

Arginine Vasopressin in Advanced Vasodilatory Shock

A Prospective, Randomized, Controlled Study

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Background—Vasodilatory shock is a potentially lethal complication of severe disease in critically ill patients. Currently, catecholamines are the most widely used vasopressor agents to support blood pressure, but loss of catecholamine pressor effects is a well-known clinical dilemma. Arginine vasopressin (AVP) has recently been shown to be a potent vasopressor agent to stabilize cardiocirculatory function even in patients with catecholamine-resistant vasodilatory shock.

Methods and Results—Forty-eight patients with catecholamine-resistant vasodilatory shock were prospectively randomized to receive a combined infusion of AVP and norepinephrine (NE) or NE infusion alone. In AVP patients, AVP was infused at a constant rate of 4 U/h. Hemodynamic, acid/base, single-organ, and tonometrically derived gastric variables were reported before the study and 1, 12, 24, and 48 hours after study entry. For statistical analysis, a mixed-effects model was used. AVP patients had significantly lower heart rate, NE requirements, and incidence of new-onset tachyarrhythmias than NE patients. Mean arterial pressure, cardiac index, stroke volume index, and left ventricular stroke work index were significantly higher in AVP patients. NE patients developed significantly more new-onset tachyarrhythmias than AVP patients (54.3% versus 8.3%). Gastrointestinal perfusion as assessed by gastric tonometry was better preserved in AVP-treated patients. Total bilirubin concentrations were significantly higher in AVP patients.

Conclusions—The combined infusion of AVP and NE proved to be superior to infusion of NE alone in the treatment of cardiocirculatory failure in catecholamine-resistant vasodilatory shock. (*Circulation*. 2003;107:2313-2319.)

Key Words: vasopressin ■ norepinephrine ■ shock, vasodilatory ■ shock, postcardiotomy ■ shock, septic

Vasodilatory shock is characterized by low arterial blood pressure due to significantly decreased systemic vascular resistance.¹ Although sepsis and cardiovascular surgery requiring cardiopulmonary bypass are the most frequent causes,² massive vasodilatation can result from shock of any origin.¹

Adequate therapy includes specific treatment of the underlying disease, volume resuscitation, and use of vasopressor drugs to restore arterial blood pressure.³ Currently, catecholamines are the clinically used vasopressor agents of choice for supporting arterial blood pressure and ensuring adequate organ perfusion. Unfortunately, development of adrenergic hyposensitivity with loss of catecholamine pressor effects is a feared complication in advanced states of vasodilatory shock.⁴ Progressively increasing catecholamine therapy frequently enters into a vicious cycle of major adverse side effects resulting in continuous clinical deterioration necessitating further catecholamine excess. In these situations, mortality rates approach 100%.⁵ Therefore, vasopressor agents able to stabilize cardiocirculatory function in situations of catecholamine excess would be of great benefit.

Arginine vasopressin (AVP) is a potent endogenous vasopressor hormone of the neurohypophysis. Case reports and small clinical trials have shown that continuous infusion of AVP can reverse hypotension in catecholamine-resistant vasodilatory shock.⁶⁻⁸ Unfortunately, little is known about possible adverse side effects of AVP used for this indication. In particular, gastrointestinal hypoperfusion, a common complication of severe critical illness, may be aggravated by AVP.⁹

Therefore, we performed a prospective, randomized, controlled study to evaluate differences in hemodynamic response and organ functions in patients with advanced vasodilatory shock receiving either a combined infusion of AVP and norepinephrine (NE) or NE alone.

Methods

The study protocol was approved by the ethics committee of the Leopold Franzens University of Innsbruck. The study was performed at the Division of General and Surgical Intensive Care Medicine, which is responsible for 23 intensive-care beds located in two separate units in a university teaching hospital.

