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Risk Factors of Vasopressor-Induced Symmetrical Peripheral Gangrene

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Background: Symmetrical peripheral gangrene (SPG) is an uncommon syndrome showing symmetrical gangrene in acral regions without evidence of large-vessel occlusion or vasculitis. Intravenous vasopressors are frequently used to manage hemodynamically unstable patients. There have been few reports about SPG after using inotropics. However, risk factors for SPG have not been extensively studied. Therefore, the objective of this study was to analyze several cases of SPG and identify risk factors for SPG.

Methods: From October 2013 to October 2016, 36 patients with SPG after using vasopressors were included in this study. SPG is an extremely rare disease entity. Therefore, this work was designed as a matched case-control study. For the control group, 42 patients (25 men and 17 women) with similar age, admission department, sex, and vasopressor usage in intensive care unit patients during the same period were selected. Retrospective chart review was performed to identify risk factors within the following categories: medical conditions, vasopressor-related factors, and Sequential Organ Failure Assessment scores.

Results: Differences between the 2 groups concerning medical condition-related variables did not exist. Statistically significant differences were found in intensive care unit duration ($P = 0.0011$) and survival. All vasopressor-related factors were adjusted according to weights of patients. Weight-compensated mean dose of dopamin significantly ($P = 0.028$) affected the occurrence of SPG. Weight-compensated peak dose of norpin, dopamin, and epinephrine also significantly contributed to SPG.

Conclusions: Symmetrical peripheral gangrene is a rare clinical syndrome related with a high mortality and up to 70% of patients who survive require amputation. Several studies have mentioned that there are several factors affecting the result of SPG. Few studies on SPG have been reported and most of them are case reports. In this study, we revealed the influence of vasopressors to the occurrence of SPG, and this was the first matched case-control study based on the analysis of multiple risk factors.

Key Words: gangrene, vasopressor agents, risk factors

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Symmetrical peripheral gangrene (SPG) is a rare condition that is defined as a clinical manifestation of evolving peripheral gangrene of acral areas without evidence of large-vessel occlusion or vasculitis.[1] This condition was first described by Hutchinson in 1891. Most cases of SPG are documented as single-case series.

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A wide range of etiological factors have been reported to be related to the development of SPG. However, the precise pathophysiology of vascular occlusion in SPG remains unclear. Low-flow state is commonly associated with hypercoagulable vasospastic condition, leading to microcirculatory occlusion. The pathogenesis of SPG may involve bacterial endotoxin release and platelet plugging in peripheral arterioles due to vascular collapse and disseminated intravascular coagulation (DIC).[2] Although up to 85% of SPG cases are linked to DIC, other factors, such as severe hypotension, septic shock, endothelial damage, and antiphospholipid syndrome, might also affect SPG development.

Recently, usage of vasopressor has been increased because they are essential for managing hemodynamically unstable hypotensive patients, such as critically ill patients with cardiogenic or septic shock.[3,4] Most vasopressors affect the contraction of peripheral vasculature. They might induce peripheral ischemic conditions and play an important role in the development of SPG.[5,6]

Although a few studies have reported SPG after vasopressor use, risk factors for SPG have not been extensively studied. Therefore, the objective of this study was to assess the risk factors for SPG, especially focusing on different types of vasopressors and their optimal levels.

METHODS

A retrospective review was performed for SPG patients included in databases. All patients with necrotic change of acral regions who were referred to our department were included in the experimental group. Between October 1, 2013, and October 30, 2016, 36 SPG patients (23 men and 13 women) with evidence of ischemia and gangrene of extremities were included for analysis. Symmetrical peripheral gangrene is an extremely rare disease entity. Hence, this work was designed as a matched case-control study. For the control group, 42 patients (25 men and 17 women) with similar age, admission department, sex, and vasopressor usage in intensive care unit (ICU) patients during the same period were selected.

