Arginine vasopressin in 316 patients with advanced vasodilatory shock*

Günter Luckner, MD; Martin W. Dünser, MD; Stefan Jochberger, MD; Viktoria D. Mayr, MD; Volker Wenzel, MD; Hanno Ulmer, PhD; Stefan Schmid, MD; Hans Knotzer, MD; Werner Pajk, MD; Walter Hasibeder, MD; Andreas J. Mayr, MD; Barbara Friesenecker, MD

Objective: **To assess the effects of arginine vasopressin (AVP) on hemodynamic, clinical, and laboratory variables and to determine its adverse side effects in advanced vasodilatory shock.**

Design: **Retrospective study.**

Patients: **A total of 316 patients.**

Interventions: **AVP infusion (4 units/hr).**

Measurements and Main Results: **Cardiocirculatory, laboratory, and clinical variables were evaluated before, 0.5, 1, 4, 12, 24, 48, and 72 hrs after administration of AVP. AVP increased mean arterial pressure, systemic vascular resistance, and stroke volume index. Heart rate, central venous pressure, mean pulmonary arterial pressure, norepinephrine, milrinone, and epinephrine requirements decreased. There was no difference in the hemodynamic response between patients with septic shock, postcardiotomy shock, or systemic inflammatory response syndrome. Cardiac index decreased in 41.1% of patients during AVP treatment. In patients with hyperdynamic circulation before AVP, cardiac index decreased, whereas it remained uncharged or tended to increase in patients with normodynamic or hypodynamic circulation. During the course of AVP treatment, liver enzymes (28.5% of patients) and total bilirubin concentrations (69.3% of patients) increased, whereas platelet count decreased (73.4% of patients). Simultaneous hemofiltration significantly contributed to the decrease in platelet count ($p < .001$) and increase in bilirubin ($p < .001$). Whereas patients with an increase in bilirubin were more likely to die, a decrease in cardiac index or platelet count and an increase in liver enzymes did not affect mortality. Systemic inflammatory response syndrome as admission diagnosis, a high degree of multiple organ dysfunction, and norepinephrine requirements of $>0.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$ before AVP treatment were independent risk factors for death from advanced vasodilatory shock treated with AVP. If norepinephrine dosages exceeded 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before AVP treatment, a substantial increase in mortality occurred.**

Conclusions: **Supplementary AVP infusion improved cardiocirculatory function in advanced vasodilatory shock, but an increase in liver enzymes and bilirubin, and a decrease in platelet count occurred during AVP therapy, particularly during simultaneous hemofiltration. Initiation of AVP infusion before norepinephrine requirements exceeding 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ may improve outcome. (Crit Care Med 2005; 33:2659–2666)**

KEY WORDS: arginine vasopressin; norepinephrine; side effects; mortality; septic shock; vasodilatory shock; cardiac index; liver enzymes; bilirubin; platelets

Advanced vasodilatory shock is a life-threatening condition in critically ill patients and the most frequent cause of death from septic shock (1). Current treatment recommendations include fluid resuscitation, inotropes, and vasopressor catecholamines (2). Unfortunately, catecholamine hyposensitivity often complicates cardiovascular stabilization (3). Intensivists may enter a *circulus vitiosus*, where any further increase in catecholamine support may produce major side effects (e.g., tachyarrhythmias), which additionally worsen cardiocirculatory function, thus contributing to poor outcome. Accordingly, >100,000 patients per year die of irreversible vasodilatory shock and multiple organ dysfunction syndrome resistant to catecholamine vasopressor effects alone in U.S. intensive care units (3).

Arginine vasopressin (AVP) has been introduced in addition to catecholamines in cardiac arrest (4, 5) and advanced vasodilatory shock (6–9). There have been numerous reports about beneficial effects of AVP in advanced vasodilatory shock, but concern has been raised because of possible adverse side effects and unknown details regarding the optimal time to start AVP therapy. A current prospective, multiple-center trial is investigating the effects of AVP on patient outcome in cases of advanced vasodilatory shock (10); results may not be available until 2006.

We have used AVP in advanced vasodilatory shock patients since 1999. A cohort of 316 patients has been analyzed retrospectively in the present study. Until more clinical data will be available, the present study may be of value for clinicians to provide the best care possible for patients with advanced vasodilatory shock.

METHODS

Demographic Data

Between January 1999 and December 2003, medical records of a 23-bed general sur-

*See also p. 2713.

From the Department of Anesthesiology and Critical Care Medicine (GL, MWD, SJ, VDM, VW, SS, HK, WP, AJM, BF) and the Institute of Medical Biostatistics and Documentation (HU), Medical University Innsbruck, Austria; and the Department of Anesthesiology and Critical Care Medicine, Krankenhaus der Barmherzigen Schwestern, Ried im Innkreis, Austria (WH).

No author has a conflict of interest in regard to the drugs discussed in this article.

DOI: 10.1097/01.CCM.0000186749.34028.40

gical and trauma intensive care unit were reviewed for patients with advanced vasodilatory shock who were treated with a supplementary AVP infusion (Pitressin, Pfizer, Karlsruhe, Germany). According to the cause of vasodilatory shock, patients were grouped into 1) patients with septic shock, 2) patients with postcardiotomy shock, and 3) patients with vasodilatory shock due to overwhelming systemic inflammatory response syndrome (SIRS). The syndromes of sepsis and SIRS were defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference criteria (11). Age, admission diagnosis, length of intensive care unit stay and AVP infusion, Simplified Acute Physiologic Score II (12), most severe multiple organ dysfunction syndrome score (13), and intensive care unit mortality were documented.

Hemodynamic Management

All patients were invasively monitored, including monitoring with a pulmonary artery catheter. Additional fluid resuscitation was performed using colloid solutions (Gelofusin, B. Braun, Melsungen, Germany) until stroke volume could not be further increased; the corresponding pulmonary artery occlusion pressure was then used to guide ongoing 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. 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 reach a cardiac index of >2 L·min^{-1}·m^{-2} otherwise or who presented with severe systolic dysfunction in transesophageal echocardiography. If mean arterial pressure (MAP) remained <70 mm Hg, a norepinephrine (NE) infusion was started, and in 218/316 patients (69%) a continuous hydrocortisone infusion (200–300 mg/day) was administered. If a stepwise increase of NE by 0.2 μg·kg^{-1}·min^{-1} over 2 hrs could not restore MAP, AVP was started as a supplementary infusion at a continuous dosage of 4 units/hr. NE infusion was then adapted to maintain MAP at >70 mm Hg, and AVP dosage remained constantly at 4 units/hr. If NE 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.