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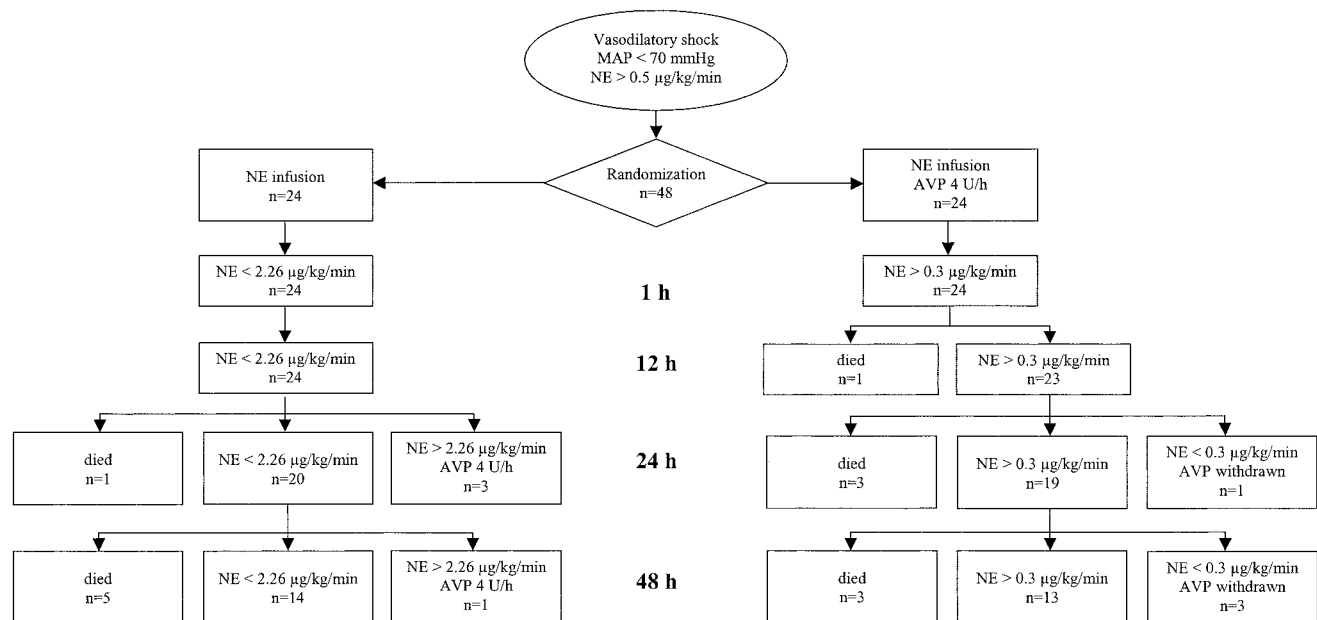
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Overview of patient enrollment and study design.

Patients

From February 2001 through April 2002, 48 critically ill patients suffering from vasodilatory shock related to cardiovascular surgery or due to the systemic inflammatory response syndrome, both with and without sepsis,¹⁰ with a mean arterial pressure (MAP) <70 mm Hg despite adequate volume resuscitation, and with NE requirements exceeding $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ were prospectively enrolled. All patients were invasively monitored, including via the use of a pulmonary artery catheter. Volume resuscitation was performed according to the response of stroke volume to fluid loading. Normovolemia was assumed when repeated infusion of colloids failed to augment stroke volume. The pulmonary capillary wedge pressure, where the stroke volume was maximal, was used as a therapeutic target for further volume resuscitation. If the stroke volume index remained $<25 \text{ mL} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ or cardiac index $<2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, milrinone infusion was started at dosages ranging from 0.3 to $0.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

Study Design

Patients were randomly assigned into an AVP group and an NE group (Figure). In the AVP group, additional AVP infusion (Pitresin, Parke Davis) was administered according to our institutional protocol, including infusion of AVP at a constant rate of 4 U/h. No bolus injections were given. NE infusion was adjusted to maintain MAP ≥ 70 mm Hg. When NE requirements decreased to $<0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, AVP infusion was tapered off stepwise according to the response of MAP to AVP reductions.

