Comparison of two dose regimens of arginine vasopressin in advanced vasodilatory shock

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Objective: **To evaluate the effects of two arginine vasopressin (AVP) dose regimens (0.033 vs. 0.067 IU/min) on treatment efficacy, hemodynamic response, prevalence of adverse events, and changes in laboratory variables.**

Design: **Retrospective, controlled study.**

Patients: **A total of 78 patients with vasodilatory shock (mean norepinephrine dosage, 1.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$; 95% confidence interval, 0.82–1.56 $\mu g \cdot kg^{-1} \cdot min^{-1}$).**

Interventions: **Supplementary infusion of AVP at 0.033 (n = 39) and 0.067 IU/min (n = 39).**

Measurements and Main Results: **Cardiocirculatory, laboratory, and clinical variables were evaluated and compared between groups before and at 0.5, 1, 4, 12, 24, 48, and 72 hrs after initiation of AVP. Treatment efficacy was assessed by the increase in mean arterial blood pressure and the extent of norepinephrine reduction during the first 24 hrs of AVP therapy. Standard tests and a mixed-effects model were used for statistical analysis. Although the relative increase in mean arterial pressure was comparable between groups (0.033 vs. 0.067 IU/min: 16.8 ± 18.4 vs. 21.4 ± 14.9 mm Hg, $p = .24$), norepinephrine could be reduced significantly more often in patients receiving 0.067 IU/min. AVP at 0.067 IU/min resulted in a higher mean arterial pressure ($p < .001$), lower central venous pressure ($p = .001$), lower mean pulmonary arterial pressure ($p = .04$), and lower norepinephrine requirements ($p < .001$) during the 72-hr observation period. Increases in liver enzymes occurred more often in patients treated with 0.033 IU/min (71.8% vs. 28.2%, $p < .001$). The prevalence of a decrease in cardiac index (69.2% vs. 53.8%, $p = .24$), decrease in platelet count (94.8% vs. 84.6%, $p = .26$), and increase in total bilirubin (48.7% vs. 71.8%, $p = .06$) was not significantly different between groups. Bilirubin levels (3.1 ± 3.4 vs. 5.2 ± 5.5 mg/dL, $p = .04$) and base deficit (−7.2 ± 4.3 vs. −3.9 ± 5.9 mmol/L, $p = .005$) were lower and arterial lactate concentrations higher (76 ± 67 vs. 46 ± 38 mg/dL, $p < .001$) in patients receiving 0.033 IU/min.**

Conclusions: **AVP dosages of 0.067 IU/min seem to be more effective to reverse cardiovascular failure in vasodilatory shock requiring high norepinephrine dosages than 0.033 IU/min. (Crit Care Med 2007; 35:●●●–●●●)**

Key Words: vasopressin; dosage; vasodilatory shock; norepinephrine; treatment efficacy

Arginine vasopressin (AVP) has been recommended by the Surviving Sepsis Campaign in patients with severe septic shock when standard catecholamine therapy fails to adequately stabilize cardiovascular function (1). When given as a supplementary infusion, AVP was shown to restore perfusion pressure and decrease high, potentially toxic catecholamine dosages (2). A recent multicenter trial evaluating the effects of AVP on outcome in septic shock suggested a survival benefit of this treatment approach in the subgroup of patients with moderate septic shock (3).

Although a retrospective study concluded that AVP infusion in septic shock should not exceed 0.04 IU/min because adverse events had been observed in five patients treated with higher AVP dosages (4), there are no data on the appropriate AVP dosage in patients with advanced vasodilatory shock. So far, detrimental effects of AVP have been shown for very high dosages of up to 1.8 IU/min (5). Although some authors reported experience with AVP infusion at 0.067 IU/min (6, 7), others observed beneficial effects at dosages from 0.02 to 0.04 IU/min (4, 8, 9). Determination of the lowest AVP dose that restores cardiovascular function in advanced vasodilatory shock may reduce the prevalence of adverse effects (increase in total bilirubin concentrations (6), decrease in platelet count (6), ischemic skin lesions (10)) while preserving beneficial treatment effects.

In this retrospective, controlled study, the effects of two commonly applied AVP dose regimens (0.033 vs. 0.067 IU/min) on treatment efficacy, hemodynamic response, prevalence of adverse events, and changes in laboratory variables were compared in patients with advanced vasodilatory shock. We hypothesized that there were no differences between groups.

