Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: Incidence and risk factors*

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Objective: **To report on the incidence and risk factors associated with the development of ischemic skin lesions (ISL) in critically ill patients with catecholamine-resistant vasodilatory shock treated with a continuous infusion of arginine-vasopressin (AVP).**

Design: **Retrospective analysis.**

Setting: **Twelve-bed general and surgical intensive care unit in a university hospital.**

Patients: **A total of 63 critically ill patients with catecholamine-resistant vasodilatory shock.**

Interventions: **Continuous AVP infusion.**

Measurements and Main Results: **Demographic, hemodynamic, laboratory data, and skin status were evaluated 24 hrs before and during AVP therapy (24 and 48 hrs). Patients were grouped according to development of new ISL during AVP therapy. A mixed-effects model was used to compare groups. A multiple logistic regression analysis was used to identify independent risk factors for the development of ISL. ISL developed in 19 of 63 patients (30.2%). Thirteen of 19 patients (68%) developed ISL in distal limbs, two patients (10.5%) developed ISL of the trunk, four patients (21%) developed ISL in distal limbs and in the trunk. Five patients (26%) had additional ischemia of the tongue. Body mass index, preexistent peripheral arterial occlusive disease, presence of septic shock, and norepinephrine requirements were significantly higher in patients developing ISL. ISL patients received significantly more units of fresh frozen plasma and thrombocyte concentrates than patients without ISL. Preexistent peripheral arterial occlusive disease and presence of septic shock were independently associated with the development of ISL during AVP therapy.**

Conclusions: **ISLs are a common complication during continuous AVP infusion in patients with catecholamine-resistant vasodilatory shock. The presence of septic shock and a history of peripheral arterial occlusive disease are independent risk factors for the development of ISL. (Crit Care Med 2003; 31:1394–1398)**

KEY WORDS: vasopressin; ischemic skin lesions; disseminated intravascular coagulation; vasodilatory shock; septic shock; peripheral arterial occlusive disease

Ischemic skin lesions (ISL) are a severe complication in critically ill patients who may deteriorate to symmetrical peripheral gangrene, necessitating surgical debridement and even amputation of ischemic limbs (1). Although the pathophysiology of ISL is still unclear, an association with cardiocirculatory shock of different etiologies and disseminated intravascular coagulation (DIC) has been suggested (2–4). ISLs have also been reported as adverse events in patients receiving high dosages of vasopressor catecholamines (e.g., norepinephrine, epinephrine, and dopamine) (5–8). Golbranson et al. (9) referred to the need of multiple limb amputations in four hypotensive patients treated with continuous high dosages of dopamine to stabilize hemodynamics.

Currently, catecholamines are the vasopressor agents usually infused to treat severe hypotension in volume-resuscitated patients with vasodilatory shock. However, development of catecholamine resistance due to excessive vasodilatation and adrenergic receptor down-regulation may become a serious clinical problem. Arginine-vasopressin (AVP) is an alternative, powerful vasopressor agent that is increasingly used in catecholamine-resistant vasodilatory shock (10–12). Continuous AVP infusion has been shown to significantly increase mean arterial pressure and decrease heart rate, mean pulmonary arterial pressure, and norepinephrine requirements in critically ill patients with septic or postcardiotomy shock (11).

However, development of ISLs has also been reported during AVP therapy (e.g., in patients with upper gastrointestinal bleeding) (13, 14). So far, no data on incidence and risk factors for the development of ISL in patients with catecholamine-resistant vasodilatory shock who were subsequently treated with a continuous AVP infusion have been reported in the literature. Therefore, we retrospectively analyzed incidence and possible risk factors for development of ISL during continuous AVP infusion in 63 patients with catecholamine-resistant vasodilatory shock.

MATERIALS AND METHODS

Between January 1998 and June 2001, all medical records of a 12-bed general and sur-

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gical intensive care unit were reviewed for patients receiving a continuous infusion of AVP (Pitressin, Parke Davis, Berlin, Germany) because of catecholamine-resistant vasodilatory shock.