Hemodynamic Response to AVP and NE Dosage for Initiation of AVP Infusion

Hemodynamic variables, including heart rate, MAP, central venous pressure, mean pulmonary arterial pressure, cardiac index, stroke volume index, and pulmonary artery occlusion pressure, and cardiovascular drug requirements were recorded before, 0.5, 1, 4, 12, 24, 48, and 72 hrs after the start of AVP infusion. Systemic vascular resistance was calculated according to standard formulas at the same time points. The hemodynamic response to AVP during the first 30 mins was compared between patients with advanced vasodilatory shock due to septic shock, after cardiac surgery, or due to SIRS.

Laboratory and Organ Function Variables During AVP Infusion

Laboratory variables (pH, arterial lactate, creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, Pao_2/Fio_2 quotient, platelet count, isoenzyme of creatinine kinase with muscle and brain subunits [CK-MB], troponin I) were recorded before, 24, 48, and 72 hrs after start of AVP infusion.

Adverse Side Effects During AVP Infusion

If adverse side effects were observed in hemodynamic or laboratory data during AVP infusion, the number of patients presenting with such a side effect was evaluated. Adverse effects were defined as follows. For example, changes in cardiac index were considered to be an adverse side effect if cardiac index at the last measurement available or at 72 hrs after the start of AVP therapy was lower than before AVP infusion. The same definitions were adopted for an increase in liver enzymes and total bilirubin concentrations and for a decrease in platelet count. Demographic, hemodynamic, laboratory data, and drug dosages before the start of AVP infusion were then entered into a two-step regression model to identify risk factors and possible reasons for the observed side effect of AVP.

Causes of and Risk Factors for Death from Advanced Vasodilatory Shock Treated With AVP

Causes of death of study patients were documented by reviewing clinical records. Furthermore, autopsy documents were reviewed for specific macroscopic or microscopic diagnoses not included in clinical reports. To identify risk factors for death from advanced vasodilatory shock treated with AVP, demographic data, hemodynamic variables, laboratory, and drug dosage data before AVP treatment were included into a two-step regression model.

Statistical Analysis

Shapiro-Wilk's tests were used to check for normality distribution of data, which was approximately fulfilled in all variables except for aspartate and alanine aminotransferase, total bilirubin, platelet count, arterial lactate, and CK-MB, which were log-transformed. Demographic data were analyzed using descriptive, statistical methods.

Hemodynamic and Laboratory Response. Repeated measurements and differences between patients with septic shock, postcardiotomy shock, and SIRS were analyzed with a mixed-effects model (SPSS, Chicago, IL) (14). If time effects were significant, comparisons vs. baseline were performed using the same model.

Adverse Side Effects. Demographic, hemodynamic, laboratory data, and drug dosages before AVP therapy were entered into a bivariate correlation model to test for univariate differences between patients with vs. patients without the observed side effect. In case of significant correlations ($p < .05$), variables were entered into a logistic regression model to identify independent risk factors. Differences in mortality between patients with vs. patients without the adverse side effect were analyzed using the Fisher's exact test.

Risk Factors for Death. Independent risk factors for death from advanced vasodilatory shock treated with AVP were analyzed using the same models as described for adverse side effects. Because of its skewed distribution, the variable "norepinephrine requirements before start of AVP therapy" was grouped into three clinically relevant dosage steps (0–0.5 μg·kg^{-1}·min^{-1}, 0.5–1 μg·kg^{-1}·min^{-1}, >1 μg·kg^{-1}·min^{-1}) and then entered into the statistical model.

Statistical significance was considered at $p < .05$. All data are given as mean values ± SD, if not indicated otherwise.

RESULTS

Demographic Data. A total of 316 patients with a mean age of 66.8 ± 14 yrs, a Simplified Acute Physiologic Score II of 46.7 ± 15.2 points, and a multiple organ dysfunction syndrome score of 11.1 ± 1.6 points (equivalent to 5.6 failed organs in each patient) received a supplementary AVP infusion (72.3 ± 78.5 hrs). A total of 103 patients had septic shock (32.6%), 135 had postcardiotomy shock (42.7%), and 78 had advanced vasodilatory shock due to overwhelming SIRS (24.7%). The underlying diagnoses leading to SIRS in these 78 patients were multiple trauma (43%), hemorrhagic shock (22%), cardiopulmonary resuscitation (20%), and acute respiratory distress syndrome (15%). Mean length of stay in the intensive care unit was 17.8 ± 15.5 days. Mor-