Data were collected from all patients to assess the risk factors. They were divided into the following categories: (1) medical condition, including demographics, admission diagnosis, preexisting diabetes mellitus, history of arterial hypertension, septic shock, DIC, myeloproliferative disease, hypothermia, immunosuppressive drug use, malignancy, renal failure, and ICU mortality; (2) vasopressor-related factors, such as types and duration of vasopressors used, weight-compensated mean dose (WCMD), and weight-compensated peak dose (WCPD); and (3) sequential organ failure assessment (SOFA) scores for all patients to assess the medical condition of critically ill patients and identify SPG risk factors. The SOFA score was introduced in 1996.[7] It can quantify the severity of a patient's illness based on the degree of organ dysfunction measured over time. The SOFA score is composed of scores from the following 6 organ systems: respiratory (PaO_2/FiO_2), renal (serum creatinine or urine output), hepatic (serum bilirubin), cardiovascular (hypotension), hematologic (platelet count), and neurologic systems (Glasgow Coma Scale) (Table 1). Each system was graded from 0 to 4 points according to degree of dysfunction. Unlike other scoring systems, such as Simplified Acute Physiology Score II or Acute Physiology and Chronic

TABLE 1. SOFA Score System[1]

	0	1	2	3	4
Respiratory: PaO_2/FiO_2, mm Hg	>400	≤400	≤300	≤200	≤100
Renal: Creatinine or urine output, mg/dL	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500 mL/d	≥5.0 or <200 ml/d
Hepatic: bilirubin, mg/dL	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	≥12.0
Cardiovascular: hypotension	No HTN	MAP < 70 mm Hg	Dopamine ≤ 5 or dobutamine (any dose)	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Hematologic: platelet count, $\times 10^3/mm^3$	>150	≤150	≤100	≤50	≤20
Neurologic: Glasgow Coma Scale	15	13–14	10–12-	6–9	<6

1. Peres Bota D et, al. The Multiple Organ Dysfunction Score (MODS) versus the Sequential Organ Failure Assessment (SOFA) score in outcome prediction. Intensive Care Med. 2002 Nov;28(11):1619–24.

Health Evaluation II system, SOFA focuses on organ dysfunction and morbidity with less emphasis on mortality prediction.

Statistical Analysis

R language ver. 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses. Statistical significance was considered at a P value less than 0.05. Regarding medical condition-related variables, descriptive statistics by each group are presented for all subjects. For continuous variables, median value and range are presented. Numbers and ratios of subjects were used to describe categorical variables. Concerning comparison between groups, Wilcoxon rank sum test was used for continuous variables, whereas χ^2 test was used for categorical variables.

For vasopressor-related variables, median value, and range compensated with weight are presented. Wilcoxon rank sum test was used or comparison between groups because it was in zero-inflated form with a lot of 0 values by additionally using permutation method. Logistic regression analysis was performed to identify factors affecting SPG. Univariable logistic regression analysis was first implemented to analyze each factor. Multivariable logistic regression analysis was then conducted for factors showing significance effects in univariable analysis.

RESULTS

During the study period, 36 patients (23 men and 13 women) with SPG were referred to our department. Their mean age was 60 years (range, 23–95 years). Of these patients, 35 were treated in the ICU with a multidisciplinary approach. Of these 36 patients, 13, 20, and 3 were attended by neurosurgery, internal medicine, and general surgery departments, respectively. Admissions were because of intracranial hemorrhage (ICH) (n = 6), sepsis (n = 4), and pneumonia (n = 26). The overall ICU mortality of the study population was 91%. All patients experienced gangrenous changes involving distal portions of 2 or more limbs after vasoconstrictor therapy just before or during the occurrence of gangrene (mean duration until SPG after vasopressor: 1.23 days).

During the same period, 42 patients (25 men and 17 women) were included in the control group. Their mean age was 64.6 years (range, 15–96 years). All patients were treated in the ICU with a multidisciplinary approach. Of these 42 patients, 20, 18, and 4 were attended by internal medicine, neurosurgery, and general surgery departments, respectively. Their overall ICU mortality was 78%.

Medical Condition of Patients

Differences between the 2 groups concerning medical condition-related variables were reviewed. Statistically significant differences were found in ICU duration ($P = 0.0011$) and survival ($P < 0.0001$) (Table 2A and 2B). However, there were no significant differences in other variables between the 2 groups. Results of logistics regression analysis showed that medical condition was not significantly different between the 2 groups (Table 3).

