Management of vasopressor induced ischemia

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ABSTRACT

Purpose: We evaluated a cohort of patients who developed vasopressor-induced limb ischemia and the management options to prevent progression or minimize morbidity of digital necrosis.

Methods: We reviewed all current literature on pressor-induced limb ischemia and report options for the management of patients requiring vasopressors who developed limb ischemia. We then retrospectively reviewed presentation, treatment, and short-term outcomes for patients at our tertiary referral academic medical center that developed this complication. Finally, we recommend guidelines for the tiered management of these complex patients.

Results: Thirty-six patients were included. Twenty-six patients (72%) required resuscitation with more than one vasopressor. Vasopressors were initiated for septic-shock (52.7%), cardiogenic-shock (16.7%), hypovolemic-shock (13.9%), acute transplant rejection (13.9%), and neurogenic-shock (2.8%). According to the tiered management recommendations, patients were managed with phase 1 care (19%), phase 2 care (8.3%), phase 3 care (50%) or phase 4 care (5.6%). The patient expired in the acute setting in 13.9% of cases.

Conclusion: Life-saving vasopressors risk digital ischemia and necrosis. Early recognition, reporting, and treatment of this complication are important in minimizing morbidity. Using a tiered approach helps organize the healthcare team's management of this iatrogenic complication while respecting the treatment paradigm of "life over limb," and may be safely performed with acceptable outcomes.

1. Introduction

Severe sepsis (acute organ dysfunction secondary to infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) pose significant problems to the healthcare system, affecting millions of individuals around the world each year, killing one in four (and often more), and increasing in incidence.^{1–3} Shock is the primary cause of admission and death in the intensive care unit. Mortality exceeds 50% with most deaths caused by multiple organ failure related to progressive hypotension despite hemodynamic support.^{3–7} In the absence of myocardial dysfunction, hypotension is predominantly caused by hypovolemia and inability for the physiologic response to self-regulate and achieve proper tissue perfusion.^{6,8} According to current guidelines, fluid replacement and vasopressor infusion, both guided by hemodynamic monitoring, must be titrated in order to increase mean arterial pressure to 65 mmHg and possibly to higher levels for patients with chronic hypertension.¹ Although these strategies can be life saving, the use of vasopressors is not always benign. Vasopressors can cause

significant vasospasm with potential ischemia to multiple areas of the body including the upper and lower extremity limbs.^{2,9–17}

The use of vasopressors is often essential to maintain perfusion to critical organs such as the brain and heart, hence, it cannot be discontinued without potentially compromising the patient's life. However, upper and lower extremity limb ischemia can markedly compromise a patient's future functional status and quality of life.¹⁸ Although a well-known problem caused by potentially lifesaving vasopressor use, there is a paucity of literature evaluating the possible ways to manage or prevent vasopressor induced limb ischemia. Hence, we aimed to (1) evaluate a cohort of patients who developed vasopressor induced limb ischemia, identifying the phases of care, (2) determine an algorithm to potentially aid medical personnel in managing these patients.

2. Methods

We performed a systematic literature review for studies describing treatment options for vasopressor-induced acral cyanosis. We queried

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the electronic databases Medline, Embase and Ovid for all relevant studies published from Jan 1980 to until April 2019 using the following search permutations to include the Boolean search strings of “limb” AND “ischem*” OR “necrosis” AND “vasopressor” OR pressor”, which revealed an initial 643 studies. The abstracts and titles of these initial studies were reviewed by two authors ML and JJJ with the following criteria that included studies published in English, level of evidence I through IV, and that evaluated patients who were managed for vasopressor limb ischemia or necrosis. Of the studies that met this inclusion criteria we later reviewed the manuscript, which was performed by JJJ, RAP, and WAE to determine the specific methods to manage these patients. We then stratified these methods according to extent of involvement and duration of presentation determining that patients could be managed in 4 phases which are classified as follows (Fig. 1 and Table 1).

Phase I – Early noninvasive measures: Limited digital involvement or patients too unstable for higher levels of intervention.

Phase II – Procedural rescue: Multiple digits affected or macroscopic vessel involvement in patients able to tolerate procedural intervention.

Phase III – Harm minimization: Prevent additional damage and soft tissue loss through ablative procedures designed at achieving stable soft tissue coverage in patients with mature necrosis.

Phase IV – Late reconstruction: Reconstructive measures for patients with high functional demands following full recovery.

The second part of this study was performed after obtaining proper Institutional Review Board approval (IRB number: HP-00083777). We retrospectively evaluated a consecutive cohort of patients in whom the orthopaedic department at tertiary referral academic medical center was consulted for evaluation of developing, or developed, vasopressor-

induced necrosis. Patients were included in our study if they were exposed to vasopressors. Patients who were not exposed to vasopressors, those who did not have limb ischemia, and those in whom acrocyanosis was explained by another etiology (e.g. cold agglutinin disease¹⁹) were excluded from our study. Extracted data included basic demographic information, underlying primary diagnosis, duration of symptoms, presence of arterial lines in any of the extremities, type of vasopressor, number of limbs and digits affected (Table 2.), intervention utilized (divided by phases), and outcome at latest follow-up. In all patients, in addition to clinical evidence of necrosis, one of several methods was utilized to confirm vasopressor induced necrosis (Table 3). After removing patient identifiers, all data was inputted into an Excel spreadsheet (Excel, Microsoft Corporation, Redmond, Washington) for initial formulation; subsequent statistical analysis was then performed with Graph Pad Prism version 5.01 (GraphPad Software Inc., La Jolla, California).

3. Results

A total of 36 patients, of which 56% were female (n = 20) and with a mean age of 56 years (range, 28–92 years) were included in our final cohort. The reasons for necessitating vasopressor support were multifactorial in many cases; the primary factor driving vasopressor initiation was septic shock in 19 patients (52.7%), cardiogenic shock in 6 patients (16.7%), hypovolemic shock in 5 patients (13.9%), acute transplant rejection in 5 patients (13.9%; 4 lung, 1 renal), and neurogenic shock in 1 patient (2.8%). Comorbidities were considered, as they may influence the vascular health of patients prior to acute insult. Review of medical records revealed that 12 patients (33.3%) were diagnosed with diabetes

Fig. 1. Diagram with stages of disease and phases of care.

Table 1
Protocol for management of vasopressor-induced ischemia.

Protocol for management of vasopressor-induced ischemia			
Phase I:			
Elevation			
Splint			
Bair Hugger			
Remove Radial/Brachial Artery Line			
Nitro Paste (topical nitroglycerin)			
Topical Amrinone			
Adjust Vasopressors If Possible			
Botox (50 units - dose)			
Nerve block			
Non-Invasive vs. Invasive Vascular Studies, Duplex, CT angiogram, Angiography			
Phentolamine (extravasation)			
Subcutaneous Terbutaline			
Phase II:			
Fasciotomies			
Mechanical Vasodilation with Intra Arterial Heparin, Tissue Plasminogen Activator (TPA), Papaverine, Lidocaine (Topical)			
Resection of Thrombosed/Damage Radial Artery with			
Mechanical Vasodilation and Irrigants			
Repair of Vessel/Radial Artery			
Brachial with Thrombectomy			
Phase III:			
Amputation			
Coverage-Groin			
Paraumbilical Perforator (PUP) Flap			
First Dorsal Metacarpal Artery (FDMA) Flap			
Web Space Deepening			
Digital Lengthening			
Phase IV:			
Prosthesis			
Hand transplantation			

Table 2
Talley of digits and extremities that developed vasopressor induced ischemia.

Upper Limb			
Extremity	Right	Left	Total
Whole Hand	15	11	26
First finger (thumb)	26	17	43
Second finger	23	22	45
Third finger	24	20	44
Fourth finger	21	17	38
Fifth finger	20	15	35
Total fingers*	189	146	335
Lower Limb			
Extremity	Right	Left	Total
Whole foot	12	14	26
First toe	12	16	28
Second toe	14	18	32
Third toe	12	17	29
Fourth toe	12	18	30
Fifth toe	12	16	28
Total toes*	122	155	277

*This sum also includes all 5 digits if the whole extremity was lost.

mellitus (DM), 7 (19.4%) with coronary artery disease (CAD), 5 (13.9%) with deep vein thrombosis/pulmonary embolism (DVT/PE), 3 (8.3%) with heparin induced thrombocytopenia and thrombosis (HITT), 2 (5.6%) with Raynaud's syndrome. Regarding additional social factors that could have influenced our studied event, 18 (50%) reported a history of smoking and 3 (8.3%) had a documented history of IV drug abuse. Multiple vasopressors were utilized for resuscitation, with norepinephrine (Levophed) being the most commonly used agent. Twenty-six patients required resuscitation with more than one vasopressor. Length of vasopressor exposure prior to documented ischemia

Table 3
Tests to evaluate perfusion to hand.

Tests to evaluate perfusion to hand	
Doppler ultrasound (audio-only)	
Color Doppler ultrasonography	
Digital plethysmography (pulse volume recordings)	
Radial-brachial index = 1.0	
Digital-brachial index = 1.0	
Less than 0.7 is abnormal, compromising healing of ulcers, wounds Less than 0.4 indicates impending cell death (hand or digital ischemia) From 0.7 to 1.0 indicates arterial flow compromise	
Color duplex imaging	
Oxygen saturation (Greater than 90% on room air; compare with contralateral side)	
Skin surface temperature determination (approximately 30° C)	
Laser Doppler fluxmetry	
Cold stress testing (Hands exposed to cool air or water (5–8C))	
Laser Doppler perfusion imaging	
Vital capillaroscopy	
Scintigraphy	
Magnetic resonance angiography	
Computed tomography angiography	
Arteriogram	

averaged 7.9 days (range 0–48). Time from the first documentation of ischemia to documentation of consult note was within 1 day in 67% of cases (range, 0–24 days). Arterial lines were present in 31 ischemic limbs (25 radial and 6 femoral) and were thought to be directly responsible for ischemia in 7 limbs. In these 7 cases, thrombosis occurred and ischemia was isolated to a single limb. Although *phase I* care was initiated, in all these patients a thrombectomy was needed, which successfully resulted in return of perfusion.

Seven patients were managed with *phase I* care alone, with resolution of symptoms of limb ischemia. Three patients were definitively managed with *phase II* care, while 18 patients necessitated additional interventions and care was progressed to *phase III* care with partial amputation. Two patients (3 limbs) were treated with hand transplantation (phase 4). Definitive treatment plans are pending for 1 patient.

The 30-day amputation rate for our overall cohort was 22.2%. The entire hand was reported to be ischemic in 26 cases, with hand amputation required in 17 cases (65.4%). A total of 335 fingers in our cohort developed this condition (including those digits in which the entire hand was involved). Amputation was performed to manage 130 (38.8%) of these digits. Eighteen patients (50%) underwent an amputation procedure. Amputation was limited to individual digits in 4 patients, while multi-limb amputation was required in 14 patients (Table 4). Five

Table 4
Talley of digits and extremities that required amputation.

Upper Limb			
Extremity	Right	Left	Total
Whole Hand	10	7	17
First finger (thumb)	4	4	8
Second finger	6	6	12
Third finger	6	6	12
Fourth finger	6	6	12
Fifth finger	5	5	10
Total fingers*	77	62	139
Lower Limb			
Extremity	Right	Left	Total
Whole foot	10	11	21
First toe	0	0	0
Second toe	0	0	0
Third toe	0	0	0
Fourth toe	0	0	0
Fifth toe	0	0	0
Total toes*	50	55	105

*This sum also includes all 5 digits if the whole extremity was lost.

Table 5
Study population demographics and treatment details.

Variable	Pressor necrosis patients (n = 36)
Age (years)	56 (± 16.2)
Sex	16 (44.4%)
Male	20 (55.5%)
Female	
Vasopressor usage	10 (27.7%)
One agent	26 (72.2%)
More than one agent	7.9 (± 10.7)
Days of pressor use	
BMI (kg/m ²)	29.8 (± 5.6)
Smoking Status	18 (50%)
Former	18 (50%)
Never	
Diagnosis requiring pressor initiation	19 (52.7%)
Septic shock	6 (16.7%)
Cardiogenic shock	5 (13.9%)
Hypovolemic shock	5 (13.9%)
Acute transplant rejection	1 (2.8%)
Neurogenic shock	
Medical comorbidities	
Diabetes mellitus	12 (33.3%)
Coronary artery disease	7 (19.4%)
Deep vein thrombosis/pulmonary embolism	5 (13.9%)
Heparin induced thrombocytopenia and thrombosis	3 (8.3%)
Raynaud's syndrome	2 (5.6%)
Intravenous drug abuse	3 (8.3%)
Phase used for definitive management	7 (19.4%)
Phase I	3 (8.3%)
Phase II	19 (52.8%)
Phase III	2 (5.5%)
Phase IV	

patients expired in the acute period before definitive management of the affected limb could be determined (see Table 5).

We present below four selected cases. While the presentations below are widely variable, the same approach to care was taken in addressing each, and each required a different phase of care for definitive management.

The first case is that of an eighty-one year-old male with a history of coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD) and hypertension who suffered a C6–C7 fracture dislocation injury and developed neurogenic shock. He underwent surgical intervention and was started on norepinephrine in order to maintain adequate spinal perfusion. The day following initiation of vasopressors, the patient's hand demonstrated color change consistent with ischemia and the orthopaedic team was consulted due to concern for decreased perfusion throughout his left hand. Phase 1 care was initiated. A Bair Hugger (3 M Bair Hugger; St. Paul, Minnesota) was applied to the affected limb, and the limb was elevated. A peripheral nerve block was performed. Perfusion returned to the limb with no residual perfusion deficits.

The second case we present is that of a thirty-five year-old female with a history of liver transplantation for sclerosing cholangitis. She underwent urgent C-section due to rising creatinine, which was complicated by uterine atony and post-partum hemorrhage. Total abdominal hysterectomy was performed in attempt to manage blood loss. The patient developed disseminated intravascular coagulation (DIC). The patient was started on norepinephrine. She subsequently lost pulses in her right hand. There is no documentation of a recent a-line in the right upper extremity. The orthopaedic team was consulted for management. Given the acuity of presentation, phase 2 management was initiated. A radial artery thrombectomy and dorsal and volar compartment forearm fasciotomy was performed. A heparin drip was initiated, Bair Hugger applied to the affected limb, and the limb elevated. Additionally, a peripheral nerve block was performed. Perfusion was successfully restored to the limb without functional deficit.

The third case is a fifty-six year old female with a history of Diabetes Mellitus (DM), coronary artery disease (CAD), hypertension, and heparin induced thrombocytopenia and thrombosis (HITT). She presented to our institution following NSTEMI in acute respiratory failure. CABG was performed. The patient required ventilator and pressor support with both epinephrine and norepinephrine. An arterial line was placed in the left radial artery. The patient developed ischemic changes in digits 1–4 of her left hand, digits 1 and 3 of her right hand, as well as in toes of both feet. Phase 1 care was initiated. A bair hugger was applied to the ischemic limbs, which were elevated. Nitro paste was applied to the LUE. A botox injection and regional block were performed. Ultimately, the patient was advanced to phase 3 care. Amputation of digits 1–4 was performed on the left hand with soft-tissue obtained from first dorsal metacarpal artery flap. Final management of the right hand is pending, with plan for amputation.

The fourth case is a sixty-one year old female with a history of HITT. She presented to our institution with a viral syndrome. She developed toxic shock syndrome and respiratory failure. She required high dose vasopressor support with both norepinephrine and epinephrine. She was placed on VV ECMO. She developed 4 limb ischemia. Phase one management was initiated. A Bair Hugger was applied to the affected limbs, which were elevated. Unfortunately, her limbs were not able to be saved from necrosis, and she required 4 limb amputation. Following discharge, this patient sought care at an outside hospital in hope of regaining some function of her limbs. Recently, she successfully underwent hand transplantation.

4. Discussion

Necrosis of the extremities is a known risk associated with the use of life-saving vasopressors in critically ill patients. To our knowledge, this is the first study to review a large series and propose tiered management guidelines for patients with ischemic or necrotic appendages. The morbidity associated with vasopressors is significant with 30-day amputation rates reported to range from 10% to 30% and a mortality rate of 15%.²⁰ Our findings were comparable, with a 22.2% 30-day amputation rate and a mortality rate of 13.9%. We believe that morbidity can be minimized and function optimized by early recognition and a structured management strategy.

Phase I –should be implemented in all patients in whom vasopressor induced ischemic changes are noted and it can be utilized by multiple members of the managing team, and not only by hand surgeons.

We recommend as the first phase of management, elevation of the extremity and splinting in attempt to minimize local edema. A Bair Hugger ought to be used in order to warm the affected limb to assist in vasodilation, encouraging blood flow to the compromised area. Arterial lines may injure blood vessels and promote thrombosis; they ought to be removed from the involved extremity if reasonably possible. Vasodilation is paramount and many pharmacologic agents exist that will increase blood to hypo-perfused tissue. Numerous case reports have demonstrated a reversal of ischemia following application of topical nitroglycerin.^{21–23} Amrinone (phosphodiesterase III inhibitor) has been shown to be an effective vasodilating agent in the management of vasospasm in a rat model.²⁴ We recommend the use of phentolamine in the setting of vasopressor extravasation. Phentolamine, an alpha-adrenergic blocking agent, has been shown to be effective in reversing the local vasoconstrictive effect of epinephrine in numerous cases of epinephrine-induced digital ischemia.^{25–28} In addition to topical medications, there is a role for injected medications. Botox injections have demonstrated efficacy in the management of nonhealing ulcers and have been found to increase digital perfusion in patients with vasospastic disease such as Raynaud's Disease.^{29,30} Sympathetic blocks with local anesthetic may improve tissue perfusion as well.^{31–33} Vascular studies such as duplex or CTA may be valuable at this time as well. If it is possible to decrease the dose of vasopressors without putting the patient at risk, then vasopressors ought to be titrated down.

We believe the Phase I interventions we have described are most important as they can be deployed in any hospital setting and require minimal expertise. Early initiation of management as soon as there is suspicion of ischemia is paramount and the importance of this approach can not be overly emphasized. Elevation and warming with Bair hugger are quick, inexpensive and simple interventions that are often overlooked even at our institution. Phase I treatments can be maximized by maintaining a high suspicion of ischemia in any patients getting vasopressors and should be exhausted before moving to Phase II interventions which require more expertise.

If Phase I modalities fail to improve perfusion to ischemic digits, more invasive techniques may be indicated in certain circumstances. Careful assessment is paramount as rapid determination will allow potentially limb-saving management.

Phase II is somewhat more complex and a member of the surgery team (orthopaedic, plastic, or vascular surgery) is needed, but it consists of mechanical interventions to aid in limb reperfusion and to prevent reperfusion injury when indicated.

It is commonly accepted that tissue may be compromised when fascial compartment pressures exceed perfusion pressures. Intuitively, the absolute threshold that compartment pressures must reach in order to inhibit perfusion will be less in a hypotensive patient than in a normotensive patient; consistent with this reasoning is the recommendation that compartment syndrome be defined based on the differential between compartment pressure and diastolic blood pressure.³⁴ Fasciotomies may be necessary to improve blood flow to threatened tissue. Topical lidocaine has been widely shown to promote vasodilation, decrease vasospasm and to absorb rapidly.^{35–37} Similarly, Papaverine has been shown to be effective for management of vasospasm.³⁸

It is important to consider that blood flow may be impaired by a thrombus; thrombosis may occur in association with arterial lines,³⁹ which are ubiquitous in the ICU. In the setting of thrombosis, mechanical vasodilation with intraarterial heparin, TPA or thrombectomy may be used to restore the patency of a vessel. Damaged vessels may be repaired or resected on a case-by-case basis. For patients with threatened limbs, the choice between surgical and endovascular revascularization is primarily based on time to revascularization.⁴⁰

Phase III, the necrosis has been completely established; these interventions aid in improving hand function.

In the cases where digital necrosis cannot be prevented, one must again assess the affected limb and make another determination – how can the function of this limb be maximized? Reconstructive options are considered even prior to amputation and often occur outside of the acute phase. