Does Arginine Vasopressin Influence the Coagulation System in Advanced Vasodilatory Shock with Severe Multiorgan Dysfunction Syndrome?

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Arginine vasopressin (AVP) is a potent supplementary vasopressor in advanced vasodilatory shock, but decreases in platelet count have been reported during AVP therapy. In this study we evaluated the effects of AVP infusion on the coagulation system in advanced vasodilatory shock when compared to norepinephrine (NE) infusion alone. Forty-two patients with advanced vasodilatory shock (NE requirements >0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, mean arterial blood pressure <70 mm Hg) were prospectively randomized to receive an additional AVP infusion (4 U/h) or NE infusion alone. Most patients received coagulation active treatment (fresh-frozen plasma, thrombocyte concentrates, coagulation factors, and continuous veno-venous hemofiltration with heparin). At baseline and 1, 24, and 48 h after randomization, coagulation laboratory variables and a modified thrombelastography were measured. There were no differences between groups in plasmatic coagulation variables. Although there was no significant difference between groups, platelet count significantly decreased in AVP patients ($P = 0.036$). There were no differences in results of modified thrombelastography analyses between groups. AVP infusion in advanced vasodilatory shock with severe multiorgan dysfunction syndrome does not increase plasma concentrations of Factor VIII, von Willebrand Factor antigen, and ristocetin Co-Factor but may stimulate platelet aggregation and induce thrombocytopenia. Global coagulation, assessed by modified thrombelastography, is not different from patients receiving NE infusion alone.

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Vasodilatory shock, characterized by decreased systemic vascular resistance and a poor response to vasopressor drugs, is a severe, life-threatening complication of critical illness, associated with frequent mortality. Currently, catecholamines are the first-line vasopressor drugs to preserve organ perfusion pressure during vasodilatory shock. However, hyposensitivity of arterial resistance vessels to catecholamines can complicate advanced vasodilatory shock and may result in loss of catecholamine vasopressor effects (1). In recent years, several investigations showed that a continuous arginine vasopressin (AVP) infusion can successfully stabilize cardiocirculatory function in vasodilatory shock that is refractory to standard vasopressor therapy with catecholamines (2–4).

However, only few data exist on possible adverse side effects of a continuous AVP infusion in advanced vasodilatory shock. A retrospective study in surgical patients with vasodilatory shock reported a significant decrease in platelet count during AVP infusion (5). AVP-mediated platelet aggregation via V_1-receptors has been speculated as a possible mechanism (6). In vasodilatory shock commonly associated with severe multiorgan dysfunction syndrome (MODS), additional activation of the coagulation system by AVP could be disadvantageous and may further compromise microcirculatory homeostasis (7). Therefore, in this study wee sought to analyze the effects of a combined infusion of AVP and norepinephrine (NE) on the coagulation system in advanced vasodilatory shock when compared with infusion of NE alone.

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Methods

The study protocol was approved by the ethical committee of the Leopold Franzens University of Innsbruck. Written informed consent was obtained, if possible, from all subjects or otherwise from the closest family members. As a separate study arm, the study protocol was partly performed in the same study population ($n = 40$) as a recently published trial on the effects of AVP on hemodynamic and laboratory variables (8). After inclusion of the first 8 patients into the original protocol, data collection to examine the coagulation system was started and performed along with the hemodynamic protocol in 40 patients. For the present trial, 2 further patients, not included in the hemodynamic trial, were randomized.

Critically ill patients suffering from vasodilatory shock after cardiovascular surgery or resulting from systemic inflammatory response syndrome with and without sepsis (9) with a mean arterial blood pressure (MAP) <70 mm Hg despite adequate volume resuscitation, and NE requirements $>0.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$ were prospectively enrolled.

In all patients, fresh-frozen plasma was infused if prothrombin time (<50%) and activated partial thromboplastin time (>45 s) were prolonged. Clotting factors (PPSB-concentrate; Beriplex® P/N; Aventis Behring GmbH, Vienna, Austria) or antithrombin concentrates (Kybernin® P; Aventis Behring GmbH) were administered if prothrombin time or antithrombin plasma activity was ever less than 50%. In view of our experience that most patients receiving AVP at our institution have a high degree of MODS and are at a high risk to develop disseminated intravascular coagulation and microcirculatory failure (5), strict platelet transfusion criteria were also applied to this study population. Thus, platelet concentrates were transfused to maintain platelet count >30,000/μL in patients without an increased risk for bleeding, >50,000/μL in patients with increased risk for bleeding, and >100,000/μL in patients with active bleeding. Two senior intensivists exclusively assessed the risk of bleeding in each study patient and ordered transfusion of thrombocyte concentrates.

