
AVP	2.87 ± 0.75	2.75 ± 0.79	2.26 ± 0.70	2.25 ± 0.67	0.11	
NE	3.33 ± 1.75	2.90 ± 2.44	2.74 ± 2.04	2.49 ± 1.26	0.81	
Mixed venous O ₂ saturation (%)						0.87
AVP	68 ± 8	66 ± 6	65 ± 6	65 ± 8	0.66	
NE	65 ± 7	68 ± 9	68 ± 8	65 ± 7	0.74	
Indexed O ₂ delivery (ml min ⁻¹ m ⁻²)						0.23
AVP	581 ± 124	462 ± 108*	506 ± 121	423 ± 103*	0.01	
NE	537 ± 143	630 ± 327	537 ± 192	474 ± 306	0.66	
Indexed O ₂ consumption, (ml min ⁻¹ m ⁻²)						0.14
AVP	148 ± 30	133 ± 26	155 ± 19	128 ± 35	0.10	
NE	157 ± 42	171 ± 72	149 ± 30	146 ± 72	0.80	
Modified SOFA score						0.001
AVP	8.5 ± 1.3	7.8 ± 2.4	7.0 ± 1.3	6.2 ± 2.8*	0.04	
NE	9.3 ± 1.4	8.6 ± 1.2	8.9 ± 0.9	8.0 ± 1.6	0.19	
PaO ₂ /FIO ₂ ratio						0.17
AVP	133 ± 69	154 ± 84	200 ± 88	200 ± 108	0.16	
NE	168 ± 108	198 ± 91	233 ± 78	230 ± 73	0.36	
Creatinine clearance (ml min ⁻¹ 1.73 m ⁻²)						0.001
AVP	50 ± 37	105 ± 85	122 ± 66*	106 ± 58	0.04	
NE	47 ± 45	47 ± 37	54 ± 38	73 ± 42	0.46	
Daily urine output (ml)						0.38
AVP	1420 ± 656	–	2049 ± 562	3051 ± 1666*	0.008	
NE	1146 ± 700	–	1895 ± 1292	2644 ± 1060	0.07	
Bilirubin (μmol/l)						0.03
AVP	26 ± 42	29 ± 44	25 ± 39	21 ± 28	0.98	
NE	11 ± 12	11 ± 10	10 ± 12	12 ± 17	0.99	
Alanine transaminase (U/l; IQR)						0.06
AVP	26 (25–41)	34 (25–49)	34 (29–44)	37 (26–47)	0.83	
NE	39 (21–60)	47 (24–63)	40 (24–54)	38 (24–100)	0.99	
Platelet count (× 10 ³ /μl)						0.13
AVP	194 ± 128	148 ± 91	148 ± 91	135 ± 86	0.49	
NE	141 ± 105	134 ± 91	113 ± 68	110 ± 62	0.83	
PrCO ₂ – PaCO ₂ difference (mmHg)						0.35
AVP	7 ± 6	10 ± 6	6 ± 5	8 ± 9	0.60	
NE	10 ± 9	9 ± 7	10 ± 6	8 ± 5	0.98	

* *p* < 0.05 vs. baseline

level of 0.8 μg/l in the AVP patient and of 0.6 μg/l in the NE patient. The latter patient had stable coronary artery disease. Coronary angiography demonstrated severe right coronary and circumflex stenosis. The AVP patient had no cardiovascular disease prior to admission, and angiography performed during infusion of AVP at 0.2 U/min revealed an occlusion of a small marginal artery. ECG changes (ST segment depression in lateral precordial leads) subsequently disappeared after tapering the AVP infusion to 0.04 U/min. None of these patients developed Q waves and creatine kinase levels remained normal. No tachyarrhythmia was observed during the first 48 h.