PATIENTS AND METHODS

The study protocol was approved by the Institutional Review Board of the Department of Anesthesiology and Critical Care Medicine of the Innsbruck Medical University, Innsbruck, Austria. Written informed consent was waived because of the retrospective study design.

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All study patients were treated in a 12-bed general and surgical intensive care unit in a tertiary university teaching hospital. An institutional database including all patients treated with AVP at our intensive care unit from January 1, 1999, to December 31, 2006, was used to identify study patients.

Patient Recruitment. The inclusion criterion was vasodilatory shock as the indication for AVP therapy. Exclusion criteria for patient enrolment were age of <18 yrs and AVP infusion because of other indications than vasodilatory shock. Vasodilatory shock was defined as cardiovascular failure with lowered systemic vascular resistance requiring vasopressor therapy (11). Although sepsis is the most frequent cause of vasodilatory shock (11), patients with cardiovascular failure after cardiac surgery or due to overwhelming systemic inflammation after major surgery can present with vasodilatory shock, too (11), and were thus included in this analysis.

First, the institutional AVP database was searched for patients with vasodilatory shock who received AVP at 0.033 IU/min during the time from January 1, 2004, to December 31, 2006. After identification of these patients, a comparable historical group of patients with vasodilatory shock treated with an AVP infusion at 0.067 IU/min was extracted from the same database from January 1, 1999, to December 31, 2003 (6). With descending priority, patients receiving AVP at 0.067 IU/min were matched in a blinded fashion with the study population receiving 0.033 IU/min AVP based on norepinephrine requirements and mean arterial blood pressure (MAP) levels before start of AVP, severity of multiple organ dysfunction syndrome, age, and milrinone and epinephrine dosages.

Hemodynamic Management of Study Patients. All patients with vasodilatory shock were managed according to an institutional hemodynamic protocol (initiated in January 1999) and invasively monitored, including arterial (BD arterial cannula with FloSwitch, Becton Dickinson, Swingdon, UK), central venous (Quad-Lumen central venous catheterization set with Blue Flex Tip, Arrow International, Erding, Germany), and pulmonary artery catheters (Swan-Ganz thermodilution catheter, Edwards Lifesciences, Irvine, CA). Fluid resuscitation was performed using colloid solutions (Gelofusin, B. Braun, Melsungen, Germany) until stroke volume could not be further increased; the corresponding central venous and pulmonary artery occlusion pressures were then used to guide fluid resuscitation. If stroke volume index remained at <25 mL·beat^{-1}·m^{-2} or cardiac index was <2.0 L·min^{-1}·m^{-2}, milrinone was started as a continuous infusion (0.3–0.7 μg·kg^{-1}·min^{-1}) without an initial bolus injection. An additional epinephrine infusion was administered at dosages ranging from 0.05 to 0.3 μg·kg^{-1}·min^{-1} only in patients with severe cardiac failure who did not achieve a cardiac index of >2 L·min^{-1}·m^{-2} otherwise or in those patients who presented with severe systolic dysfunction in transesophageal echocardiography. If MAP remained at <65–70 mm Hg, a norepinephrine infusion was started. If a stepwise increase of norepinephrine by 0.2 μg·kg^{-1}·min^{-1} in 2 hrs could not restore MAP, AVP was started as a supplementary continuous infusion. From 1999 until 2003 the AVP dosage was 0.067 IU/min, whereas from 2004 until 2006, 0.033 IU/min was generally used. Norepinephrine infusion was then adapted to maintain MAP at >70 mm Hg. If norepinephrine dosages could be decreased to <0.3 μg·kg^{-1}·min^{-1}, AVP infusion was slowly tapered off according to the response in blood pressure.

Data Collection. In all study patients, demographic data, preexisting chronic diseases, admission diagnosis, duration of AVP infusion, need for continuous venovenous hemofiltration, length of intensive care unit stay, 28-day mortality, and clinical causes of death were recorded. A modified Goris multiple organ dysfunction syndrome score (12) was calculated for most aberrant clinical and laboratory variables.

Hemodynamic data documentation was performed before start of AVP infusion and at 30 mins and 1, 4, 12, 24, 48, and 72 hrs after start of AVP infusion. Hemodynamic variables included heart rate, MAP, central venous pressure, mean pulmonary artery pressure, pulmonary artery occlusion pressure, cardiac index, stroke volume index, and norepinephrine, milrinone, and epinephrine requirements. Systemic and pulmonary vascular resistance indices were calculated according to standard formulas.