Table 1. Details of hemodynamic response to arginine vasopressin infusion

	Baseline	30 mins	1 hr	4 hrs	12 hrs	24 hrs	48 hrs	72 hrs	*p* Value
Patients, n	316	316	311	302	262	218	169	126	
HR, beats/min	111 ± 24[a]	108 ± 21[b]	105 ± 21[b]	100 ± 21[b]	97 ± 18[b]	94 ± 19[b]	92 ± 18[b]	87 ± 15[b]	<.001[c]
MAP, mm Hg	55 ± 14[a]	75 ± 13[b]	78 ± 14[b]	76 ± 11[b]	75 ± 11[b]	76 ± 12[b]	77 ± 10[b]	77 ± 10[b]	<.001[c]
CVP, mm Hg	13 ± 4[a]	13 ± 4	13 ± 4	13 ± 4	13 ± 4	13 ± 4	12 ± 4[b]	12 ± 3[b]	.001[c]
MPAP, mm Hg	29 ± 7[a]	28 ± 7	29 ± 7	28 ± 7[b]	28 ± 6[b]	27 ± 6[b]	27 ± 6[b]	27 ± 5[b]	.021[c]
PAOP, mm Hg	16 ± 4		16 ± 5	16 ± 4	16 ± 4	16 ± 4	16 ± 4	16 ± 3	.953
CI, mL/m^2/min	3.6 ± 1.5		3.4 ± 1.2	3.4 ± 1.2	3.4 ± 1.2	3.4 ± 1.1	3.4 ± 1.0	3.3 ± 1.0	.271
SVI, mL/beat/m^2	34 ± 12[a]		33 ± 11	35 ± 12[b]	36 ± 12[b]	36 ± 11[b]	37 ± 11[b]	38 ± 11[b]	.002[c]
SVR, dyne sec/cm^5	718 ± 345[a]		914 ± 434[b]	914 ± 395[b]	867 ± 330[b]	916 ± 367[b]	901 ± 322[b]	957 ± 366[b]	<.001[c]
NE, μg/kg/min (n = 316)	1.06 ± 1.25[a]	0.91 ± 1.1[b]	0.8 ± 0.92[b]	0.65 ± 0.84[b]	0.53 ± 0.94[b]	0.45 ± 0.63[b]	0.41 ± 0.66[b]	0.31 ± 0.3[b]	<.001[c]
Mil, μg/kg/min (n = 187)	0.41 ± 0.21[a]	0.4 ± 0.22	0.4 ± 0.21	0.41 ± 0.21	0.41 ± 0.2	0.38 ± 0.2[b]	0.34 ± 0.21[b]	0.31 ± 0.21[b]	.001[c]
E, μg/kg/min (n = 66)	0.2 ± 0.23[a]	0.18 ± 0.23	0.17 ± 0.23	0.16 ± 0.25	0.14 ± 0.34	0.07 ± 0.12[b]	0.05 ± 0.1[b]	0.02 ± 0.03[b]	<.001[c]

HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance; NE, norepinephrine requirements; Mil, milrinone requirements; E, epinephrine requirements.

[a]Significant time effect; [b]significant effect versus baseline; [c]$p < .05$ = significant. Data are given as mean values ± SD.

tality of the study population was 50.9% (n = 161). Seventy-nine percent of the study patients (n = 251) were receiving continuous venovenous hemofiltration (CVVHF) for renal indications only. A total of 114 study patients have already been included in previous study protocols examining different clinical end points (15–17).

Hemodynamic Response to AVP Infusion. Heart rate, central venous pressure, and mean pulmonary arterial pressure significantly decreased during AVP infusion, whereas MAP, stroke volume index, and systemic vascular resistance increased. NE, milrinone, and epinephrine dosages could be significantly reduced during the 72-hr observation period (Table 1). Except for a more pronounced decrease in epinephrine requirements in patients with SIRS, there were no differences in the immediate hemodynamic response to AVP infusion between vasodilatory shock patients with sepsis, patients after cardiac surgery, or patients with SIRS (Fig. 1).

Laboratory and Organ Function Variables. Table 2 displays laboratory and organ function variables during AVP infusion. pH, aspartate and alanine aminotransferase, and total bilirubin increased, whereas arterial lactate concentrations and platelet count decreased. Bilirubin levels significantly increased in patients receiving CVVHF but increased only nonsignificantly in patients without CVVHF. Similarly, platelet count decreased only in patients receiving CVVHF, whereas patients without CVVHF experienced no decrease in platelet count. No significant changes in serum creatinine, Pa_{O_2}/F_{IO_2} quotient, CK-MB, or troponin I serum concentrations occurred during AVP therapy.

Adverse Side Effects during AVP Infusion. Table 3 presents the prevalence of and risk factors for adverse side effects during AVP therapy. Cardiac index decreased in 130 of 316 patients (41.1%); a high cardiac index before AVP therapy was independently associated with a decrease in cardiac index during AVP infusion. There was no mortality difference between patients with and without a decrease in cardiac index (52.2% vs. 48.2%, $p = .909$). The response in cardiac index to AVP infusion was significantly different between patients with a hyperdynamic (cardiac index, >3.6 $L \cdot min^{-1} \cdot m^{-2}$, n = 135), normodynamic (2.8–3.6 $L \cdot min^{-1} \cdot m^{-2}$ (18), n = 93), and hypodynamic circulation (cardiac index, <2.8 $L \cdot min^{-1} \cdot m^{-2}$, n = 88) ($p < .001$) (Fig. 2). Whereas cardiac index decreased in patients with hyperdynamic circulation (from 5.4 $L \cdot min^{-1} \cdot m^{-2}$ before AVP therapy to 4.9 $L \cdot min^{-1} \cdot m^{-2}$ at 72 hrs after start of AVP therapy), it remained unchanged in patients with normal cardiac index (from 3.1 $L \cdot min^{-1} \cdot m^{-2}$ before AVP therapy to 3 $L \cdot min^{-1} \cdot m^{-2}$ at 72 hrs after start of AVP therapy) and slightly increased in patients with hypodynamic circulation (from 2.1 $L \cdot min^{-1} \cdot m^{-2}$ before AVP therapy to 2.4 $L \cdot min^{-1} \cdot m^{-2}$ at 72 hrs after start of AVP therapy). Stroke volume index increased irrespective of the circulatory state, with the most pronounced increase in patients with a cardiac index of <2.8 $L \cdot min^{-1} \cdot m^{-2}$. There was no difference in milrinone requirements between patients with different cardiac indices.

An increase in total bilirubin concentrations occurred in 219 patients (69.3%) and was significantly associated with a high degree of multiple organ dysfunction, high NE requirements, and arterial lactate concentrations before the start of AVP infusion. Patients experiencing an increase in total bilirubin concentrations were significantly more likely to die than patients without such an increase (55.3% vs. 41.2%, $p = .029$). Whereas patients requiring CVVHF experienced a significant increase in total bilirubin concentrations, patients without CVVHF only demonstrated a nonsignificant increase in total bilirubin levels (Table 2). The increase in total bilirubin concentrations was significantly more pronounced in patients requiring CVVHF when compared with patients without CVVHF ($p < .001$, corrected for baseline differences).

An increase in aminotransferase concentrations during AVP infusion was observed in 28.5% (90/316) of study patients and was related to low MAP before AVP therapy. In these patients, liver enzymes increased until 24 (aspartate aminotransferase) and 48 hrs (alanine aminotransferase) after start of AVP and decreased again afterward (Fig. 3). An increase in liver enzymes during AVP infusion was not associated with mortality (48.9% vs. 51.8%, $p = .709$).

A decrease in platelet count occurred in 73.4% (232/316) of study patients during AVP infusion and was independently associated with the magnitude of baseline platelet count, the degree of multiple organ dysfunction, and high NE require-

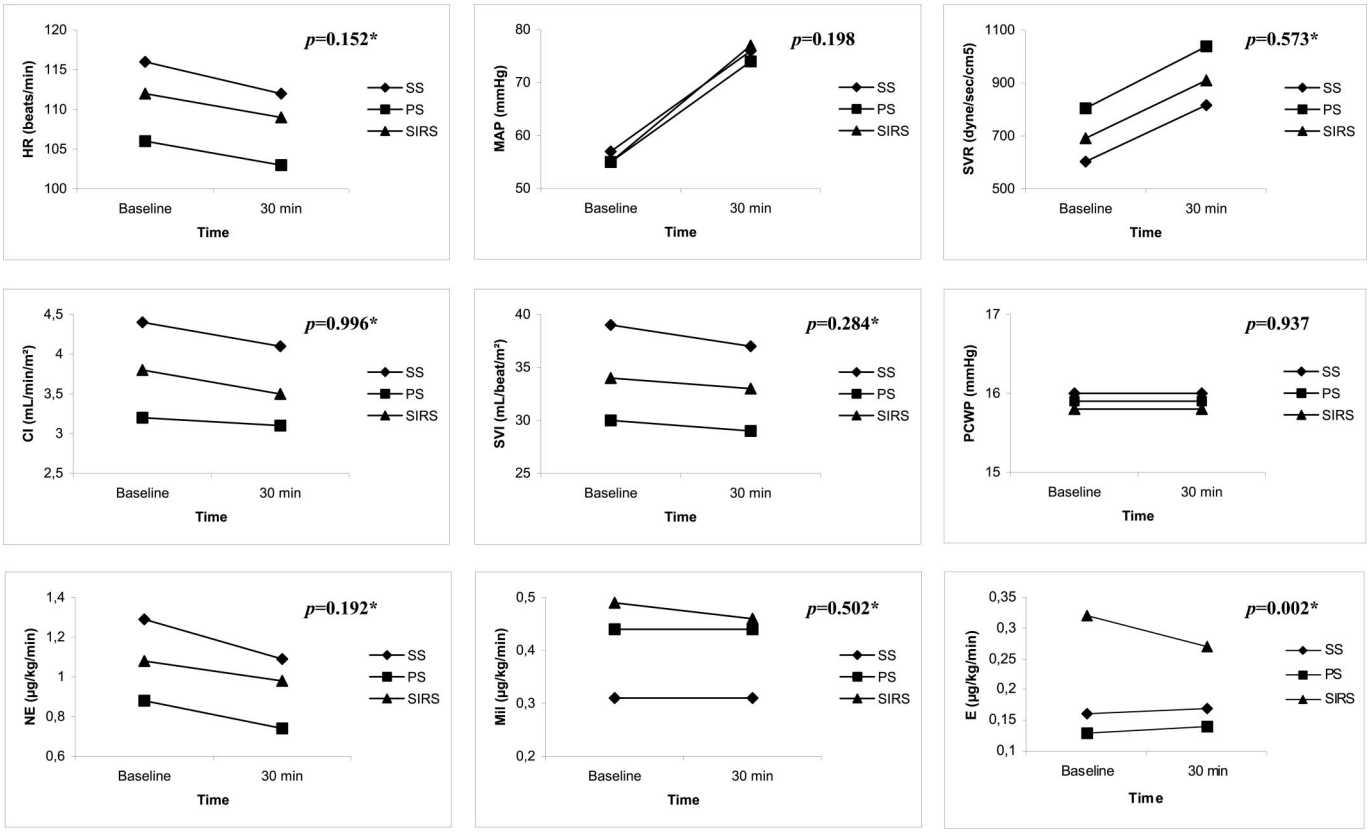

Figure 1. Hemodynamic response to arginine vasopressin in patients with advanced vasodilatory shock caused by sepsis, after cardiac surgery, and due to severe systemic inflammatory response syndrome (*SIRS*). *SS*, septic shock; *PS*, postcardiotomy shock; *HR*, heart rate; *MAP*, mean arterial pressure; *SVR*, systemic vascular resistance; *CI*, cardiac index; *SVI*, stroke volume index; *PCWP*, pulmonary capillary wedge pressure; *NE*, norepinephrine requirements; *Mil*, milrinone requirements; *E*, epinephrine requirements. * *p*-Values corrected for baseline differences.

ments before AVP therapy. CVVHF also had a significant influence on the course of platelet count ($p < .001$). Whereas patients without CVVHF exhibited no significant decrease in platelets, platelet count significantly decreased in patients requiring CVVHF (Table 2). However, occurrence of a decrease in platelet count (52.6% vs. 46.4%, $p = .373$) did not affect patient mortality.

Causes of and Risk Factors for Death from Advanced Vasodilatory Shock Treated with AVP. Table 4 presents clinical and additional postmortem diagnoses of patients who died of advanced vasodilatory shock treated with a supplementary AVP infusion. Refractory multiple organ dysfunction syndrome was the most frequent cause of death in this study population. A total of 48 (29.8%), 19 (22.8%), 17 (10.6%), 3 (1.8%), 19 (11.8%), and 55 (34.2%) nonsurviving study patients (n = 161) died within 12, 24, 48, and 72 hrs or after 72 hrs with and without AVP infusion.

SIRS at admission, the degree of multiple organ dysfunction before start of AVP infusion, and NE requirements of >0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before AVP therapy were independent risk factors associated with death caused by advanced vasodilatory shock treated with AVP (Table 5).

NE Dosage to Initiate AVP Therapy. Patients' NE requirements before onset of AVP infusion and their corresponding mortality rates were grouped according to clinically relevant dosage steps. Figure 4 shows the dependency between mortality and the initiation of AVP therapy at different NE requirements. When AVP was started at NE dosages between 0.2 and 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, mortality was 46% and increased rapidly to a maximum of 77% if AVP was initiated at NE dosages of >0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$. All patients presented with a comparable multiple organ dysfunction syndrome score (9.2 ± 1.8) before the start of AVP infusion.

DISCUSSION

Similar to previous studies in advanced vasodilatory shock (8, 9, 15–17, 19), an AVP infusion successfully stabilized cardiovascular function by increasing both systemic vascular resistance and MAP, and high NE dosages could be significantly reduced. The significant decrease in NE dosages may have contributed to other beneficial cardiocirculatory effects during AVP infusion, such as significant reductions in heart rate and pulmonary arterial pressure. The results of this analysis underline and reconfirm that a supplementary AVP infusion in advanced vasodilatory shock is a potential adjunct vasopressor agent to bridge precarious cardiovascular dysfunction when high dosages of catecholamines remain ineffective and may even be harmful.

Hemodynamic response to AVP was not different between patients with septic shock, postcardiotomy shock, or vasodilatory shock due to overwhelming SIRS in this study. Pathophysiology of intractable vasodilatation in sepsis, after cardiac surgery, or due to massive systemic inflammation is very similar (1) and may explain the homogeneous response to AVP therapy in patients with advanced vasodilatory shock originating from dif-

Table 2. Laboratory and organ function parameters during arginine vasopressin infusion

	Baseline	24 hrs	48 hrs	72 hrs	*p* Value
Patients, n	316	218	169	126	
pH	7.32 ± 0.11[a]	7.38 ± 0.09[b]	7.41 ± 0.08[b]	7.42 ± 0.07[b]	<.001
Lactate, mg/dL	43 ± 38[a]	32 ± 32	25 ± 24	21 ± 21	<.001
Creatinine, mg/dL	2.1 ± 1	2.2 ± 09	2.1 ± 0.8	2.0 ± 0.7	.137
ASAT, U/L	264 ± 951[a]	380 ± 868[b]	267 ± 600	198 ± 458	.009
ALAT, U/L	162 ± 485[a]	236 ± 452[b]	221 ± 416[b]	181 ± 336[b]	.019
Total bilirubin, mg/dL	3.2 ± 3.7[a]	4.2 ± 2.5[b]	4.7 ± 4.5[b]	5.2 ± 5[b]	.03
With CVVHF	3.4 ± 3.9	4.4 ± 4.5	4.8 ± 4.8[b]	5.3 ± 5.1[b]	.002
Without CVVHF	2.5 ± 2.9	3.6 ± 4.3	4.2 ± 5.2	4.3 ± 4.9	.348
Pao_2/Fio_2	193 ± 89	210 ± 85	220 ± 79	221 ± 79	.087
Platelets, 1,000 cells/μL	143 ± 107[a]	111 ± 85[b]	98 ± 71[b]	93 ± 56[b]	.001
With CVVHF	142 ± 106	103 ± 73[b]	89 ± 60[b]	87 ± 53[b]	<.001
Without CVVHF	151 ± 113	143 ± 118	138 ± 96	123 ± 60	.249
CK-MB, U/L	29 ± 47	29 ± 65	38 ± 58	28 ± 90	.176
Troponin I, mg/dL	53 ± 113	60 ± 122	48 ± 133	40 ± 101	.326

ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; CK-MB, creatinkinase MB.
[a]Significant time effect; [b]significant effect versus baseline. Data are given as mean values ± SD.

Table 3. Incidence of and independent risk factors for adverse side effects during arginine vasopressin infusion (logistic regression) and differences between patients with and without adverse side effect (bivariate analysis)

	Logistic Regression			Bivariate Analysis		
	Odds Ratio	95% CI	*p* Value	Patients with Side Effects	Patients without Side Effects	*p* Value
Decrease in cardiac index (I = 41.1%)						
Cardiac index before AVP, $L/m^2/min$	6.76	1.06–47.69	.048	4.3 ± 1.5	3.1 ± 1.2	<.001
Increase in bilirubin concentrations (I = 69.3%)						
Severest MODS during ICU stay, patients	135	1.09–1.67	.007	11.4 ± 1.4	10.5 ± 1.8	<.001
Norepinephrine dosage before AVP, μg/kg/min	1.55	1.02–2.34	.038	1.25 ± 1.42	0.65 ± 0.56	<.001
Arterial lactate before AVP, mmol/L	1.02	1–1.03	.02	49.9 ± 40.5	28.2 ± 25.8	<.001
Increase in serum transaminases L = 28.5%						
MAP Before AVP, mm Hg	0.97	0.95–1	.021	53.6 ± 10.3	56.5 ± 10.3	<.001
Decrease in platelet count (I = 73.4%)						
Platelet count before AVP, 1,000 cells/μL	1.003	1.001–1.005	<.001	160 ± 108	97 ± 92	<.001
Severest MODS during ICU stay, patients	1.29	1.06–1.57	.012	10.7 ± 1.8	11.3 ± 1.48	<.001
Norepinephrine dosage before AVP, μg/kg/min	1.69	1.12–2.54	.012	1.21 ± 1.38	0.66 ± 0.66	<.001

CI, confidence interval; I, incidence of adverse side effect; AVP, arginine vasopressin; MODS, multiple organ dysfunction syndrome score; ICU, intensive care unit; MAP, mean arterial pressure.
Data are given as mean values ± SD.

ferent underlying diseases. Together with a decrease in central venous pressure, the observation that stroke volume index significantly increased despite a substantial decrease in inotropic support can be interpreted as an improvement of cardiac performance during AVP therapy. This confirms the results of recent studies (9, 16), but it is in contrast to most animal and some clinical reports describing a significant decrease in cardiac index and systemic oxygen supply during AVP infusion (15, 20–23). A two-step regression analysis revealed that a decrease in cardiac index during AVP infusion was mostly observed in patients with a high cardiac index, indicating a hyperdynamic circulation. This suggests that AVP infusion in advanced vasodilatory shock reverses a hyperdynamic circulation and tends to improve cardiac performance at normodynamic or hypodynamic circulation states. Mechanisms of improved myocardial performance during AVP therapy have been hypothesized to include a reduction of cardiotoxic and proarrhythmic effects by decreasing high catecholamine dosages, an AVP-induced increase in intramyocardial calcium concentrations, and an improvement of myocardial blood flow due to increased systemic perfusion pressure and selective coronary vasodilatation (9).