Discussion

In this randomized trial high-dose AVP alone did not maintain the mean arterial pressure above 70 mmHg in

the early resuscitation phase of hyperdynamic septic shock in most patients. Although patients were exposed to relatively lower doses of NE, no exquisite sensitivity to AVP was observed. More than one-half of AVP-infused patients were still on NE and required the maximal dose of AVP after 1 h, and one-third were still on NE at 48 h. Patients enrolled in this trial were in septic shock for less than 12 h. Since vasopressin depletion is believed to occur 36 h from the onset of septic shock [7], enrolled patients may have not been AVP depleted. We did not measure AVP levels, and the dose used probably led to supranormal AVP levels. On the other hand, the relationship between circulating vasoactive hormones and pharmacological effects is complex. Jochberger et al. [22] recently demonstrated that there is no correlation between AVP serum levels and hemodynamic parameters in critically ill patients. Moreover, decreased AVP sensitivity, partly related to receptor downregula-

Table 4 Vasoactive drug requirements (NE norepinephrine, DU dobutamine, AVP arginine-vasopressin, IQR interquartile range)

	Baseline	1 h	6 h	12 h	24 h	48 h	p over time	p between groups
NE use								
AVP	11/13 (85%)	8/13 (62%)	4/13 (31%)	4/13 (31%)	3/11 (27%)	4/11 (36%)	-	-
NE	7/10 (70%)	10/10 (100%)	10/10 (100%)	10/10 (100%)	9/9 (100%)	6/9 (100%)	-	-
NE dose ($\mu\text{g kg}^{-1} \text{min}^{-1}$; IQR)								<0.001
AVP	0.16 (0.08-0.61)	0.08 (0.00-0.47)	0.00 (0.00-0.24)	0.00 (0.00-0.41)	0.00 (0.00-0.12)*	0.00 (0.00-0.05)*	0.04	
NE	0.20 (0.17-0.46)	0.58 (0.16-1.21)	0.61 (0.19-1.57)	0.50 (0.28-1.27)	0.42 (0.12-0.88)	0.10 (0.02-0.49)	0.06	
DU use								
AVP	0/13 (0%)	0/13 (0%)	1/13 (8%)	3/13 (23%)	2/11 (18%)	1/11 (9%)	-	-
NE	0/10 (0%)	0/10 (0%)	2/10 (20%)	3/10 (30%)	3/9 (33%)	3/9 (33%)	-	0.11
DU dose, ($\mu\text{g kg}^{-1} \text{min}^{-1}$; IQR)								
AVP	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-2.50)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.27	
NE	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-1.25)	0.00 (0.00-2.90)	0.00 (0.00-3.60)	0.00 (0.00-3.60)	0.18	
AVP use								
AVP	0/13 (0%)	13/13 (100%)	13/13 (100%)	12/13 (92%)	10/11 (91%)	5/11 (45%)	-	-
NE	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/9 (0%)	0/9 (0%)	-	-
AVP (U/min)								0.01
AVP	0.0 \pm 0.0	0.15 \pm 0.07*	0.14 \pm 0.07*	0.12 \pm 0.07*	0.09 \pm 0.08*	0.06 \pm 0.08*	<0.001	
NE	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0	1.00	

* $p < 0.05$ vs. baseline

tion [23], has recently been demonstrated during septic shock [24].

However, this trial demonstrates that the infusion of AVP, in contrast to NE, improves SOFA scores in early septic shock. Rapid improvement in SOFA score has been associated with lower mortality rates [25, 26, 27]. More specifically, improvement in renal dysfunction from baseline to day 1 is an independent predictor of 28-day survival [25]. In this trial improved SOFA score in AVP-treated patients was due mainly to its effect on renal function. Vasopressin-induced favorable effects on renal function have previously been reported in a randomized double-blind trial [18] and are supported by experimental data [28]. AVP increases renal blood flow in endotoxic animals [28, 29] independently of its effect on mean arterial pressure [18, 29]. Unlike NE, AVP exhibits selective vasoconstrictive properties on the efferent arteriole [30] and vasodilatory effects on the afferent arteriole which are thought to be related to nitric oxide production [31]. As for NE, this overall effect on renal microperfusion can be blunted by using higher doses of AVP [32].