Vasopressors

During the observation period, 5 different kinds of vasopressors were used: norepinephrine, dopamine hydrochloride, dobutamine hydrochloride, vasopressin, and epinephrine. All vasopressor-related factors were adjusted according to weight of patient. The most frequently used vasopressor was norepinephrine. It was used in 59 (76%) patients. The second most frequently used drug was dopamine hydrochloride. It was used in 36 (46%) patients. During the observation period, a mean of 1.84 (range, 0–4) vasopressors were used in the study population and a mean of 1.46 vasopressors were used in control group.

In univariable logistic regression, the duration of usage (period) of all vasopressors showed no significant difference between the 2 groups (Table 4). However, WCMD of dopamin significantly

TABLE 2A. Baseline Characteristics (Continuous Variables)

	Non-SPG Patients (N = 42)		SPG Patients (N = 36)		
	Median	Range	Median	Range	*P*
Age	72.5	15–96	68	1–97	0.5374
ICU duration	10	4–32	18	3–105	0.0011*
Weight	59	35–78	59.3	1.04–76	0.3134

*$P < 0.05$.

TABLE 2B. Baseline Characteristics (Categorical Variables)

	Non-SPG Patients (N = 42)		SPG Patients (N = 36)		
	N	%	N	%	*P*
Sex					0.8716
Male	25	59.52	23	63.89	
Female	17	40.48	13	36.11	
Survival					<0.0001*
Yes	9	22.00	3	8.33	
No	33	78.00	33	91.67	

*$P < 0.05$.

TABLE 3. Summary of Medical Condition

	Non-SPG Patients (N = 42)		SPG Patients (N = 36)		
	N	%	N	%	*P*
HTN					0.8474
No	23	54.76	18	50.00	
Yes	19	45.24	18	50.00	
DM					0.3479
No	32	76.19	23	63.89	
Yes	10	23.81	13	36.11	
LF					1.0000
No	39	92.86	34	94.44	
Yes	3	7.14	2	5.56	
SLE					1.0000
No	41	97.62	35	97.22	
Yes	1	2.38	1	2.78	
Hematologic Disease					0.7188
No	37	88.10	33	91.67	
Yes	5	11.90	3	8.33	
CKD					0.2341
No	36	85.71	26	72.22	
Yes	6	14.29	10	27.78	
Heart Disease					0.2089
No	37	88.10	35	97.22	
Yes	5	11.90	1	2.78	
CVA					0.9542
No	29	69.05	26	72.22	
Yes	13	30.95	10	27.78	

*$P < 0.05$.

HTN, hypertension; DM, diabetes mellitus; LF, liver failure; SLE, systemic lupus erythematosus; CKD, chronic kidney disease; CVA, cerebrovascular accident.

(P = 0.0285) affected the occurrence of SPG. The WCPD of norpin, dopamin, and epinephrine also significantly contributed to SPG. Weight-compensated peak dose of norpin, dopamin, and epinephrine showed statistically significant difference between SPG and non-SPG groups (P = 0.0004, P = 0.0236, and P = 0.0220, respectively) (Table 4, Fig. 1). Results of Wilcoxon rank sum test and permutation rank sum test were generally similar for all variables tested. In multivariable analysis, WCPD of dopamin also showed significantly increased odds of SPG (odds ratio, 1.202; 95% confidence interval, 0.037–1.662; P = 0.024).

SOFA Scores

The SOFA scores were obtained to reflect the function of each organ. Statistical analysis showed that cardiovascular, hematologic, and neurologic functions were significantly different between the 2 groups. Mean SOFA scores for the case group and control group were 13.5 and 5.45, respectively. Statistical analysis showed that SOFA score could significantly (P = 0.002) predict the incidence of SPG in ICU patients (Table 5).