In NE patients, MAP ≥ 70 mm Hg was achieved by adjusting NE infusion as necessary. For those patients in whom NE requirements exceeded $2.26 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the study protocol was abandoned, and additional AVP infusion was initiated at 4 U/h. In a previous retrospective study, we have determined NE dosages exceeding $2.26 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to be significantly associated with intensive care unit (ICU) mortality.⁹

Study End Points

The primary study end point was to evaluate differences in hemodynamics between groups during the 48-hour observation period. As a secondary study end point, changes in other single-organ functions, including tonometrically derived gastric parameters during the study period, were evaluated.

Demographic Data

Age, American Society of Anesthesiologists classification,¹¹ admission diagnosis, and the Simplified Acute Physiological Score II¹² during the first 24 hours after admission to the ICU were recorded. At study entry, a modified Goris Multiple Organ Dysfunction Syndrome Score⁹ was calculated from worst clinical and laboratory data. Length of ICU stay and ICU mortality were documented.

Hemodynamics

Heart rate, MAP, mean pulmonary arterial blood pressure, pulmonary capillary wedge pressure, and cardiac and stroke volume indices were recorded in all patients and documented together with NE and milrinone requirements before study entry and at 1, 12, 24, and 48 hours after study entry. Systemic vascular resistance index, left ventricular stroke work index (LVSWI), systemic oxygen transport, and consumption index were calculated according to standard formulas. Incidence and types of new-onset tachyarrhythmias were monitored during the study. Tachyarrhythmias were defined as nonsinus rhythm with heart rates exceeding 100 bpm. Twelve-lead ECG examinations and serum troponin I determinations were performed before study entry and 24 and 48 hours after study entry to scan for myocardial ischemia or infarction.

Single-Organ Functions

Gut mucosal PCO_2 (PrCO_2) and PrCO_2 to arterial PCO_2 gradient (Pr-aCO_2), as indicators of splanchnic perfusion, were assessed by using an automated recirculating air tonometer (Tonocap, Datex) before study entry and 1, 24, and 48 hours after study entry. The Tonocap system was used to analyze CO_2 content by infrared absorption at set intervals. In patients on enteral feeding, feeding was interrupted at least 1.5 hours before measurements. All patients received H_2 -blockers or proton pump inhibitors during the observation period.

Arterial acid/base status and arterial lactate concentrations were documented before study entry and 1, 24, and 48 hours after study entry. A $\text{PaO}_2/\text{FiO}_2$ quotient was calculated at the same intervals. Measurements were performed using Rapidlab 860 (Chiron Diagnostics). Serum concentrations of creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and platelet count were recorded before study entry and 24 and 48 hours after study entry. Incidence of veno-venous hemofiltration and occurrence of new ischemic skin lesions, defined as new areas of mottled or livid

TABLE 1. Characteristics of AVP and NE Patients

	AVP Patients (n=24)	NE Patients (n=24)	<i>P</i>
Age, y	68±9.4	68±13.5	0.961
ASA	3.7±0.7	3.5±0.9	0.280
Diagnosis, n (%)			
SIRS	7/24 (29.2)	7/24 (29.2)	0.942
SS	7/24 (29.2)	8/24 (33.3)	0.942
PS	10/24 (41.6)	9/24 (37.5)	0.862
SAPS II	51.6±16.8	49.7±18.3	0.701
MODS	12.1±0.9	11.8±0.9	0.353
ICU stay, d	19.5±16.8	13.6±12.5	0.174
ICU mortality, n (%)	17/24 (70.8)	17/24 (70.8)	1

Values are mean±SD or n/N (%). ASA indicates American Society of Anesthesiologists classification; SIRS, systemic inflammatory response syndrome; SS, septic shock; PS, postcardiotomy shock; SAPS II, Simplified Acute Physiologic Score II; and MODS, Multiple Organ Dysfunction Syndrome score.

skin in one or more body locations, were documented during the study period.

Statistical Analysis

The sample size was precalculated on the basis of a previous retrospective study.⁹ To detect clinically relevant differences in main outcome variables and assuming an alpha error of 0.05 and a power of 80%, a sample size of at least 20 patients in each group was calculated. The number of patients enrolled was increased to 48 to compensate for death-related data dropout. Randomization of patients was performed by using a random number-generating scheme.

Demographic data, incidence of new-onset tachyarrhythmias and myocardial ischemia/infarction, occurrence of ischemic skin lesions, and number of patients on veno-venous hemofiltration were compared with the use of Student's *t* tests, χ^2 tests, or Mann-Whitney *U* tests, as appropriate.

Differences in hemodynamic and single-organ variables between groups and within repeated measurements were analyzed by using linear mixed-effects models to account for death-related dropouts.¹³ Main effects between groups and within repeated measurements were given and considered to indicate statistical significance if <0.05. Shapiro-Wilks tests were used to check for normality, which was approximately fulfilled in all reported variables except for PrCO_2 and Pr-aco_2 , which were log-transformed. All data are given as mean values±SD, if not indicated otherwise.

Results

Table 1 shows characteristics of AVP and NE patients. There were no significant differences in age, American Society of Anesthesiologists classification, incidence of systemic inflammatory response syndrome, septic and postcardiotomy shock, Simplified Acute Physiological Score II at ICU admission, severity of multiple organ dysfunction syndrome, length of ICU stay, and ICU mortality between groups.

Hemodynamics

Table 2 shows changes in hemodynamic variables of AVP and NE patients. AVP patients exhibited a significantly higher heart rate at baseline ($P=0.033$). During AVP infusion, heart rate decreased ($P=0.003$) and was significantly lower when compared with NE patients, whereas MAP increased ($P<0.001$) and remained significantly higher than in NE patients. Cardiac index, stroke volume index, and LVSWI were significantly higher, with NE requirements

significantly lower in AVP patients. We observed a significant increase in LVSWI ($P=0.004$) simultaneously with a significant reduction in NE support ($P=0.001$) in AVP patients. In contrast, NE requirements significantly increased in NE patients ($P=0.019$). In both groups, 75% of patients (18 of 24) received a continuous milrinone infusion.

We observed a significant difference in the incidence of new-onset tachyarrhythmias between groups. Two of 24 patients (8.3%) receiving AVP developed new-onset tachycardic atrial fibrillation, whereas 14 of 24 NE patients (54.3%) experienced new-onset tachycardic atrial fibrillation during the observation period ($P<0.001$). There were no differences in the incidence of myocardial ischemia and myocardial infarction between groups. Two NE patients developed myocardial ischemia, and 1 NE patient developed myocardial infarction during the study. There were no differences in troponin I values between AVP and NE patients (Table 3).

Single-Organ Functions

Changes in tonometrically derived gastric variables, acid/base status, arterial lactate concentrations, $\text{PaO}_2/\text{FiO}_2$ gradient, serum creatinine concentrations, liver enzymes, total bilirubin concentrations, and platelet counts are displayed in Table 3. PrCO_2 and Pr-aco_2 were significantly lower in study patients when compared with NE patients. PrCO_2 significantly increased in NE patients ($P=0.027$) during the observation period.

Arterial lactate concentrations significantly decreased in AVP ($P=0.002$) and NE ($P=0.005$) patients, whereas platelet count significantly decreased ($P=0.018$) in AVP patients only. Total bilirubin concentrations were significantly higher in AVP patients when compared with NE patients and significantly increased during the observation period ($P=0.037$). There were no differences between groups in other variables. During the study period, 22 of 24 AVP and NE patients (91.7%) were on continuous veno-venous hemofiltration.