Continuous veno-venous hemofiltration was initiated for renal indications only. For anticoagulation, unfractionated heparin was continuously infused in patients without active bleeding to achieve a partial thromboplastin time between 40 to 45 s.

At study entry, patients were randomized to AVP or NE treatment using a random-number generating computer program. In the AVP group, AVP (Pitressin®; Parke Davis, Berlin, Germany) was additionally infused at a constant rate of 4 U/h (no bolus injections were given); NE infusion was adjusted to maintain MAP ≥70 mm Hg. In NE patients, MAP ≥70 mm Hg was achieved by adjusting NE infusion as necessary.

The end-point of this study was to detect differences between the effects of a combined AVP and NE infusion on variables of the coagulation system when compared with NE infusion alone.

Age, admission diagnosis, a modified Goris MODS Score (10), length of intensive care unit (ICU) stay, and ICU mortality were documented in all patients. The following coagulation variables were collected at baseline and 1, 24, and 48 h after randomization: prothrombin time, activated partial thromboplastin time, and plasma concentrations of fibrinogen (immunoturbimetric test; Dade Behring, Marburg, Germany), antithrombin activity, D-dimers, Factor VIII (coagulometric test; Dade Behring, Marburg Germany), von Willebrand Factor antigen (vWF:Ag) (latex agglutination test; Roche Diagnostics, Mannheim, Germany), and ristocetin Co-Factor (RCoF) (agglutination test; Dade Behring, Marburg, Germany), as well as platelet count.

To assess global coagulation, modified thrombelastography (ROTEG®; Pentapharm, Munich, Germany), which is based on the thrombelastography system after Hartert (11,12), was performed at baseline, 1, 24, and 48 h after randomization. The variables analyzed were coagulation time, clot formation time, and maximum clot firmness for ExTEG®, InTEG®, and FibTEG® analyses. Thrombelastography assesses global coagulation by evaluation of key markers of clot formation *in vitro*. In modified thrombelastography, activation of test samples accelerates measurements and enhances reproducibility as compared with conventional thrombelastography (11). Thus, ExTEG® analysis reflects activity of the cellular and extrinsic plasmatic coagulation system, InTEG® activity of the cellular and intrinsic plasmatic coagulation system, and FibTEG® fibrinogen polymerization. Simplified, coagulation time represents activity of clotting factors, whereas clot formation time and maximum clot firmness both evaluate fibrinogen polymerization and platelet activity.

Demographic and clinical data were compared with the use of Student's *t*-, χ^2, or Mann-Whitney *U*-tests, as appropriate. Differences between groups and within repeated measurements were analyzed using linear mixed effects models (SPSS® 11.0 for Windows; SPSS Inc., Chicago, USA) to account for death-related dropouts (13). P values < 0.05 were considered to indicate statistical significance. Shapiro-Wilks tests were used to check for normality, which was approximately fulfilled in all reported variables except for RCoF, clotting time of ExTEG® analysis, as well as clot formation time of ExTEG® and InTEG® analyses, which were log-transformed. All data are given as mean values ± SD, if not indicated otherwise.

Table 1. Characteristics of Vasopressin and Norepinephrine Patients

	Vasopressin (n = 21)	Norepinephrine (n = 21)
Age (yr)	68.6 ± 9.7	69.6 ± 13.9
Diagnosis (n/%)		
SIRS	7/21 (33.3)	7/21 (33.3)
SS	7/21 (33.3)	6/21 (28.6)
PS	7/21 (33.3)	8/21 (38.1)
Surgery (n/%)	18/21 (85.7)	21/21 (100)
MODS	11.9 ± 0.8	11.8 ± 0.9
ICU stay (days)	18.6 ± 17.3	13.4 ± 12.4
ICU Mortality (n/%)	14/21 (66.7)	15/21 (71.4)
Therapeutic Interventions		
NE requirements (μg/kg/min)*	0.63 ± 0.47	0.97 ± 0.99
Heparin (n/%)	19/21 (90.5)	20/21 (95.2)
FFP requirements/48 h (n)	7.5 ± 12.3	5.4 ± 13.6
Patients receiving FFP (n/%)	11/21 (52.4)	10/21 (47.6)
TC requirements/48 h (n)*	0.4 ± 1	1.1 ± 2.6
Patients receiving TC (n/%)	5/21 (23.8)	8/21 (38.1)
PPSB requirements/48 h (U)	1421 ± 1606	933 ± 1352
Patients receiving PPSB (n/%)	16/21 (76.2)	14/21 (66.7)
AT requirements/48 h (U)	1231 ± 1539	1630 ± 1337
Patients receiving AT (n/%)	15/21 (71.4)	19/21 (90.5)
CVVHF (n/%)	20/21 (95.2)	20/21 (95.2)

Data are given as mean values ± SD, if not indicated otherwise.
SIRS = systemic inflammatory response syndrome; SS = septic shock; PS = postcardiotomy shock; MODS = Multiple Organ Dysfunction Syndrome score; ICU = intensive care unit; NE = mean norepinephrine dosage during the study period; FFP = fresh-frozen plasma; TC = thrombocyte concentrates; AT = antithrombin concentrate; CVVHF = continuous veno-venous hemofiltration; PPSB = prothrombin-complex-concentrate.
* Significant difference between groups.

Results

During the study period, 42 patients were eligible for study entry. Table 1 presents age, admission diagnosis, MODS score, length of ICU stay, and ICU mortality, as well as need for therapeutic interventions in AVP and NE patients. Mean NE requirements during the 48 h study period were significantly less in AVP patients, compared with NE patients (P = 0.017). NE patients received significantly more platelet concentrates (P = 0.04). There were no other differences between groups.

Laboratory coagulation variables of AVP and NE patients are displayed in Table 2. Prothrombin time was significantly longer at baseline in AVP patients (P = 0.045) and during the study period (P = 0.038), when compared with NE patients. After adjustment for baseline differences, no significant differences between groups in prothrombin time could be detected (P = 0.672). There were no differences between study groups in other measured coagulation variables. No significant difference in platelet count was found between AVP and NE patients. In AVP patients, platelet count significantly decreased during the study period (P = 0.036). There were significantly more NE patients exhibiting a platelet count <30,000/μL than AVP patients (P = 0.005). In the AVP group, no patient had a platelet count <30,000/μL.

To test for the influence of the significant group difference in thrombocyte concentrates on platelet counts, patients receiving thrombocyte concentrates (AVP group, n = 5; NE group, n = 8) were excluded from the original analysis and the same model was recalculated. No significant difference was detected between study groups (P = 0.543). Although excluding the influence of thrombocyte transfusion on platelet count, platelets significantly decreased during AVP infusion (P = 0.048). Platelets at 48 h were significantly less when compared with baseline values in the AVP group (P < 0.05).

Results of modified thrombelastography analyses of AVP and NE patients are shown in Table 3. At baseline, AVP patients had a longer clotting time of EXTEM® analysis than NE patients (P = 0.041). There were no significant differences in other results of modified thrombelastography analyses between AVP and NE patients.

No significant bleeding requiring massive transfusion occurred during the observation period in any study patient.

Discussion

In this prospective study, both groups of patients with advanced vasodilatory shock exhibited highly abnormal coagulation. This corresponds to reports on coagulation failure in severe MODS (14). There were no significant differences in plasmatic, cellular, and global

Table 2. Changes in Variables of the Coagulation System in Vasopressin and Norepinephrine Patients

		0 h (n = 42)	1 h (n = 42)	24 h (n = 34)	48 h (n = 22)
PT (%)†	Vasopressin	54 ± 13	54 ± 13	59 ± 17	66 ± 17
	Norepinephrine	66 ± 23	65 ± 22	65 ± 20	74 ± 20
aPTT (s)	Vasopressin	57 ± 16	55 ± 12	54 ± 14	57 ± 34
	Norepinephrine	56 ± 20	55 ± 21	53 ± 13	56 ± 4
Fibrinogen (mg/dL)	Vasopressin	385 ± 173	391 ± 153	452 ± 164	387 ± 173
	Norepinephrine	433 ± 205	423 ± 197	460 ± 183	477 ± 142
Antithrombin (%)	Vasopressin	66 ± 18	69 ± 19	70 ± 17	64 ± 15
	Norepinephrine	60 ± 16	68 ± 69	69 ± 18	61 ± 11
D-Dimers (μg/L)	Vasopressin	6.5 ± 5.3	6.4 ± 5.3	5.9 ± 4.1	5.8 ± 4.2
	Norepinephrine	5.1 ± 4.4	5.2 ± 4.4	5.8 ± 4.3	5.7 ± 3.7
Factor VIII (%)	Vasopressin	158 ± 34	163 ± 31	163 ± 51	169 ± 40
	Norepinephrine	157 ± 44	161 ± 41	164 ± 31	176 ± 24
vWF:Ag (%)	Vasopressin	196 ± 76	191 ± 75	193 ± 79	202 ± 77
	Norepinephrine	197 ± 79	188 ± 77	196 ± 79	216 ± 79
RCoF (%)	Vasopressin	250 ± 104	263 ± 109	276 ± 133	250 ± 142
	Norepinephrine	234 ± 78	225 ± 80	234 ± 81	245 ± 70
Platelets (1000 cells/μL)‡	Vasopressin	178 ± 152	168 ± 152	127 ± 163§	80 ± 61§
	Norepinephrine	146 ± 148	136 ± 143	105 ± 90	114 ± 77
Platelets <50,000/μL n (%)	Vasopressin	2/21 (9.5)	3/21 (14.3)	2/16 (12.5)	4/10 (40)
	Norepinephrine	3/21 (14.3)	4/21 (19)	3/18 (16.8)	3/12 (25)
Platelets <30,000/μL n (%)*	Vasopressin	0/21 (0)	0/21 (0)	0/16 (0)	0/10 (0)
	Norepinephrine	3/21 (14.3)	2/21 (9.5)	2/18 (11.1)	1/12 (8.3)

Data are given as mean values ± SD.
PT = prothrombin time; aPTT = activated partial thromboplastin time; vWF:Ag = von Willebrand Factor Antigen; RCoF = ristocetin Co-Factor.
* Significant group effect; † significant baseline difference between groups; ‡ significant time effect; § significant effect versus baseline.

Table 3. Results of Modified Thrombelastogpaphy Analysis in Vasopressin and Norepinephrine Patients

	NV	Groups	0 h (n = 42)	1 h (n = 42)	24 h (n = 34)	48 h (n = 22)
ExTEG®						
CT (s)*	(<50)	Vasopressin	44 ± 16	39 ± 10	39 ± 10	48 ± 16
		Norepinephrine	36 ± 18	35 ± 17	48 ± 30	48 ± 7
CFT (s)	(<180)	Vasopressin	149 ± 142	145 ± 117	139 ± 109	180 ± 160
		Norepinephrine	133 ± 86	134 ± 107	122 ± 67	97 ± 46
MCF (mm)	(53–74)	Vasopressin	54 ± 15	56 ± 14	53 ± 13	57 ± 9
		Norepinephrine	53 ± 12	54 ± 13	50 ± 11	49 ± 13
InTEG®						
CT (s)	(<160)	Vasopressin	191 ± 65	201 ± 57	225 ± 61	217 ± 44
		Norepinephrine	185 ± 76	195 ± 73	189 ± 68	180 ± 100
CFT (s)	(<180)	Vasopressin	139 ± 136	133 ± 130	201 ± 213	181 ± 160
		Norepinephrine	157 ± 162	173 ± 215	198 ± 187	206 ± 58
MCF (mm)	(53–74)	Vasopressin	61 ± 15	60 ± 15	55 ± 18	51 ± 13
		Norepinephrine	55 ± 13	56 ± 15	50 ± 16	60 ± 10
FibTEG®						
MCF (mm)	(6–16)	Vasopressin	24 ± 12	26 ± 14	22 ± 10	18 ± 8
		Norepinephrine	19 ± 7	22 ± 8	29 ± 28	22 ± 5

Data are given as mean values ± SD.
NV = normal values; CT = clotting time; CFT = clot formation time; MCF = maximum clot firmness.
* Significant difference between study groups at baseline. There were no significant differences between groups, nor significant changes during the study period.

coagulation variables between patients receiving a combined AVP and NE infusion when compared to patients receiving NE infusion alone. A longer prothrombin time in AVP patients during the study period was attributable to a significant baseline difference between groups. Accordingly, clotting time in ExTEG® analysis was significantly longer in AVP patients at baseline. Although there was no significant difference between study groups, platelet count significantly decreased in patients receiving AVP therapy.