Organ function variables were collected before and at 24, 48, and 72 hrs after start of AVP therapy and included serum concentrations of aspartate and alanine aminotransferase, total bilirubin, creatinine, and platelet count. Acid–base variables (pH, base deficit) and arterial lactate levels were obtained before and at 1, 4, 12, 24, 48, and 72 hrs after start of AVP infusion.

Definitions. Treatment efficacy was evaluated by the prevalence and extent of an increase in MAP within 30 mins after start of AVP infusion (ΔMAP) and by the extent of norepinephrine reductions during the first 24 hrs of AVP infusion. A reduction in norepinephrine requirements was defined as a decrease in norepinephrine dosages at given time points between 30 mins and 24 hrs compared with baseline values. An increase in serum transaminases or total bilirubin serum concentrations and a decrease in cardiac index or platelet count were considered adverse events of AVP therapy. An increase in serum transaminases or total bilirubin concentrations was defined as a higher value at 72 hrs, or the last measurement available, when compared with baseline variables. A decrease in cardiac index or platelet count was similarly defined as a lower value at 72 hrs, or the last measurement available, when compared with baseline variables.

Statistical Analysis. The primary study end point was to evaluate differences in treatment efficacy and the hemodynamic response between the two AVP dose regimens (0.033 vs. 0.067 IU/min). The secondary study end point was to evaluate differences in the prevalence of adverse events and changes in laboratory variables between groups.

The SPSS 12.0.1 software (SPSS, Chicago, IL) was used for statistical analysis. Normality distribution was checked by the Kolmogorov–Smirnov test. Unpaired Student's *t*- (for normally distributed continuous variables), Fisher's exact (for categorical variables), or Mann Whitney *U* rank-sum tests (for not–normally distributed continuous variables [e.g., duration of AVP infusion, length of stay in the intensive care unit]) were used to compare demographic data and clinical variables between study groups, as appropriate. To compare the hemodynamic response and changes in laboratory variables during AVP infusion between groups, a mixed-effects model was used to account for death-related dropouts (13). In case of significant differences between groups, the same model was used to test for changes over time within single study groups. A p value of $<.05$ was considered to indicate significance. All variables are given as mean ± SD, if not indicated otherwise.

RESULTS

During the study period, 39 patients with vasodilatory shock were included in each group. Table 1 presents patient characteristics of the study population. Except for sex and the severity of multiple organ dysfunction syndrome, differences between study groups in demographic or clinical data before start of AVP therapy were statistically not significant. Patients treated with AVP at 0.033 IU/min received AVP for a significantly shorter duration than patients in the group receiving 0.067 IU/min.

Treatment Efficacy and Hemodynamic Response. There was no difference in the prevalence of an increase in MAP during the first 30 mins between groups (87.2% vs. 87.2%, $p = 1$). Similarly, ΔMAP was comparable (0.033 vs. 0.067 IU/min: 16.8 ± 18.4 vs. 21.4 ± 14.9 mm Hg, $p = .24$). During the first 24 hrs, norepinephrine dosages could be reduced significantly more often in patients receiving 0.067 IU/min AVP (Fig. 1). Norepinephrine dosages before start of AVP were not different between patients with and without a decrease in norepinephrine at 30 mins (0.033 IU/min, $p = .788$; 0.067 IU/min, $p = .26$), 1 hr (0.033 IU/min, $p = .253$; 0.067 IU/min, $p = .31$), 4 hrs

Table 1. Characteristics of study patients

	0.033 IU AVP/Hr	0.067 IU AVP/Hr	*p* Value
n	39	39	
Age, yrs	70.2 ± 11.5	68.3 ± 12.3	.48
Male sex, n (%)	26 (66.7)	14 (35.9)	.01[a]
BMI, kg/m^2	26.5 ± 5.6	25.5 ± 4.6	.39
Preexistent diseases			
cAHT n (%)	23 (59)	23 (59)	1
CHD n (%)	13 (33.3)	20 (51.3)	.17
CHF n (%)	21 (53.8)	23 (59)	.82
COPD n (%)	8 (20.5)	6 (15.4)	.77
CRI n (%)	16 (41)	10 (25.6)	.23
CLD n (%)	2 (5.1)	5 (12.8)	.43
PAOD n (%)	5 (12.8)	3 (7.7)	.71
Admission diagnosis			.61
SS n (%)	18 (46.2)	18 (46.2)	
PS n (%)	13 (33.3)	16 (41)	
SIRS n (%)	8 (20.5)	5 (12.8)	
CVVHF n (%)	30 (76.9)	27 (69.2)	.61
MODS score, pts	10.2 ± 1.3	10.9 ± 1.5	.04*
AVP infusion, hrs	31.8 ± 27.2	73.2 ± 103.7	.02*
ICU LOS, days	14.6 ± 15.2	19.8 ± 15.1	.14
28-day mortality, n (%)	24 (61.5)	20 (51.3)	.49