DISCUSSION

Symmetrical peripheral gangrene is a rare clinical syndrome characterized by bilateral distal limb gangrene in the absence of major vascular occlusive disease. It is associated with high mortality rate (up to 40%).[7–9] Up to 70% of the patients who survived SPG require amputation of the affected limb.[8] Our results revealed that medical baseline factors had no significant effect on the occurrence of SPG. However, ICU duration and survival were significantly higher in SPG group compared with those in the control group. Longer ICU duration might indicate that the medical condition of the patient is severe, thus increasing the possibility of unstable hemodynamics. Together with other underlying conditions, the amount and duration of vasopressor use were investigated to determine their effects on the occurrence of SPG. Vasopressor has been known as a major cause of SPG. The possibility of vasopressor-related SPG has increased. Therefore, this study investigated how vasopressors influenced SPG and determined the risk factors for SPG.

Currently, this is no consensus on the maximum vasopressor dose or duration for treating hemodynamically unstable patients. These are not even mentioned in the Survival Sepsis Campaign guidelines.[10,11] Survival Sepsis Campaign guidelines only recommend dopamine and norepinephrine as first-choice vasopressors for managing hypotension in septic shock with epinephrine as second-line agent for maintaining MAP ≥ 65 mm Hg.[12]

Vasopressors have different pharmacodynamic mechanisms. Their pharmacodynamic profiles have specific inotropes functioning with their individual receptor activities and mechanisms (Table 6). Adrenergic receptors are traditionally divided into α and β (subdivided into α_1, α_2, β_1, β_2, and β_3).[13] Dopamine has 3 distinct actions depending on dosage. Low doses in the range of 1 to 2 μg/kg per min will result in vasodilatation. Moderate doses of 2 to 10 μg/kg per minute will increase cardiac output due to beta adrenergic action. High doses at more than 10 μg/kg per minute will act as a potent alpha-adrenergic vasoconstrictor that might result in SPG.[14] The development of gangrene has been reported in patients with DIC and hypovolemia at dopamine dosages of 5.1 to 10.2 μg/kg per minute.[15]

Symmetrical peripheral gangrene related to infusion rate has been rarely reported. Our results revealed that the duration of usage with any vasopressor had no effect on the occurrence of SPG. In the present study, patients in the SPG group were administered with dopamine at a mean dose of 176.3 μg/kg per minute and norepinephrine at 24.0 μg/kg per minute. The non-SPG group patients were administered dopamine at 43.7 μg/kg per minute and norepinephrine at 5.28 μg/kg per minute. The mean dose of vasopressors used in the SPG group was 8.82 times more than the upper limit dose for dopamine and 48 times more than the upper limit dose for norepinephrine. However, peak dose rather than duration of drug usage might be a more important vasopressor-related factor. After adjusting for patient's weight, the peak dose of norpin, dopamin, or epinephrine was revealed as a significant factor that influenced the occurrence of SPG. In contrast, the peak dose of dobutamin or vasopressin did not significantly influence SPG. Regarding mean dose, only that of Dopamin significantly contributed to the occurrence of SPG. To the best of our knowledge, this is the first study that assesses the influence of vasopressors on SPG depending on their concentrations.

The SOFA score describes the sequence of complications in critically ill patients. It has been used to predict mortality and morbidity. Based on results of this study, it can be concluded that SOFA score might have predictive value for SPG. Automatic SOFA score calculation is available with little modification of the current database system. This could help prevent the occurrence of SPG. An interdisciplinary approach is warranted to prevent SPG when a patient's SOFA score is increased.

In a clinical situation, SPG should be suspected at the first sign of marked coldness, pallor, cyanosis, or pain in extremities during usage of inotropics. Signs of inadequate skin perfusion should be closely monitored. When needed, skin microcirculation should be assessed using noninvasive techniques, such as capillaroscopy, laser Doppler flowmeter, and transcutaneous measurement of oxygen tension, because the condition can progress rapidly.[16] Preoccupation with distal ischemic changes should be avoided and attention should

TABLE 4. Summary of Logistic Regression With Vasopressor-Related Factors

	SPG Patients (N = 36)		Non-SPG Patients (N = 42)			
	Median	**Range**	**Median**	**Range**	***P****	***P*†**
Duration of norpin	2	0–13	0.5	0–32	0.0234‡	0.0231‡
Duration of dopamin	0	0–46	0	0–12	0.3206	0.3179
Duration of vasopressin	0	0–2	0	0–2	0.2473	0.4623
Duration of dobutamin	0	0–6	0	0–3	0.0881	0.0866
Duration of epinephrine	0	0–2	0	0–2	0.0193‡	0.0280‡
WCMD of norpin	0.042	0–0.416	0.005	0–0.169	0.1128	0.1116
WCMD of dopamin	0	0–1.618	0	0–1.299	0.0285‡	0.0281‡
WCMD of vasopressin	0	0–0.014	0	0–0.010	0.2332	0.3096
WCMD of dobutamin	0	0–0.197	0	0–0.347	0.1073	0.1057
WCMD of epinephrine	0	0–0.017	0	0–0.004	0.0211‡	0.0115‡
WCPD of norpin	0.044	0–0.894	0.000	0–0.267	0.0004‡	0.0004‡
WCPD of dopamin	0	0–3.299	0	0–1.667	0.0236‡	0.0232‡
WCPD of vasopressin	0	0–0.014	0	0–0.014	0.2425	0.4623
WCPD of dobutamin	0	0–0.313	0	0–0.347	0.0692	0.0509
WCPD of epinephrine	0	0–0.017	0	0–0.007	0.0220‡	0.0134‡

	Univariable Model			
	OR	**Lower CI**	**Upper CI**	***P***
Age	0.995	0.976	1.015	0.6268
ICU duration	1.095	1.035	1.176	0.0063‡
Weight	0.974	0.937	1.009	0.1623
Sex				
Female	0.831	0.328	2.078	0.6929
Duration of norpin	0.989	0.878	1.099	0.8270
Duration of dopamin	0.950	0.827	1.036	0.3559
Duration of vasopressin	0.594	0.103	2.109	0.4569
Duration of dobutamin	0.679	0.388	1.018	0.1025
Duration of epinephrine	0.304	0.068	0.947	0.0676
WCMD of norpin	0.010	0.000	9.222	0.2182
WCMD of dopamin	1.129	0.027	2.405	0.0022‡
WCMD of vasopressin	0.000	0.000	Inf	0.5061
WCMD of dobutamin	0.015	0.000	30.097	0.3135
WCMD of epinephrine	0.000	0.000	0.000	0.0807
WCPD of norpin	1.010	0.000	1.087	0.0162‡
WCPD of dopamin	1.199	0.057	2.492	0.0024‡
WCPD of vasopressin	0.000	0.000	Inf	0.6392
WCPD of dobutamin	0.000	0.000	0.634	0.0802
WCPD of epinephrine	1.000	0.001	2.000	0.0674

**P* values of Wilcoxon rank sum test.

†*P* values of permutation rank sum test.

‡$P < 0.05$.

be focused on correcting the underlying cause(s) of ischemic phenomenon.[17] Up to date, there is no relevant consensus for treatment of SPG. A few case reports are available on treating SPG using pentoxyfyilline, antiplatelet agents, systemic hyperbaric oxygen therapy, epoprostenol, tissue plasminogen activator, sildenafil citrate, or topical nitric oxide ointment therapy.[18–21] In the present study, immediate workup, including CT angiography, was performed to rule out major vessel occlusion. Patients were treated with tapering vasopressors and prostaglandin E1.

This study has some limitations. First, a limited number of patients was included. Selection bias might have occurred. Considering the high mortality rate of patients with SPG, peripheral vasoconstriction that usually occurs in hemodynamically unstable patients might inevitably lead to SPG at the end of life. Patients in this study used a mean of 1.84 (range, 0–4) vasopressors during the observation period. These vasopressors might have additive effects on SPG development. However, we could not analyze cases in which 2 or more vasopressors were used. An interaction or synergetic effect between drugs might have occurred. We were unable to assess toe perfusion pressure at our institute because we did not have a skin-perfusion oximetry instrument. Hence, we could not compare toe perfusion pressure with data available in the literature.