AVP increased systemic vascular resistance and was a valuable NE-sparing agent. It decreased cardiac index by lowering heart rate rather than stroke volume. It also reduced O_2 delivery without affecting mixed venous oxygen saturation or lactate levels. These results are consistent with those of Albanèse et al. [33], who used 1 mg terlipressin, a AVP analog with 6-h half-life. Three small randomized trials [17, 18, 19] found no adverse effect of AVP on cardiac output, in opposition to case series [11, 12, 13, 15]. Luckner et al. [8] recently reported decreased cardiac index induced by AVP mainly in patients with hyperdynamic circulation, as was the case in our patients. On contrast to to Holmes et al. [15], who used AVP a dose as high as 0.6 U/min in some cases, no life-threatening decrease in cardiac index was observed after initiation of high-dose AVP in this trial. On the other hand, one patient developed AVP-induced acute coronary syndrome, although ischemic ECG changes disappeared upon reduction in the amount of AVP infused, which is consistent with dose-dependent coronary vasoconstriction observed in experimental models [34, 35].

As opposed to Luckner et al. [8], we did not find that AVP impaired liver function by inducing cholestasis and increasing liver enzymes. No $\text{PrCO}_2 - \text{PaCO}_2$ difference deterioration was observed, as opposed to the findings of Klinzing et al. [11] who used similar AVP doses previously described to reduce bleeding from ruptured esophageal varices [36] (mean dose 0.47 /min, maximal 1.8 U/min). In this respect our results confirm those observed previously in two randomized controlled trials [17, 18]. Furthermore, deleterious effects of AVP on splanchnic perfusion may be explained by inadequate fluid resuscitation [37].

Even with large doses of AVP mean pulmonary artery pressure and resistance did not change over time in this trial compared to those in the NE group. Animal experi-

ments demonstrate that low-dose AVP, which activates endothelial isoforms of nitric oxide synthase via endothelial oxytocin receptors [38], induces pulmonary vasodilation [39] and decreases lung hyperpermeability induced by endotoxin [28]. The former effect is not sustained with higher levels of AVP (>300 pg/ml) [40], whereas recent clinical data show that an AVP dose of 0.04–0.1 U/min does not change or slightly decreases pulmonary artery pressure [13, 14, 15, 17], in contrast to terlipressin which enhances it [33].

To our knowledge, this is the first trial evaluating the effects of AVP infusion in the first 12 h of hyperdynamic septic shock. Previous trials used AVP as a rescue therapy for refractory septic shock [17, 18, 19] or after equivocal delay from sepsis onset [11]. This study has several limitations. The unblinded design may have introduced confounders and affected measurements despite the fact that many measured variables are not prone to subjective interpretation. Also, the small sample size precludes definitive conclusions about the potential effect of AVP on clinically important benefits (such as less need for renal replacement or lower mortality suggested by improved renal function and SOFA scores) or clinically important harms (such as splanchnic and coronary adverse effects).

Conclusion

This multicenter, open-label randomized trial in early hyperdynamic septic shock found that initial management with high-dose AVP used as a single vasopressor agent initially failed to maintain the mean arterial pressure above 70 mmHg. Nevertheless AVP is a NE-sparing agent that decreases cardiac index mainly by decreasing heart rate rather than cardiac contractility. AVP may have favorable effects on renal function that translate into a lower modified SOFA score at 48 h. Although not designed to comprehensively assess gastrointestinal effects, no deterioration in the PrCO₂ – PaCO₂ difference was observed in the AVP group. Before becoming a standard of care in the management of early hyperdynamic septic shock, AVP needs to be further evaluated in a large double-blind randomized controlled trial to determine its effects on overall morbidity and mortality.

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