AVP, arginine vasopressin; BMI, body mass index; cAHT, chronic arterial hypertension; CHD, coronary heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; CLD, chronic liver disease; PAOD, peripheral arterial occlusive disease; SS, septic shock; PS, post-cardiotomy shock; SIRS, systemic inflammatory response syndrome; CVVHF, continuous venovenous hemofiltration; MODS, multiple organ dysfunction syndrome; pts, patients; ICU, intensive care unit; LOS, length of stay.

[a]Significant difference between groups. Data are given as mean ± SD, if not indicated otherwise.

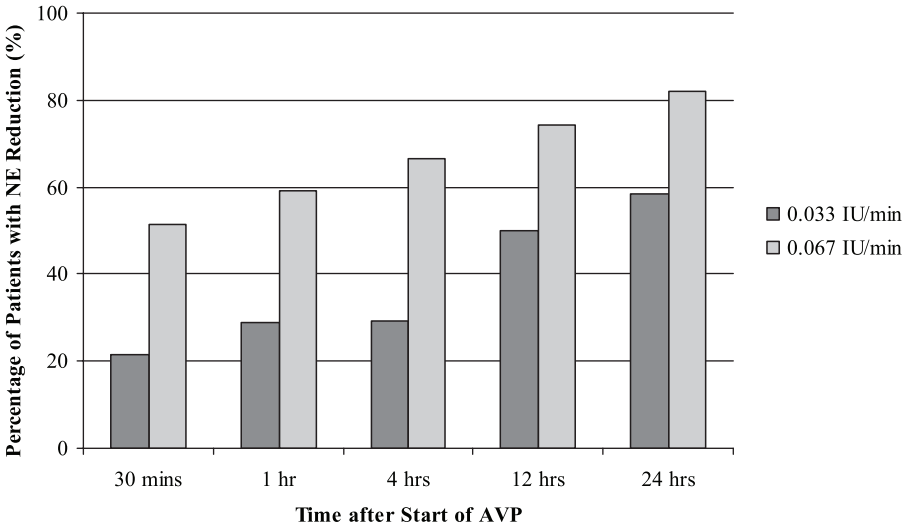

Figure 1. Rate of a norepinephrine (*NE*) reduction in patients treated with 0.033 IU/min arginine vasopressin (*AVP*) when compared with patients receiving 0.067 IU/min AVP.

(0.033 IU/min, $p = .16$; 0.067 IU/min, $p = .39$), 12 hrs (0.033 IU/min, $p = .12$; 0.067 IU/min, $p = .62$), or 24 hrs (0.033 IU/min, $p = .15$; 0.067 IU/min, $p = .29$).

The hemodynamic response of the two study groups is given in Table 2. There were no differences at baseline between groups. During AVP infusion, patients in the group receiving 0.033 IU/min had a lower MAP and higher central venous pressure, higher mean pulmonary artery pressure, and higher norepinephrine requirements than patients receiving 0.067 IU/min. Heart rate decreased in the group receiving 0.067 IU/min only ($p < .001$), whereas MAP increased in both groups ($p < .001$ each). Pulmonary artery occlusion pressure in the group receiving 0.033 IU/min increased significantly ($p = .03$), and systemic vascular resistance initially increased but decreased after 24 hrs ($p = .005$). Whereas norepinephrine requirements continued to increase until 24 hrs after start of AVP in the group receiving 0.033 IU/min ($p = .001$), they consistently decreased in the group receiving 0.067 IU/min ($p = .001$).

Adverse Events and Changes in Laboratory Variables. An increase in serum transaminase concentrations occurred more often in patients receiving AVP at 0.033 than 0.067 IU/min (71.8% vs. 28.2%, $p < .001$). The prevalence of a decrease in cardiac index (0.033 vs. 0.067 IU/min: 69.2% vs. 53.8%, $p = .24$), decrease in platelet count (0.033 vs. 0.067 IU/min: 94.8% vs. 84.6%, $p = .26$), and increase in total bilirubin (0.033 vs. 0.067 IU/min: 48.7% vs. 71.8%, $p = .06$) was not significantly different between groups.

Table 3 displays changes in laboratory variables during AVP infusion. Platelet count was significantly higher at baseline in the group receiving 0.067 IU/min. During the study period, total bilirubin concentrations and base deficit were lower and arterial lactate concentrations higher in patients receiving 0.033 IU/min when compared with patients treated with 0.067 IU/min. When corrected for baseline differences, platelet count during AVP infusion was not significantly different between groups. Platelet count significantly decreased in both groups (0.033 IU/min, $p = .03$; 0.067 IU/min, $p = .02$). Arterial lactate concentrations increased in the group receiving 0.033 IU/min ($p < .001$) and decreased in the group receiving 0.067 IU/min ($p < .001$). Changes in pH and base deficit showed a comparable pattern, with a decrease in the group receiving 0.033 IU/min (pH, $p < .001$; base deficit, $p < .001$) and an increase in the group receiving 0.067 IU/min (pH, $p < .001$; base deficit, $p < .001$).

DISCUSSION

In this retrospective study, infusion of 0.067 IU/min AVP in patients with advanced vasodilatory shock was more effective than 0.033 IU/min in reducing norepinephrine dosages. This dose regimen resulted in a higher MAP and lower central venous pressure, lower mean pulmonary artery pressure, and lower norepinephrine requirements. Although increases in liver enzymes occurred more often in patients treated with 0.033 IU/min, there was no difference in the prevalence of other adverse events between

Table 2. Hemodynamic response to arginine vasopressin (AVP) in patients receiving 0.033 IU AVP/hr and 0.067 IU AVP/hr

	Baseline	30 Mins	1 Hr	4 Hrs	12 Hrs	24 Hrs	48 Hrs	72 Hrs	*p* Value
HR, beats/min									
0.033 IU/hr	109 ± 27	104 ± 19	102 ± 20	102 ± 16	98 ± 19	96 ± 19	91 ± 14	96 ± 17	.70
0.067 IU/hr	111 ± 24[a]	111 ± 21	103 ± 21	100 ± 18	95 ± 17	93 ± 17	90 ± 18	87 ± 12	
MAP, mm Hg									
0.033 IU/hr	52 ± 9[a]	69 ± 17	71 ± 14	68 ± 13	70 ± 13	71 ± 15	66 ± 8	73 ± 9	<.001[b]
0.067 IU/hr	52 ± 12[a]	74 ± 12	80 ± 14	78 ± 11	77 ± 10	75 ± 11	74 ± 8	80 ± 8	
CVP, mm Hg									
0.033 IU/hr	12 ± 3	13 ± 3	13 ± 3	13 ± 3	13 ± 3	12 ± 3	13 ± 3	14 ± 3	.001[b]
0.067 IU/hr	12 ± 4	11 ± 4	11 ± 4	12 ± 4	12 ± 4	13 ± 3	12 ± 3	12 ± 2	
MPAP, mm Hg									
0.033 IU/hr	28 ± 5	31 ± 7	31 ± 6	31 ± 6	31 ± 8	29 ± 7	28 ± 7	30 ± 5	.04[b]
0.067 IU/hr	28 ± 6	28 ± 7	29 ± 7	28 ± 6	28 ± 6	27 ± 5	28 ± 6	29 ± 5	
PAOP, mm Hg									
0.033 IU/hr	16 ± 3[a]	—	17 ± 4	17 ± 3	18 ± 3	17 ± 3	15 ± 4	17 ± 2	.23
0.067 IU/hr	16 ± 3	—	17 ± 4	16 ± 4	16 ± 4	17 ± 5	15 ± 3	17 ± 3	
CL, L/min/m^2									
0.033 IU/hr	3.5 ± 1.4	—	3.5 ± 1.2	3.3 ± 1	3.1 ± 0.8	3.4 ± 1.1	3.6 ± 0.9	3.7 ± 1.2	.83
0.067 IU/hr	4 ± 1.5	—	3.3 ± 1.2	3.4 ± 1.1	3.3 ± 0.9	3.1 ± 0.8	3.3 ± 0.8	3.2 ± 1	
SVI, mL/beat/m^2									
0.033 IU/hr	34 ± 11	—	35 ± 12	32 ± 11	32 ± 9	37 ± 11	40 ± 5	37 ± 7	.58
0.067 IU/hr	36 ± 12	—	33 ± 11	35 ± 10	36 ± 7	34 ± 9	38 ± 8	40 ± 10	
SVR, dyne·sec·cm^{-5}									
0.033 IU/hr	723 ± 332[a]	—	927 ± 356	861 ± 294	865 ± 343	928 ± 310	678 ± 144	622 ± 149	.06
0.067 IU/hr	665 ± 357	—	926 ± 399	861 ± 343	829 ± 315	904 ± 326	853 ± 253	1008 ± 356	
PVR, dyne·sec·cm^{-5}									
0.033 IU/hr	219 ± 168	—	200 ± 91	192 ± 105	153 ± 65	168 ± 58	147 ± 36	132 ± 75	.32
0.067 IU/hr	154 ± 86	—	177 ± 95	152 ± 69	173 ± 69	173 ± 101	174 ± 86	160 ± 97	
NE, μg/kg/min									
0.033 IU/hr	1.07 ± 1.1[a]	1.35 ± 1.13	1.3 ± 0.95	1.56 ± 1.83	1.7 ± 2.14	0.63 ± 0.5	0.48 ± 0.43	0.59 ± 0.52	<.001[b]
0.067 IU/hr	1.07 ± 1.1[a]	0.84 ± 0.77	0.79 ± 0.75	0.77 ± 0.8	0.61 ± 0.64	0.42 ± 0.44	0.38 ± 0.42	0.33 ± 0.35	
Mil, μg/kg/min									
0.033 IU/hr	0.37 ± 0.23	0.42 ± 0.19	0.41 ± 0.19	0.42 ± 0.2	0.44 ± 0.17	0.38 ± 0.18	0.34 ± 0.19	0.35 ± 0.15	.28
0.067 IU/hr	0.4 ± 0.21	0.4 ± 0.21	0.40 ± 0.21	0.41 ± 0.23	0.39 ± 0.2	0.36 ± 0.23	0.31 ± 0.22	0.26 ± 0.21	
E, μg/kg/min									
0.033 IU/hr	0.04 ± 0.07	0.06 ± 0.07	0.05 ± 0.07	0.06 ± 0.07	0.08 ± 0.16	0.03 ± 0.02	0.04 ± 0.03	0.04 ± 0.02	.99
0.067 IU/hr	0.07 ± 0.05	0.06 ± 0.04	0.04 ± 0.02	0.07 ± 0.08	0.07 ± 0.08	0.03 ± 0.02	0.03 ± 0.03	0.02 ± 0.01	