Clinical complication occurrence during the study period is as follows: 7 of 24 AVP patients (29.2%) and 6 of 24 NE patients (25%) developed new ischemic skin lesions ($P=1$). One patient of the NE group died of total intestinal ischemia and necrosis during the study period.

Discussion

In this prospective, randomized, controlled study, combined infusion of AVP and NE proved to be an effective vasopressor regimen to treat cardiocirculatory failure in patients with catecholamine-resistant vasodilatory shock. Patients receiving an additional AVP infusion had higher MAP, cardiac index, stroke volume index, and LVSWI and needed less vasopressor support than patients receiving NE alone.

The significantly higher MAP in study patients can be explained by AVP-induced intense constriction of peripheral resistance vessels. In arteriolar smooth muscle cells, stimulation of V1a-receptors leads to an increase in cytoplasmic ionized calcium via the phosphatidylinositol-bisphosphonate cascade and thus causes vasoconstriction.¹⁴ Unlike catecholamine-mediated vasoconstriction, vasopressor effects of AVP

TABLE 2. Changes in Hemodynamic Variables of AVP and NE Patients

	0 Hours (n=48)	1 Hour (n=48)	12 Hours (n=47)	24 Hours (n=39)	48 Hours (n=27)	P
HR, bpm						
AVP group†§	115±17	103±16‡	99±16‡	99±15‡	93±15‡	0.003*
NE group	103±20	102±15	103±15	108±20	98±19	
MAP, mm Hg						
AVP group†	63±7	82±10‡	78±9‡	76±9‡	81±8‡	<0.001*
NE group	67±8	71±12	67±9	66±11	75±12	
MPAP, mm Hg						
AVP group	31±8	29±6	26±5	28±9	30±10	
NE group	29±7	28±6	29±8	28±7	25±5	
PCWP, mm Hg						
AVP group	17±3	16±5	16±4	15±4	17±3	
NE group	16±6	16±6	17±6	15±5	15±4	
CI, L · min ⁻¹ · m ⁻²						
AVP group	4.1±1.4	3.7±1.2	4.3±1.7	4.1±1.1	4.1±1	0.001*
NE group	3.5±1	3.5±1.2	3.4±1.1	3.3±1	3.6±1.2	
SVI, mL · beat ⁻¹ · m ⁻²						
AVP group	36±12	35±11	42±14	41±14	44±15	0.005*
NE group	36±12	34±11	34±10	32±12	36±10	
LVSWI, gxm · m ⁻² · beat ⁻¹						
AVP group†	23±10	31±13‡	35±14‡	34±14‡	39±16‡	<0.001*
NE group	24±10	26±11	24±11	24±10	30±12	
SVRI, dyne · cm ⁻⁵ · xm ⁻²						
AVP group	1160±567	1697±702	1383±528	1340±438	1334±517	
NE group	1452±689	1645±919	1435±642	1484±571	1613±513	
Do ₂ , mL · min ⁻¹ · m ⁻²						
AVP group	566±222	513±154	...	559±139	574±143	
NE group	504±139	495±170	...	472±165	525±201	
Vo ₂ , mL · min ⁻¹ · m ⁻²						
AVP group	157±58	148±42	...	155±27	154±37	
NE group	140±40	142±51	...	131±46	151±56	
NE requirements, μg · kg ⁻¹ · min ⁻¹						
AVP group†	0.84±0.55	0.55±0.31	0.5±0.4	0.59±0.54‡	0.34±0.25‡	<0.001*
NE group†	0.84±0.41	1.05±0.87	1.21±1‡	1.36±1.86‡	0.54±0.42‡	
Mil requirements, μg · kg ⁻¹ · min ⁻¹						
AVP group	0.32±0.3	0.31±0.3	0.29±0.29	0.21±0.27	0.19±0.26	
NE group	0.24±0.25	0.25±0.26	0.26±0.26	0.27±0.28	0.18±0.27	

Values are mean±SD. HR indicates heart rate; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index; Do₂, systemic oxygen transport index; Vo₂, systemic oxygen consumption index; Mil, milrinone; and ellipses (...), not measured.