Lacking effects of a continuous AVP infusion on plasmatic coagulation tests in this study are in contrast to known clinical effects of AVP and its analogue, desmopressin, on the coagulation system. Physiologically, V_2-receptor stimulation induces hemostatic effects by liberation of vWF:Ag, Factor VIII, and tissue

type plasminogen activator from the endothelium and bone marrow (15). Accordingly, comparable dosages of AVP, as used in this protocol, significantly increased plasma concentrations of Factor VIII and vWF:Ag in healthy volunteers (16). However, in our study, patients with advanced vasodilatory shock associated with severe MODS, AVP infusion did not affect plasma concentrations of Factor VIII, vWF:Ag, or RCoF. In MODS, where endothelial dysfunction is prominent (17), impairment of endothelial synthesis and depletion of endogenous stores of Factor VIII and vWF may explain the lacking effects of AVP. Precedent exposure to drugs which stimulate and activate the endothelium may have resulted as well in depletion of endothelial vWF:Ag and Factor VIII stores, irrespective of endothelial dysfunction. Additionally, extensive coagulation active treatment administered to these study patients with severe MODS may have masked AVP-induced changes of the plasmatic coagulation system. Therefore, the results of the present study may only be considered valid for patients with severe MODS requiring extensive coagulation active treatment, such as fresh-frozen plasma, thrombocyte concentrates, coagulation factors, continuous veno-venous hemofiltration, or heparin.

Although differences between groups were not significant, platelet count significantly decreased during AVP infusion but never reached values less than 30,000/μL. This finding corresponds with recent data on decreases in platelet count in patients with advanced vasodilatory shock receiving a combined infusion of AVP and NE (5). In contrast, in healthy subjects, the AVP analogue desmopressin was even shown to increase platelet count by platelet expulsion from the bone marrow (18). However, according to this study, such an AVP-mediated increase in platelets does not seem to exist in critically ill patients with advanced vasodilatory shock and MODS, where dysfunction of the hematopoietic bone marrow has been reported (19).

Interestingly, however, although platelets significantly decreased during AVP therapy, modified thrombelastography did not show differences in global coagulation between groups. Considering smaller platelet counts in AVP patients, one would expect maximum clot firmness, reflecting platelet number and function in thrombelastography, to be smaller. However, maximum clot firmness was not different between study groups, indicating comparable clot stability and platelet function in AVP- and NE-treated patients. A possible explanation for this observation could be that the decrease in platelet count in AVP patients was compensated by an AVP-mediated increase in platelet aggregation (6). Stimulation of V_1-receptors on the platelet membrane activates the phosphatidyl-inositol-cascade leading to an increase in cytoplasmatic calcium and stimulation of platelet forming and aggregation (20,21).

As a limitation of this study, one has to be aware of the problematic interpretation of the results in view of coagulation active treatment in many study patients. Whereas there was no difference in administration of fresh-frozen plasma, clotting factors, antithrombin concentrates, continuous veno-venous hemofiltration, and heparin infusion, NE patients received significantly more thrombocyte concentrates than AVP patients. This finding, resulting from the fact that significantly more NE patients had a platelet count $<$30,000/μL, might be a possible explanation for the observed decrease in platelets in AVP patients during the study period. To evaluate the influence of this significant difference in platelet transfusion between groups on platelet count, we excluded all study patients who received platelets during the study period from the original analysis and recalculated the same model. Again, no significant difference between study groups was detected, whereas platelets significantly decreased during the study period in AVP patients. Thus, it is obvious that factors other than a significant difference in platelet transfusion (e.g., AVP-induced platelet aggregation) are responsible for the decrease in platelet count in AVP patients.

Another major limitation of this study is the fact that the majority of patients (95%) were on continuous veno-venous hemofiltration resulting from acute renal failure. Since activation of the plasmatic coagulation system and induction of thrombocytopathy is a well known complication of extracorporeal circulation (22,23), the frequent use of continuous veno-venous hemofiltration in this study population might have modulated the effects of AVP on the coagulation system, in particular platelet count and function.

In conclusion, a combined AVP and NE infusion in advanced vasodilatory shock with severe MODS does not increase plasma concentrations of Factor VIII, vWF:Ag, and RCoF but may stimulate platelet aggregation and induce thrombocytopenia. However, platelets do not decrease to less than 30,000/μL without affecting clot formation and hemostasis when compared with patients receiving NE infusion alone. Therefore, AVP infusion must not be withheld from patients with refractory cardiocirculatory failure because of considerations of adverse effects on the coagulation system.

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