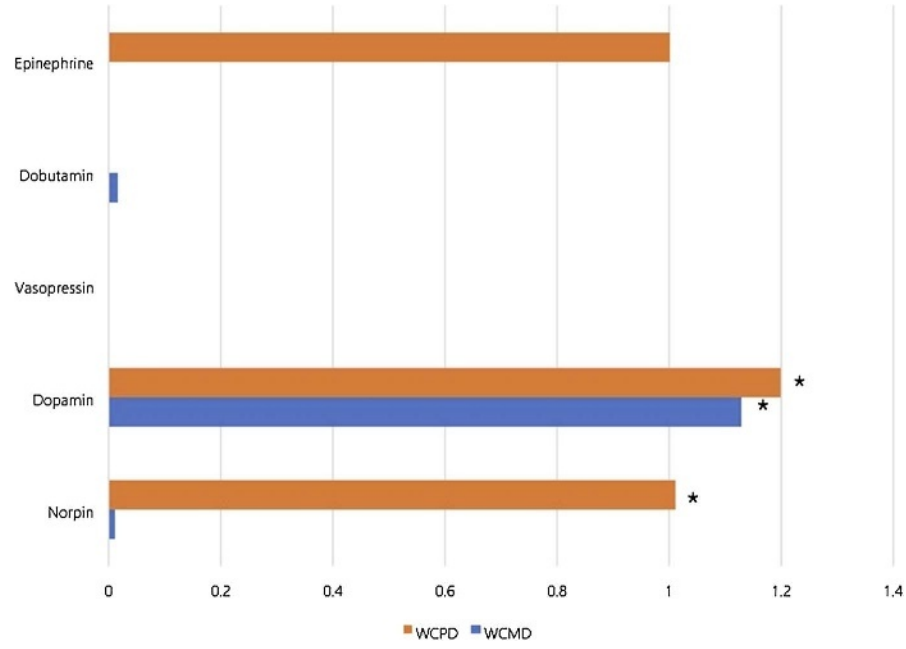

FIGURE 1. Comparison of odds ratio between groups in univariate analysis. WCPD of norpin, dopamin, and epinephrine showed statistically significant difference between SPG and non-SPG groups ($P = 0.0004$, $P = 0.0236$, and $P = 0.0220$) and WCMD of Dopamin showed significant difference ($P = 0.0285$).

TABLE 5. SOFA Scores

Organ System	Groups	Mean	Range	*P*
Respiratory: PaO_2/FiO_2, mm Hg	Case	203.9	52–385	0.163
	Control	285.5	66–894	
Renal: creatinine or urine output, mg/dL	Case	1.7	1–3	0.913
	Control	1.9	0–7	
Hepatic: bilirubin, mg/dL	Case	1.03	0–2	0.091
	Control	0.64	0–2	
Cardiovascular: hypotension	Case	55.6	40–64	0.001
	Control	88.8	57–116	
Hematologic: platelet count, $\times 10^3/mm^3$	Case	98.2	50–199	0.002
	Control	196	33–333	
Neurologic: Glasgow Coma Scale	Case	6.8	5–10	0.025
	Control	10.9	3–15	

Few studies on SPG have been reported. Most of them are case reports. This was the first matched case-control study based on the analysis of the medical condition of patients. However, prospective, multicenter, randomized, and controlled studies are needed in the future to further explore the etiology, clinical presentation, and appropriate treatment of this serious illness.

CONCLUSIONS

Symmetrical peripheral gangrene can occur as a complication in critically ill patients. Several vasopressor-related risk factors for the occurrence of SPG were found in this study, including WCMD of dopamin and WCPD of Norpin, dopamin, and epinephrine. The SOFA score had a predictive value for the occurrence of SPG. It could help medical staff make better decisions when administering vasopressors. Early intensive treatments with a multidisciplinary approach are required to reduce life-threatening complications of SPG

TABLE 6. Receptor Activity, Physiologic Effects and Dose of Vasopressors and Inotropes

Drug	$\alpha/\beta_1/\beta_2$ Receptor	Cardiac Output	Heart Rate	SVR	MAP	PVR	Bolus Dose	Infusion Dose
Epinephrine	++/++/++	↑	↑	↑	↑	0	5–10 μg, up to 1 mg for cardiac arrest	0.02–0.3 μg/kg per min
Norepinephrine	+++/++/0	0	0	↑	↑	↑	No bolus dosing	0.05–0.5 μ/kg per min
Dopamine	++/++/0	↑	↑	↑	↑	0	No bolus dosing	1–20 μg/kg per min
Dobutamine	0/+++/+	↑	↑	↓	↓	↓	No bolus dosing	2–20 μg/kg per min
Vasopressin	0/0/0	0	0	↑	↑	0	0.5–2 units for mild hypotension, 20 units	0.1–0.4 μ/min

Vasopressors and Inotropes, Josh Zimmerman, Michael Cahalan, Pharmacology and Physiology for Anesthesia, Chapter 22, 390–404.

Effects vary significantly with dose and between individuals.

Increasing levels of stimulation of adrenergic receptors are represented by +, ++, +++.

MAP, mean arterial pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

with high mortality rates and high frequency of multiple limb amputations in surviving patients. This was the first study that determined risk factors for SPG.

REFERENCES

1. Suárez-Amor O, Casado-Arroyo R, Cabanillas M, et al. Symmetrical peripheral gangrene and disseminated intravascular coagulation associated with pneumococcal sepsis. *Actas Dermosifiliogr*. 2009;100:334–335.
2. Tripathy S, Rath B. Symmetric peripheral gangrene: catch it early! *J Emerg Trauma Shock*. 2010;3:189–190.
3. Hollenberg SM. Vasoactive drugs in circulatory shock. *Am J Respir Crit Care Med*. 2011;183:847–855.
4. Jentzer JC, Coons JC, Link CB, et al. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. *J Cardiovasc Pharmacol Ther*. 2015, 20:249–260.
5. Symmetrical Peripheral Gangrene. www.ePlasty.com, *Interesting Case*, July 2, 2012.
6. Ghosh SK, Bandyopadhyay D, Ghosh A. Symmetrical peripheral gangrene: a prospective study of 14 consecutive cases in a tertiary-care hospital in eastern India. *J Eur Acad Dermatol Venereol*. 2010;24:214–218.
7. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707–710.
8. Ghosh SK, Bandyopadhyay D. Symmetrical peripheral gangrene. *Indian J Dermatol Venereol Leprol*. 2011;77:244–248.
9. Molos MA, Hall JC. Symmetrical peripheral gangrene and disseminated intravascular coagulation. *Arch Dermatol*. 1985;121:1057–1061.
10. Sharma L, Mehta S, Rajaram S, et al. Postpartum peripheral symmetrical gangrene: a case report. *J Reprod Infertil*. 2012;13:117–119.
11. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med*. 2008;34:17–60.
12. Skin necrosis after high dose vasopressor infusion in septic shock. *Korean J Crit Care Med*. 2012;27:182–186.
13. Zimmerman J, Cahalan M. Vasopressors and inotropes. *Pharmacol Physiol Anesth*. Chapter 22. Philadelphia, PA: Elsevier, Inc; 390–404.
14. Stetson JB, Reading GP. Avoidance of vascular complications associated with the use of dopamine. *Can Anaesth Soc J*. 1977;24:727–733.
15. Barriere SL, Hudson LD, Huseby JS. Gangrene and dopamine. *Ann Intern Med*. 1977;86:366–367.
16. Kim EH, et al. Skin necrosis after a low-dose vasopressin infusion through a central venous catheter for treating septic shock. *Korean J Intern Med*. 2006;21:287–290.
17. Parmar MS. Symmetrical peripheral gangrene: a rare but dreadful complication of sepsis. *CMAJ*. 2002;167:1037–1039.
18. Liao CY, Huang SC, Lin CH, et al. Successful resolution of symmetrical peripheral gangrene after severe acute pancreatitis: a case report. *J Med Case Rep*. 2015;9:213.
19. Stewart S. Symmetrical peripheral gangrene and the use of systemic hyperbaric oxygen therapy. *J Wound Care*. 2012;21:615–616, 618–9.
20. Hayes MA, Yau EH, Hinds CJ, et al. Symmetrical peripheral gangrene: association with noradrenaline administration. *Intensive Care Med*. 1992;18:433–436.
21. Gandhi V, Sharma R, Raizada A, et al. Peripheral symmetrical gangrene treated with sildenafil citrate. *J Cutan Aesthet Surg*. 2012;5:57–58.