*Significant group effect.

†Significant time effect.

‡Significant effect vs baseline.

§Significant difference at baseline between groups.

seem to be preserved during hypoxia and acidosis.¹⁵ In vasodilatory shock, AVP has also been shown to influence several mechanisms causally involved in the pathogenesis of vasodilatation. Such AVP-mediated effects include blockage of ATP-activated potassium channels, attenuation of nitric oxide production, as well as reversal of adrenergic receptor downregulation.^{16–18}

As recent investigations have reported inadequately low AVP serum concentrations in patients with vasodilatory shock,¹⁹ it is speculated that deficiency of endogenous AVP may contribute to loss of vascular tone in vasodilatory shock.¹ Dysfunction of the baroreceptor reflex, inhibition of AVP production, and depletion of AVP stores during sustained hypotension have been discussed as responsible mecha-

TABLE 3. Changes in Single-Organ Laboratory Variables of AVP and NE Patients

	0 Hours (n=48)	1 Hour (n=48)	24 Hours (n=39)	48 Hours (n=27)	P
P _r CO ₂ , mm Hg					
AVP group	53±18	55±15	60±21	63±25	0.03*
NE group†	54±17	64±23‡	71±20‡	67±24‡	
P _r -aco ₂ , mm Hg					
AVP group	9±15	11±12	17±17	20±24	0.014*
NE group	12±17	21±25	26±21	21±24	
PH					
AVP group	7.35±0.11	7.31±0.1	7.36±0.09	7.41±0.07	
NE group	7.34±0.11	7.33±0.11	7.34±0.12	7.40±0.06	
Paco ₂ , mm Hg					
AVP group	45±9	44±8	44±9	43±6	
NE group	42±8	43±7	46±9	46±4	
Arterial lactate, mmol/L					
AVP group†	48±44	50±45	37±30	20±12‡	
NE group†	45±47	46±47	42±47	20±12	
PaO ₂ /Fio ₂					
AVP group	194±76	...	205±84	233±91	
NE group	207±94	...	197±87	232±98	
Creatinine, mg/dL					
AVP group	2.2±0.91	...	2.1±0.82	2.1±0.98	
NE group	2.14±0.74	...	2.3±0.88	2.2±1.04	
ASAT, U/L					
AVP group	351±822	...	458±992	153±313	
NE group	131±208	...	312±700	46±46	
ALAT, U/L					
AVP group	217±498	...	273±506	178±345	
NE group	126±222	...	291±631	72±105	
Bilirubin, mg/dL					
AVP group†	4.64±3.87	...	6.9±5.2‡	9.26±5.81‡	0.001*
NE group	2.87±2.96	...	3.75±3.52	3.86±5.56	
Platelets, 1000 cells/L					
AVP group†	165±147	...	116±151‡	74±54‡	
NE group	144±144	...	122±103	135±93	
Troponin I, mg/dL					
AVP group	20±33	...	11±17	8±15	
NE group	57±154	...	43±113	27±81	

Values are mean±SD. P_rCO₂ indicates arterial P_rCO₂; PaO₂, arterial P_rO₂; Fio₂, fractional inspiratory oxygen concentration; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; and ellipses (...), not measured.

*Significant group effect.

†Significant time effect.

‡Significant effect vs baseline.

nisms.²⁰ A continuous infusion of AVP at 2 to 4 U/h restores AVP serum concentrations to values observed in other types of hypotension.¹⁹ Therefore, infusion of AVP may reverse AVP deficiency and restore endogenous vasopressor effects in vasodilatory shock.

Patients receiving AVP in the present study had a significantly better myocardial performance, as assessed by cardiac index, stroke volume index, and LVSWI, than NE patients.

These data are in accordance with results of a recent retrospective analysis²¹ and findings by other authors.^{22,23} Several mechanisms may explain this improvement of myocardial performance during AVP infusion. First, study patients received significantly lower NE dosages, which are known to have cardiotoxic and proarrhythmic effects.²⁴ Therefore, study patients probably had a lower incidence of tachyarrhythmias. Second, AVP has been shown to attenuate

endotoxin- and interleukin-1 β -stimulated generation of nitric oxide,¹⁷ thus possibly reversing negative inotropic effects of cardiodepressant mediators. Third, recent studies have shown that AVP increases intracellular calcium in myocardial cells through stimulation of V1a-receptors, leading to a direct positive inotropic response.^{25,26} Fourth, AVP may increase myocardial blood flow due to increased systemic perfusion pressure and selective coronary vasodilatation.²⁷

In both groups, 75% of patients received a milrinone infusion because of low cardiac output. Therefore, hemodynamic effects of AVP do not seem to be biased by unequal milrinone treatment in study groups. Furthermore, an additional model that integrated milrinone as a cofactor in the mixed-effects model demonstrated that milrinone infusion did not influence any of the results of this study.

Study patients had a significantly lower incidence of new-onset tachyarrhythmias. It may be speculated that the significant reduction in NE dosages, known to have substantial proarrhythmic effects,²⁴ together with an improvement of myocardial blood flow, has contributed to this finding. Severity of cardiovascular failure, which is mainly determined by the extent of catecholamine support, was identified to be an independent predictor for the development of tachyarrhythmias in cardiac surgery patients in a previous study.²⁸

Another important finding of this study was that gastrointestinal perfusion assessed by gastric tonometry was significantly better during combined AVP and NE infusion when compared with patients receiving NE alone. These results are in striking contrast to reports on significant deteriorations of gastrointestinal blood flow after AVP therapy in upper gastrointestinal bleeding²⁹ and during AVP infusion in catecholamine-resistant hypotension.³⁰ Whereas bolus injections and high AVP dosages have been applied in these studies, AVP dosages in this protocol never exceeded 4 U/h. In low dosages, AVP-mediated vasodilatation of the splanchnic vascular bed has been reported.³¹ Significantly improved systemic perfusion pressure may further explain lower PrCO₂ and Pr-aco₂ in patients receiving AVP. However, it must be considered that gastric tonometry does not directly measure gastrointestinal perfusion and cannot be regarded as an accurate indicator of splanchnic circulation under pathophysiological conditions.³² Therefore, interpretation of tonometrically derived results can only be done very cautiously in these patients.

In patients treated with AVP, total bilirubin concentrations not only increased during the observation period but were also significantly higher than in control patients. A significant increase in total bilirubin has already been reported in patients with septic and postcardiotomy shock.⁹ However, direct AVP-induced hepatic dysfunction has not been described before. Possible mechanisms for the increase in bilirubin may be an AVP-mediated reduction in hepatic blood flow³³ or a direct impairment of hepatocellular function.

AVP is a potent arteriolar vasoconstrictor in the skin.³⁴ Ischemic skin lesions have been reported in patients receiving AVP treatment.³⁵ In the present study, the incidence of ischemic skin lesions was not different between groups. In advanced cardiovascular failure, ischemic skin lesions seem

to be an epiphenomenon of severe underlying disease rather than a specific complication of AVP administration.

In this prospective, randomized, controlled study, the combined infusion of AVP and NE proved to be superior when compared with NE alone in the treatment of cardiocirculatory failure in catecholamine-resistant vasodilatory shock. Patients receiving AVP had a significantly higher blood pressure, had improved cardiac performance, and needed less NE. A continuous infusion of AVP further reduced cardiotoxic effects of high catecholamine dosages, such as new-onset tachyarrhythmias. Gastrointestinal perfusion as assessed by gastric tonometry seemed to be better preserved in AVP-treated patients. However, larger studies will be needed to evaluate advantages of a combined infusion regimen of AVP and NE on mortality and morbidity in catecholamine-resistant vasodilatory shock.

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