HR, heart rate; MAP, mean arterial blood pressure; CVP, central venous blood pressure; MPAP, mean arterial blood pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; NE, norepinephrine; Mil, milrinone; E, epinephrine; —, not measured.

[a]Significant difference over time within group; [b]significant difference between groups. Data are given as mean± SD.

the two AVP dose regimens. Total bilirubin levels and base deficit were lower and arterial lactate concentrations higher in patients receiving AVP at 0.033 IU/min.

Although MAP increased in both groups, the increase in perfusion pressure was more significant and sustained in patients treated with 0.067 IU/min. In addition, considering the continuing increase of norepinephrine requirements in the group receiving 0.033 IU/min and the consistent decrease of norepinephrine after initiation of AVP at 0.067 IU/min, higher AVP dosages seem to have been more effective to reverse vasodilatory shock in our study population. These results are in accordance with data from an animal study showing a more sustained increase in systemic vascular resistance and MAP with increasing AVP dosages in healthy and endotoxemic sheep. In contrast to our data, however, the authors observed a concomitant decrease in cardiac index (14). Because quantitative and qualitative AVP receptor down-regulation was reported in sepsis and during endotoxemia (15, 16), it can be hypothesized that AVP dosages of 0.033 IU/min were too low to exert sufficient V_{1a}-receptor–mediated vasoconstriction. Moreover, other potentially dose-dependent mechanisms for AVP-related hemodynamic effects (e.g., inhibition of adenosine triphosphate-sensitive potassium channels, substitution of AVP deficiency) have been suggested (2, 11).

Interestingly, norepinephrine requirements at baseline were not different between patients with and without a reduction of norepinephrine during the first 24 hrs of AVP infusion. This observation suggests that at norepinephrine dosages applied in this study population, only the AVP dosage determined the extent of decrease in catecholamine support. Nonetheless, our data are not in contrast to results from studies reporting beneficial cardiovascular effects of AVP at dosages ranging from 0.01 to 0.04 IU/min. With a mean norepinephrine dosage of 1.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (95% confidence interval, 0.82–1.56 $\mu g \cdot kg^{-1} \cdot min^{-1}$), our study patients received substantially higher dosages than patients in earlier trials (6.8 μg/min [$\sim$0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in a 70-kg patient] (17), 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (18), 25 μg/min [$\sim$0.36 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in a 70-kg patient] (9)). It is therefore conceivable that 0.033 IU/min AVP may reverse cardiovascular failure in vasodilatory shock requiring moderate norepinephrine dosages but seems to be inadequate to stabilize hemodynamic function when norepinephrine requirements are high (e.g., >0.82 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which was the lower limit of the 95% confidence interval in this study population). Aside from the severity of disease, infusion of the phosphodiesterase inhibitor milrinone as the

Table 3. Changes in laboratory parameters in study groups

	Baseline	1 Hr	6 Hrs	12 Hrs	24 Hrs	48 Hrs	72 Hrs	*p* Value
pH								
0.033 IU/hr	7.28 ± 0.09[a]	7.26 ± 0.08	7.26 ± 0.1	7.31 ± 0.16	7.4 ± 0.08	7.42 ± 0.09	7.42 ± 0.06	.13
0.067 IU/hr	7.31 ± 0.13[a]	7.31 ± 0.11	7.3 ± 0.11	7.33 ± 0.09	7.37 ± 0.07	7.38 ± 0.09	7.42 ± 0.06	
BD, mmol/L								
0.033 IU/hr	−5 ± 5.8[a]	−7.2 ± 4.3	−5.4 ± 6.4	−5 ± 6.2	−0.2 ± 4.2	0.8 ± 5.1	2.1 ± 2.4	.005[b]
0.067 IU/hr	−3.5 ± 7[a]	−3.9 ± 5.9	−3.9 ± 6.4	−2.9 ± 5.9	−0.3 ± 4.7	0.9 ± 5	4.3 ± 5.1	
Lactate, mg/dL								
0.033 IU/hr	45 ± 34[a]	73 ± 49	73 ± 60	76 ± 67	39 ± 51	37 ± 35	15 ± 5	<.001[b]
0.067 IU/hr	46 ± 36[a]	48 ± 34	49 ± 42	46 ± 38	25 ± 21	22 ± 28	16 ± 5	
Creatinine, mg/dL								
0.033 IU/hr	2 ± 1	—	—	—	2.1 ± 0.9	1.8 ± 0.6	2 ± 0.8	.70
0.067 IU/hr	2 ± 0.9	—	—	—	2.1 ± 0.8	2.1 ± 0.9	2 ± 0.9	
ASAT, IU/L								
0.033 IU/hr	330 ± 682	—	—	—	541 ± 741	387 ± 664	233 ± 296	.22
0.067 IU/hr	97 ± 351	—	—	—	386 ± 907	114 ± 148	104 ± 115	
ALAT, IU/L								
0.033 IU/hr	211 ± 617	—	—	—	188 ± 255	452 ± 1256	55 ± 47	.20
0.067 IU/hr	38 ± 84	—	—	—	159 ± 309	78 ± 84	80 ± 72	
tBilirubin, mg/dL								
0.033 IU/hr	2.8 ± 3	—	—	—	2.1 ± 1.4	2.9 ± 3	3.1 ± 3.4	.04[b]
0.067 IU/hr	3 ± 3.7	—	—	—	4.3 ± 5.1	5 ± 5.4	5.2 ± 5.5	
Platelets, g/L								
0.033 IU/hr	107 ± 70[a,c]	—	—	—	95 ± 68	68 ± 57	57 ± 26	.24[d]
0.067 IU/hr	165 ± 93[a]	—	—	—	212 ± 74	104 ± 55	109 ± 48	

BD, base deficit; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; tBilirubin, total bilirubin; —, not measured.

[a]Significant difference over time within group; [b]significant difference between groups; [c]significant baseline difference between groups; [d]corrected for baseline differences. Data are given as mean ± SD.

fist-line inotropic agent has contributed to the loss of vascular tone and need for high norepinephrine dosages in this study population (19).

Our results are similar to the preliminary results of a recently completed multicenter trial evaluating AVP effects on outcome in septic shock. In this study, a significant survival benefit could only be detected in the subgroup of patients requiring norepinephrine dosages of <15 μg/min (~0.21 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in a 70 kg patient), whereas this effect was lost in patients with higher norepinephrine requirements (>15 μg/min) (Annual Conference of the ESICM, Barcelona, September 2006). Accordingly, patients treated with 0.067 IU/min AVP in our study showed improved acid–base variables, which, together with decreasing arterial lactate concentrations, may indicate reestablishment of organ perfusion. In contrast, progressive lactic acidosis during the first 24 hrs of AVP infusion in patients receiving 0.033 IU/min suggests ongoing tissue hypoperfusion.

The observation that patients in the group administered 0.033 IU/min received AVP for a shorter duration than patients administered 0.067 IU/min cannot be elucidated by the reported data. Although the difference was not statistically significant, more patients in the group receiving 0.033 IU/min died within 72 hrs after the start of AVP infusion than in the group receiving 0.067 IU/min; it may be speculated that this finding could partly explain the longer duration of AVP infusion in patients receiving AVP at 0.067 IU/min. Interestingly, although again not statistically significant, 25% of patients receiving 0.033 IU/min AVP died of refractory cardiovascular failure, whereas 15% of patients in the group receiving 0.067 IU/min died of refractory cardiovascular failure. When reviewing norepinephrine requirements in the group receiving 0.033 IU/min AVP, it is noteworthy that norepinephrine dosages continued to increase until 12 hrs and then rapidly decreased at 24 hrs. This finding most likely reflects death of patients with refractory cardiovascular failure who could not be stabilized with AVP at 0.033 IU/min.

Except for a higher prevalence of an increase in serum transaminases in the group receiving 0.033 IU/min AVP, occurrence of adverse events was comparable between the two AVP dose regimens. Because elevations of liver enzymes typically result from hepatic hypoperfusion (20), less-efficient restoration of arterial blood pressure in the group receiving 0.033 IU/min could explain the higher prevalence of ischemic hepatic injury. A decrease in platelet count was observed in 73.4% of patients receiving AVP in vasodilatory shock in an earlier study (6) and occurred with a slightly higher frequency in this study population. The lack of difference in the prevalence of a decrease in platelets between the two study groups suggests that AVP-stimulated platelet aggregation (21) occurs either according to an "all-or-nothing" principle or is initiated already at AVP dosages of <0.033 IU/min. The reduction of platelet count during AVP infusion is caused by an induction of platelet aggregation through V_1-receptors (21) but does not impair net hemostasis (22). This effect seems to be especially pronounced during extracorporeal blood flow, such as continuous venovenous hemofiltration, and not associated with increased mortality (6).

Although not significant, there was a trend ($p = .06$) toward a higher prevalence of an increase in total bilirubin levels in patients receiving AVP at 0.067 IU/min. Together with the observation that serum bilirubin concentrations were higher in the group receiving 0.067 IU/min than in the group receiving 0.033 IU/min, a dose-dependent effect of AVP may be suspected. From experimental studies, it is known that AVP reduces bile secretion and induces cholestasis by modulation of hepatocyte tight junc-

tional permeability and glutathione efflux (23, 24). In view of decreased survival rates in patients who exhibited an increase in total bilirubin levels during AVP infusion (6), the observation that patients receiving AVP at 0.067 IU/min tended to present with higher bilirubin concentrations than patients in the group receiving 0.033 IU/min needs detailed evaluation in future studies.

When interpreting the results of this study, more limitations need to be kept in mind. Clearly, the retrospective study design substantially limits interpretation of the results. Comparison of two patient groups treated during different time periods (1999–2003 vs. 2004–2006) bears the risk of neglecting relevant changes in management. However, because the same hemodynamic protocol was applied in both patient groups, this limitation seems to be more important when interpreting patient outcome than when interpreting hemodynamic response to AVP. Differences between study groups in sex and the severity of multiple organ dysfunction further complicate data interpretation. The difference in multiple organ dysfunction syndrome score count was statistically significant but, in its clinical relevance, rather negligible. In contrast, a greater severity of multiple organ dysfunction in the group receiving 0.067 IU/min AVP would have made AVP treatment efficacy less likely. Although statistically not significant, it cannot be excluded that there were further differences in baseline variables between groups. Because the institutional database does not include reliable photographic documentation to diagnose skin ischemia, it was not possible to evaluate differences in the prevalence of ischemic skin lesions between the AVP dose regimens. In a former study, we could not, however, find an association between AVP dosage (0.067 vs. 0.1 IU/min) and the prevalence of ischemic skin lesions (10).

In conclusion, AVP dosages of 0.067 IU/min seem to be more effective to reverse cardiovascular failure in advanced vasodilatory shock requiring high norepinephrine dosages than 0.033 IU/min. Prospective studies are needed to confirm these results and evaluate the effects of AVP at 0.067 IU/min on outcome.

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