In our institution, catecholamine resistance is defined as a failing effect of a stepwise increase of norepinephrine by 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over a 2-hr period to keep mean arterial pressure at >60 mm Hg. All patients investigated were invasively monitored, including a pulmonary artery catheter, and volume-resuscitated according to the response of stroke volume index to volume infusion. AVP infusion was given continuously with dosages ranging from 4 to 6 units/hr. No bolus injections were used. After initiating AVP, infusion norepinephrine therapy was targeted to maintain mean arterial pressure at ≥60 mm Hg in all patients. Norepinephrine was not completely withdrawn in any patient. AVP infusion was continuously reduced and tapered off when norepinephrine requirements fell below a dosage of 0.3–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

As part of the daily routine at our institution, the skin is inspected in detail in every patient. Every significant change of skin status is photographically documented and archived with exact description of location and time of development within the patients' charts. In addition, changes in skin status are examined and discussed twice daily during ward rounds. Medical records, including daily reports of patients skin status and digital photographs (EOS D30, Canon, Vienna, Austria) of skin lesions of all patients receiving continuous AVP infusion, were reviewed for documentation of ISL during AVP therapy. ISLs were defined as the occurrence of new areas of mottled or livid skin in one or more body areas of the patient.

To assess risk factors for development of ISLs, the following data were collected from all patients: Demographics included age, sex, body mass index, admission diagnosis, preexistent diabetes mellitus, peripheral arterial occlusive disease, coronary artery disease or history of arterial hypertension, presence of postcardiotomy shock, systemic inflammatory response syndrome or septic shock, the Simplified Acute Physiologic Score within the first 24 hrs, dosage and length of AVP infusion, and intensive care unit mortality. Systemic inflammatory response syndrome and septic shock were defined according to the definitions of the American College of Chest Physicians/Society of Critical Care Medicine (15). Postcardiotomy shock was defined as progressive low systemic vascular resistance with or without low cardiac index after cardiac surgery necessitating vasopressor and, occasionally, inotropic therapy.

The following data were collected during 24 hrs before initiation of AVP infusion: cumulative numbers of fresh frozen plasma and thrombocyte concentrates infused, highest norepinephrine requirements, lowest mean arterial pressure and cardiac index, worst values of prothrombin time, partial thromboplastin time, fibrinogen concentrations, and multiple organ dysfunction syndrome score.

During AVP therapy, cumulative requirements for transfusion of fresh frozen plasma and thrombocyte concentrates, norepinephrine requirements at 24 and 48 hrs after start of AVP infusion, and a multiple organ dysfunction syndrome score (16) at 24 and 48 hrs after start of continuous AVP infusion were recorded.

Statistical Analysis. Patients' characteristics were compared between ISL and non-ISL patients with the use of chi-square test, Fisher's exact test, or Mann-Whitney U rank-sum test, as appropriate. Repeated measurements were analyzed using a mixed-effects model (SAS PROC MIXED, SAS Institute, Cary, NC) to account for death-related dropouts (17). All variables univariately associated with ISL were entered into a multiple logistic regression model. The final model identified two variables with predictive value for the incidence of ISL during continuous AVP infusion. Adjusted odds ratios and a 95% confidence interval were calculated to represent the relative risk of the predictive variables; p values of <.05 were considered statistically significant. Data are given as median values and range.

RESULTS

During the observation period, 63 patients (men, n = 40; women, n = 23) with catecholamine-resistant vasodilatory shock were treated with continuous AVP infusion (median dosage, 0.0009 $units \cdot kg^{-1} \cdot min^{-1}$; range, 0.0001–0.0022 $units \cdot kg^{-1} \cdot min^{-1}$) for a median period of 53 hrs (range, 2–308 hrs). Median age was 70 yrs (range, 28–83 yrs), median multiple organ dysfunction syndrome score was 11 points (range, 8–13 points). Fifteen patients were in vasodilatory shock associated with systemic inflammatory response syndrome, 21 patients in septic shock, and 27 patients in postcardiotomy shock. Overall intensive care unit mortality of the study population was 63%.

During AVP infusion, ISL developed in 19 of 63 patients (30.2%) (Fig. 1). Thirteen of 19 patients (68%) developed ISL in distal limbs, two patients (10.5%) developed ISL in the trunk, four patients (21%) developed ISL in distal limbs and the trunk. Five patients (26%) had additional ischemia of the tongue (Fig. 2).

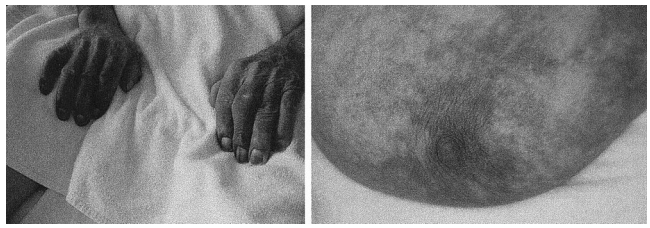

Figure 1. Ischemic skin lesions of the hands (*left*) and of the breast (*right*) during continuous arginine-vasopressin infusion in catecholamine-resistant vasodilatory shock.

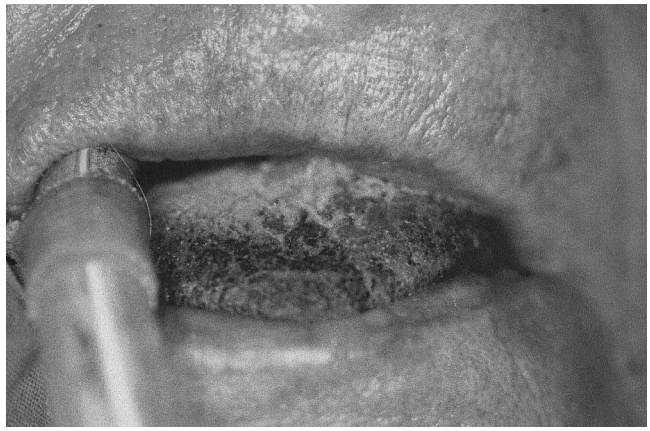

Figure 2. Ischemic lesions of the tongue during continuous arginine-vasopressin infusion in catecholamine-resistant vasodilatory shock.

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Neither amputation of limbs nor plastic surgical interventions were performed in any of the study patients developing ISL during their intensive care unit stay.

Table 1 presents results of univariate analysis concerning demographic data, premorbidity, incidence of systemic inflammatory response syndrome, septic shock and postcardiotomy shock, admission SAPS, and intensive care unit mortality. Body mass index and preexistent peripheral arterial occlusive disease were significantly higher in patients developing ISL during AVP therapy. Patients with ISL had less systemic inflammatory response syndrome, but a significantly higher incidence of septic shock.

Table 2 presents results of univariate analysis concerning clinical and laboratory data 24 hrs before and 24 and 48 hrs after start of AVP therapy. There were no significant differences in hemodynamics, coagulation variables, number of fresh frozen plasmas, or thrombocyte concentrates infused 24 hrs before initiation of AVP infusion between study groups. Norepinephrine requirements 24 and 48 hrs after initiation of AVP were significantly higher in patients developing ISL during continuous AVP infusion. ISL patients received significantly more units of fresh frozen plasma and thrombocyte concentrates during the first 48 hrs of AVP therapy. There were no differences in AVP dosages and length of AVP infusion between study groups.

Results of the multiple logistic regression analysis are presented in Table 3. Presence of septic shock and preexistent peripheral arterial occlusive disease were significant independent risk factors for the development of ISL during continuous AVP infusion in catecholamine-resistant vasodilatory shock.

Table 1. Results of univariate analysis of demographic data, premorbidity, incidence of systemic inflammatory response syndrome (SIRS), septic shock, postcardiotomy shock, admission Simplified Acute Physiology Score (SAPS), and intensive care unit (ICU) mortality

	ISL Patients n (%); median (Range)	Patients Without ISL n (%); Median (Range)	*p* Value
No. of patients	19 (30.2)	44 (69.8)	
Demographics			
Men	10 (52.6)	30 (68.2)	
Women	9 (47.4)	14 (31.8)	.266
Age, yrs	71 (33–83)	70 (28–80)	.554
BMI	26.5 (18.5–55.4)	24.2 (14.8–35.2)	.049[a]
Diabetes mellitus	6 (31.6)	9 (20.5)	.353
PAOD	4 (21.1)	1 (2.3)	.026[a]
Coronary artery disease	16 (84.2)	28 (63.6)	.139
Hypertension	15 (78.9)	31 (70.5)	.552
SIRS	0 (0)	15 (34.1)	.003[a]
Septic shock	10 (52.6)	11 (25)	.044[a]
Postcardiotomy shock	9 (47.4)	18 (40.9)	.782
SAPS	15 (4–28)	14 (6–25)	.934
ICU mortality	16 (84.2)	27 (61.4)	.086

ISL, ischemic skin lesions; BMI, body mass index; PAOD, peripheral arterial occlusive disease.
[a]Significant group effect.

Table 2. Results of univariate analysis of clinical and laboratory data 24 hrs before start of arginine-vasopressin (AVP) therapy and during continuous AVP infusion at 24 and 48 hrs

	ISL Patients n (%); Median (Range)	Patients without ISL n (%); Median (Range)	*p* Value
No. of patients	19 (30.2)	44 (69.8%)	
24 hrs before AVP infusion			
FFP	5 (9–10)	0 (0–26)	.112
TC	0 (0–2)	0 (0–2)	.837
NE, $\mu g \cdot kg^{-1} \cdot min$	0.67 (0.25–4.86)	0.65 (0.11–6.9)	.708
MAP	45 (40–65)	50 (40–60)	.513
SVR	700 (380–1485)	715 (347–2118)	.815
CI	2.4 (1.5–3.7)	2.6 (1.6–6.2)	.367
PT, %	53 (17–70)	54 (27–92)	.228
PTT, secs	56 (33–100)	53 (36–153)	.312
Fibrinogen, mg/dL	308 (77–772)	364 (50–698)	.958
AT III, %	54 (22–97)	54 (29–97)	.847
Thrombocytes, 1000 cells/mL	113 (24–399)	117 (11–486)	.463
MODS score	10 (7–12)	10 (6–12)	.459
During AVP infusion			
FFP after 24 hrs	5 (0–27)	0 (0–11)	.077
TC after 24 hrs	0 (0–2)	0 (0–2)	.112
FFP after 48 hrs	5 (0–37)	0 (0–15)	.030[a]
TC after 48 hrs	0 (0–6)	0 (0–3)	.034[a]
NE after 24 hrs, $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.45 (0.1–3.7)	0.34 (0.1–3.5)	.047[a]
NE after 48 hrs, $\mu g \cdot kg^{-1} \cdot min^{-1}$	0.38 (0.1–2.21)	0.22 (0.1–12)	.005[a]
MODS score 24 hrs	11 (6–12)	10 (5–13)	.143
MODS score 48 hrs	11 (6–12)	10 (6–13)	.122
AVP, $units \cdot \mu g^{-1} \cdot min^{-1}$	0.001 (0.0001–0.0021)	0.0009 (0.0003–0.0021)	.970
Length of AVP infusion	53 (6–308)	55.5 (2–277)	.988

ISL, ischemic skin lesions; FFP, fresh frozen plasma; TC, thrombocyte concentrate; NE, norepinephrine requirements; MAP, mean arterial pressure; SVR, systemic vascular resistance; CI, cardiac index; PT, prothrombin time; PTT, partial thromboplastin time; AT III, antithrombin III; MODS score, multiple organ dysfunction syndrome score.
[a]Significant group effect.

DISCUSSION

In this retrospective analysis, 30% of patients treated with AVP because of catecholamine-resistant vasodilatory shock developed ISL. Preexistent peripheral arterial occlusive disease and presence of septic shock proved to be independent risk factors for development of ISL during continuous AVP infusion.

AVP, a physiologic hormone of the neurohypophysis, is a potent vasopressor agent. AVP-induced arteriolar vasoconstriction is primarily mediated by stimulation of vascular smooth muscle V_1-receptors due to an increase of cytoplasmic ionized calcium via the phosphatidyl-inositol-bisphosphonate cascade (10). In vasodilatory shock, additional vasoconstrictive mechanisms such as antagonism of the inducible nitric oxide synthase, inhibition of activated ATP/potassium channels, and reversal of adrenergic receptor down-regulation have been discussed (11). AVP-mediated vasoconstriction is expressed the most in the skin (18). Therefore, AVP has even been used to reduce intraoperative blood loss during surgical repair of burn wounds (19, 20).

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Table 3. Results of multiple regression analysis

Variables	ISL Patients n (%)	Patients Without ISL n (%)	Odds Ratio	95% CI	*p* Value
Sepsis	10 (52.6)	11 (25)	3.46	1.004–12.14	.049[a]
PAOD	4 (21.1)	(2.3)	12.02	1.006–143.74	.049[a]

ISL, ischemic skin lesions; CI, confidence interval, PAOD, peripheral arterial occlusive disease.
[a]Significant group effect.

Sixty-eight percent of ISLs were observed to occur in distal limbs; 26% exhibiting ISL showed additional ischemia of the tongue. Although lingual ischemia has been reported after chemotherapy (21) or as a complication of giant cell arteritis (22), it has never been described in critically ill patients receiving vasopressor drugs including AVP.

Interestingly, we found no significant relationship between AVP dosages or length of infusion and the development of ISL. In addition, only one third of patients receiving continuous AVP developed ISLs. Therefore, ISLs most probably resulted from a specific combination of predisposing factors. High body mass index and presence of peripheral arterial occlusive disease were significantly associated with occurrence of ISLs (Table 1). In addition, preexistent peripheral arterial occlusive disease was an independent risk factor for development of ISLs, increasing the relative risk by a factor of 12 (Table 3). Acrocyanosis and peripheral gangrene have already been shown to occur more frequently in patients with preexisting vascular disorders (23). Therefore, it is conceivable that in critically ill patients with peripheral arterial occlusive disease and vasodilatory shock, AVP-mediated vasoconstriction may significantly exacerbate tissue hypoxia within the skin and tongue.

Presence of septic shock was an independent risk factor for development of ISLs increasing the relative risk by a factor of 3.5. The pathogenesis of ISLs in septic shock is multifactorial and may include the Schwartzmann reaction known as the combination of bacterial endotoxin release, platelet sludging caused by vascular collapse, and DIC (24). Kingston and Mackey (25) suggested five possible pathomechanisms of skin lesions in septic shock: 1) DIC, 2) direct vascular invasion and occlusion by bacteria and fungi, 3) immune vasculitis and immune complex formation, 4) emboli from endocarditis, and 5) vascular effects of toxins. Reinstein and Govindan concluded that DIC was the major pathophysiologic mechanism responsible for peripheral gangrene after systemic infection (26). Therefore, ISLs in critically ill patients have been considered to represent a cutaneous marker of DIC (27).

In this study, patients with ISL had a significantly higher requirement for transfusion of fresh frozen plasma and thrombocyte concentrates, indicating a higher degree of coagulopathy when compared with patients without ISLs (Table 2). The potential risk of vasoconstrictors to induce ISLs during septic shock with DIC is supported by experimental work demonstrating that gangrene can be induced in animals with DIC by administration of norepinephrine. Therefore, thrombotic complications of DIC are more likely to occur in the presence of vasopressor drugs (28). AVP-induced stimulation of thrombocyte aggregation may further facilitate platelet sludging (29).

Several authors consider ISLs in critically ill patients as an expression of severity of the underlying disease (5). In this analysis, we could not demonstrate a significant difference in multiple organ dysfunction syndrome scores between groups. However, there was a tendency toward higher multiple organ dysfunction syndrome scores and mortality in patients developing ISLs (Table 2). The observation that norepinephrine requirements could be reduced significantly less indicates that these patients at least experienced more severe cardiovascular failure.

CONCLUSION

ISLs are a common complication during continuous AVP infusion in patients with catecholamine-resistant vasodilatory shock and multiple organ dysfunction syndrome. Most of the ISLs were located in the distal limbs and the trunk. However, lingual ischemia may develop in up to 20% of patients receiving vasopressor catecholamines and AVP. The presence of septic shock and a history of arterial occlusive disease were the only independent risk factors for the development of ISLs during continuous AVP infusion. Our data support the hypothesis that ISLs are a multifactorial disease. Premorbidity factors and development of severe systemic infection are important contributors for the development of ISLs in catecholamine-resistant vasodilatory shock treated with a continuous AVP infusion.

The presence of septic shock and a history of peripheral arterial occlusive disease are independent risk factors for the development of ischemic skin lesions.

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