Negative influences of AVP therapy on liver function have been described before. Although an increase in total bilirubin concentrations in these study patients is in accordance with earlier observations (9, 15), an association of AVP with increased serum aminotransferase levels in ~30% of patients has not yet been observed. One of the most important factors that has contributed to an increase in total bilirubin levels during AVP therapy in this study is the simultaneous need for CVVHF. Additional stimulation of blood cells by the extracorporal circuit of CVVHF can intensify the inflammatory stress on hepatocellular function and may thus increase total bilirubin levels (24). Another mechanism possibly contributing to an increase in total bilirubin concentrations is the reduction of biliary output and bile flow by AVP itself. Hamada et al. (25) found that the physiologic bile flow response to AVP is biphasic, with a sharp increase in bile secretion

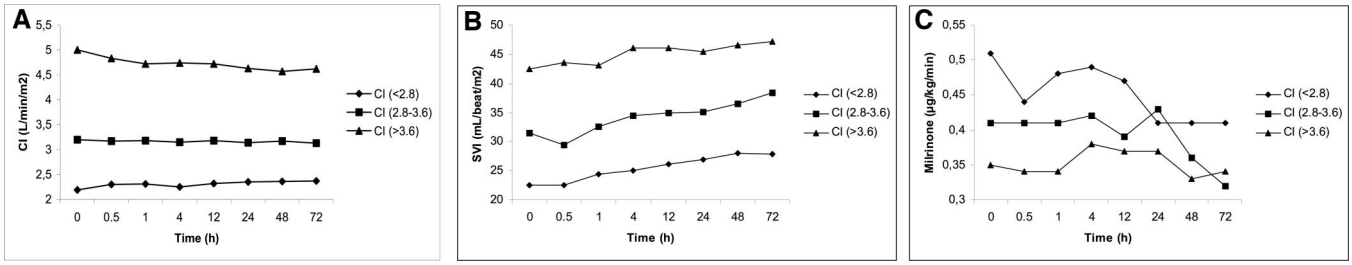

Figure 2. Time courses of cardiac index (*CI*), stroke volume index (*SVI*), and milrinone-requirements in hypodynamic (cardiac index, <2.8 L·min^{-1}·m^{-2}; n = 88), normodynamic (cardiac index, 2.8–3.6 L·min^{-1}·m^{-2}; n = 93), and hyperdynamic (>3.6 L·min^{-1}·m^{-2}, n = 135) patients with vasodilatory shock treated with arginine vasopressin. All *p*-values corrected for baseline differences.

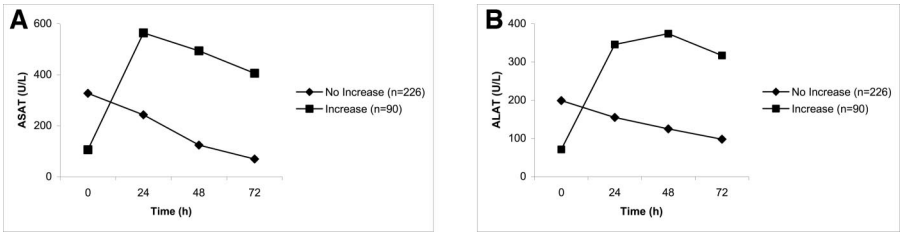

Figure 3. Changes of serum aspartate aminotransferase (*ASAT*) and alanine aminotransferase (*ALAT*) during arginine vasopressin infusion in patients with an increase in liver enzymes (n = 90) and patients without an increase in liver enzymes (n = 226).

Table 4. Causes of death from advanced vasodilatory shock treated with arginine vasopressin

	n	Frequency (%)
Clinical diagnoses		
Refractory multiple organ dysfunction syndrome	110/161	68.3
Refractory cardiovascular failure	38/161	23.7
Refractory pulmonary failure	6/161	3.7
Refractory central nervous system failure	7/161	4.3
Additional post-mortem diagnoses		
Acute myocardial infarction	39/161	24
Right heart failure	25/161	15.5
Signs of hypoxic liver cell necrosis	15/161	9.3
Non-occlusive mesenteric ischemia	7/161	4.3
Signs of pathologic intestinal mucosa	7/161	4.3
Severe liver failure	5/161	3.1
Acute pulmonary embolism	5/161	3.1
Acute pancreatitis	5/161	3.1
Ischemic colitis	1/161	0.6

Table 5. Risk factors for death from advanced vasodilatory shock in patients treated with arginine vasopressin

	Odds Ratio	95% CI	*p* Value
Admission diagnoses	Reference	Reference	.015
Admission diagnosis SIRS	2.64	1.36–5.14	.004
MODS before AVP, patients	1.39	1.19–1.62	<.001
PH before AVP	0.7	0.01–33.5	.855
Arterial lactate before AVP, mmol/L	1	0.99–1.01	.787
NE group <0.5 µg/kg/min (*n* = 140)	Reference	Reference	.017
NE group 0.5–1 µg/kg/min (*n* = 104)	2.22	1.25–3.93	.007
NE group >1 µg/kg/min (*n* = 72)	1.12	0.58–2.17	.736

CI, confidence interval; SIRS, systemic inflammatory response syndrome; MODS, multiple organ dysfunction syndrome score; AVP, arginine vasopressin; NE, norepinephrine.

within 1 min of AVP administration followed by a decline in bile secretion for the remaining time of AVP infusion. It is hypothesized that AVP, comparable with other stress hormones such as epinephrine and cortisol, can modulate hepatocyte tight junctional permeability and thus produce cholestasis (26). These effects, however, seem to be mitigated during cholestasis (27). In view of the finding that the need for CVVHF, high arterial lactate concentrations, high NE requirements, and a high degree of multiple organ dysfunction were independently associated with an increase in bilirubin levels, it cannot be determined if higher mortality rates observed in patients with an increase in total bilirubin concentrations during AVP therapy result from adverse effects of AVP infusion itself or are more likely the consequence of the more severe underlying disease of these patients, particularly the ones who require additional CVVHF because of acute renal failure.

Whereas an increase in total bilirubin is more suggestive of direct hepatocellular dysfunction, elevated liver enzymes may reflect hepatic hypoperfusion and liver hypoxia (28, 29). Study patients presenting with an increase in liver enzymes had significantly lower MAP before the start of AVP therapy than patients without this side effect. Because liver enzymes usually increase with a delay of 12 to 24 hrs after hepatic hypoperfusion (27), it may be speculated that more severe hypotensive episodes before the start of AVP infusion resulted in more pronounced hypoxic hepatitis. The renewed decrease of liver enzyme concentrations during AVP therapy would support such a hypothesis of a multifactorial hypoxic effect on the hepatocellular system before AVP therapy. Low cardiac output due to hypovolemia or reduced myocardial contractility are known predisposing factors

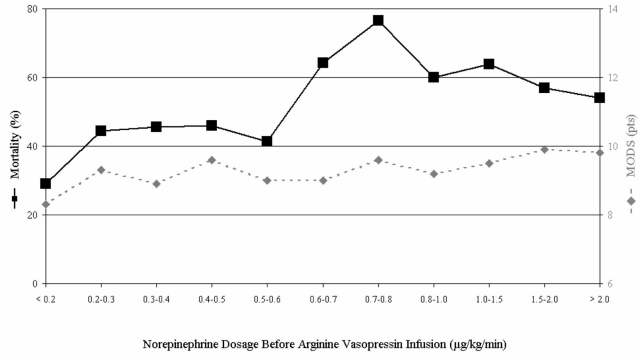

Figure 4. Mortality in dependence of norepinephrine dosage and multiple organ dysfunction syndrome score (*MODS*) before start of an arginine vasopressin infusion in all study patients (n = 316).

Initiation of arginine vasopressin therapy before norepinephrine requirements exceed a dosage of 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ may improve outcome of advanced vasodilatory shock.

for hepatosplanchnic hypoperfusion during AVP therapy (30, 31). Although there was no difference in cardiac index between patients with and without an increase in liver enzymes, it cannot be excluded that AVP induced hepatosplanch nic vasoconstriction and has thus caused hypoperfusion of the liver, resulting in an increase in serum transaminase concentrations.

Although neither gut nor liver perfusion were clinically measured in these study patients, postmortem analysis indicates that nonocclusive mesenteric ischemia or acute hypoxic liver failure were only rare causes of death from vasodilatory shock treated with AVP, occurring in 4.3% and 3.1% of deceased study patients, respectively. If gastrointestinal ischemia develops during AVP therapy, as observed in selected animal and human reports (32–34), it does not seem to have significantly contributed to mortality in this study population.

A significant decrease in platelet count during AVP infusion was observed in 73.4% of study patients. This finding is in agreement with previous studies (15, 35). Normal platelet count and high NE requirements before AVP together with the degree of multiple organ dysfunction were independent risk factors for a decrease in platelet count during AVP infusion. Aside from these risk factors, need for CVVHF was the most important factor leading to a decrease in platelet count during AVP therapy in this study. Increased consumption and destruction of thrombocytes in the extracorporal circuit of CVVHF (36) could explain such a reduction of platelet count during CVVHF. Although in the present study there was no difference in mortality between patients experiencing a decrease in platelet count and patients who did not, it cannot be excluded that a possibly AVP-mediated stimulation of thrombocyte aggregation may exert adverse effects on the microcirculation.

Overwhelming SIRS as the cause of vasodilatory shock, a high multiple organ dysfunction syndrome score, and NE requirements of >0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before onset of AVP infusion were independent risk factors for death from advanced vasodilatory shock treated with AVP. One reason why the diagnosis of SIRS was associated with a significantly worse prognosis might be the fact that patients after cardiopulmonary resuscitation were included in this group, and these patients are known to have a particularly bad prognosis (73.3% in this study population). The degree of multiple organ dysfunction before start of AVP therapy, as a critical determinant of subsequent outcome, underlines the importance of implementing AVP therapy before a severe, uncontrollable degree of multiple organ dysfunction necessitating excessive NE dosages (>0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) has developed.

The correlation of mortality rates and NE dosages before start of AVP therapy (Fig. 1) displays that mortality rapidly increases if NE dosages exceed 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before AVP infusion has been implemented. Increasing NE as the single vasopressor agent to dosages of >0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ may not only represent severe underlying cardiovascular failure, but it may itself result in substantial catecholamine toxicity, leading to tachyarrhythmias and myocardial ischemia. In a recent prospective trial, our working group could show that patients treated with high-dose NE therapy alone developed significantly more new-onset tachyarrhythmias than patients receiving a supplementary AVP infusion (8.3% vs. 54.3%, $p < .001$) (9). Reports on myocardial ischemia and infarction during high catecholamine support have been reported in several publications (37, 38).

CONCLUSION

AVP therapy in addition to NE infusion is a beneficial tool to stabilize cardiocirculatory function and reduce high, potentially toxic NE dosages in advanced vasodilatory shock. Nonetheless, in some patients and particularly during simultaneous CVVHF, an increase in liver enzymes and in total bilirubin and a decrease in platelet count occurred during AVP therapy. Initiation of AVP therapy before NE requirements exceed a dosage of 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ may improve outcome of advanced vasodilatory shock.

REFERENCES

1. Landry DW, Oliver JA: The pathogenesis of vasodilatory shock. *N Engl J Med* 2001; 345: 588–595
2. Dellinger RP: Cardiovascular management of septic shock. *Crit Care Med* 2003; 31: 946–955
3. Parillo J: Pathogenetic mechanisms of septic shock. *N Engl J Med* 1993; 328:1471–1477
4. Chen P: Vasopressin: New uses in critical care. *Am J Med Sci* 2002; 324:146–154
5. Wenzel V, Krismer AC, Arntz HR, et al: A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004; 350:105–113
6. Holmes CL, Landry DW, Granton JT: Science Review: Vasopressin and the cardiovascular system part 2. Clinical physiology. *Crit Care* 2004; 8:15–23
7. Dünser MW, Wenzel V, Mayr AJ, et al: Management of vasodilatory shock: Defining the role of arginine vasopressin. *Drugs* 2003; 63: 237–256
8. Patel BM, Chittock DR, Russell JA, et al: Beneficial effects of short-term vasopressin

infusion during severe septic shock. *Anesthesiology* 2002; 96:576–582
9. Dünser MW, Mayr AJ, Ulmer H, et al: Arginine vasopressin in advanced vasodilatory shock: A prospective, randomized, controlled study. *Circulation* 2003; 107:2313–2319
10. Russell JA, Cooper DJ, Walley KR, et al: Vasopressin and Septic Shock Trial (VASST): Baseline characteristics and organ dysfunction in vasopressor dependent patients with septic shock. *Am J Respir Crit Care Med* 2003; 167:A548
11. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20:864–874
12. Le Gall JR, Lemeshow S, Saulnier F: A new Simplified Acute Physiologic Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; 270:2957–2963
13. Goris RJ, te Boekhorst TP, Nuytinck JK, et al: Multiple-organ failure: Generalized autodestructive inflammation? *Arch Surg* 1985; 120:1109–1115
14. Laird NM, Ware JH: Random-effects models for longitudinal data. *Biometrics* 1982; 38: 963–974
15. Dünser MW, Mayr AJ, Ulmer H, et al: The effects of vasopressin on systemic hemodynamics in catecholamine-resistant septic and postcardiotomy shock: A retrospective analysis. *Anesth Analg* 2001; 93:7–13
16. Dünser MW, Mayr AJ, Stallinger A, et al: Cardiac performance during vasopressin infusion in postcardiotomy shock. *Intensive Care Med* 2002; 28:746–751
17. Dünser MW, Mayr AJ, Tür A, et al: Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: Incidence and risk factors. *Crit Care Med* 2003; 31: 1394–1398
18. Appel PL, Kram HB, Mackabee J, et al: Comparison of measurements of cardiac output by bioimpedance and thermodilution in severely ill surgical patients. *Crit Care Med* 1986; 14:933–935
19. Landry DW, Levin HR, Gallant EM, et al: Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med* 1997; 25:1279–1282
20. Westphal M, Stubbe H, Sielenkämper AW, et al: Effects of titrated arginine vasopressin on hemodynamic variables and oxygen transport in healthy and endotoxemic sheep. *Crit Care Med* 2003; 31:1502–1508
21. Scharte M, Meyer J, van Aken H, et al: Hemodynamic effects of terlipressin (a synthetic analogue of vasopressin) in healthy and endotoxemic sheep. *Crit Care Med* 2001; 29:1756–1760
22. Holmes CL, Walley KR, Chittock DR, et al: The effects of vasopressin on hemodynamics and renal function in severe septic shock: A case series. *Intensive Care Med* 2001; 27: 1416–1421
23. O'Brien A, Clapp L, Singer M: Terlipressin for norepinephrine-resistant septic shock. *Lancet* 2002; 359:1209–1210
24. Schlee H, Prondzinsky R, Osten B, et al: Systemic inflammatory reactions to extracorporeal therapy measures: Hemodialysis and hemofiltration. *Wien Klin Wochenschr* 1997; 109:301–311
25. Hamada Y, Karjalainen A, Setchell BA, et al: Concomitant stimulation by vasopressin of biliary and perfusate calcium fluxes in the perfused rat liver. *Biochem J* 1992; 281: 387–392
26. Ballatori N, Truong AT: Cholestasis, altered junctional permeability, and inverse changes in sinusoidal and biliary glutathione release by vasopressin and epinephrine. *Mol Pharmacol* 1990; 38:64–71
27. Hamada Y, Karjalainen A, Bygrave FL: Hormone-induced bile flow and hepatobiliary calcium fluxes are attenuated in the perfused liver of rats made cholestatic with ethynylestradiol in vivo and with phalloidin in vitro. *Hepatology* 1995; 21:1455–1464
28. Henrion J, Schapira M, Luwaert R, et al: Hypoxic hepatitis: Clinical and hemodynamic study in 142 consecutive cases. *Medicine* 2003; 82:392–406
29. Seeto RK, Fenn B, Rockey DC: Ischemic hepatitis: Clinical presentation and pathogenesis. *Am J Med* 2000; 109:109–113
30. Asfar P, Pierrot M, Veal N, et al: Low-dose terlipressin improves systemic and splanchnic hemodynamics in fluid-challenged endotoxic rats. *Crit Care Med* 2003; 31:215–220
31. Sun Q, Dimopoulos G, Nguyen DN, et al: Low dose vasopressin in the treatment of septic shock in sheep. *Am J Respir Crit Care Med* 2003; 168:481–486
32. Westphal M, Freise H, Kehrel BE, et al: Arginine vasopressin compromises gut mucosal microcirculation in septic rats. *Crit Care Med* 2004; 32:194–200
33. Martikainen TJ, Tenhunen JJ, Uusaro A, et al: The effects of vasopressin on systemic and splanchnic hemodynamics and metabolism in endotoxin shock. *Anesth Analg* 2003; 97: 1756–1763
34. Van Haren FM, Rozendaal FW, van der Hoeven JG: The effect of vasopressin on gastric perfusion in catecholamine-dependent patients in septic shock. *Chest* 2003; 124: 2256–2260
35. Dünser MW, Fries DR, Schobersberger W, et al: Does arginine vasopressin influence the coagulation system in advanced vasodilatory shock with severe multiorgan dysfunction syndrome? *Anesth Analg* 2004; 99:201–206
36. Mulder J, Tan HK, Bellomo R, et al: Platelet loss across the hemofilter during continuous hemofiltration. *Int J Artif Organs* 2003; 26: 906–912
37. Biccard BM, Gopalan PD: Phaeochromocytoma and acute myocardial infarction. *Anaesth Intensive Care* 2002; 30:74–76
38. Goldspink DF, Burniston JG, Clark WA, et al: Catecholamine-induced apoptosis and necrosis in cardiac and skeletal myocytes of rat in vivo: The same or separate death pathways? *Exp Physiol* 2004; 89:407–416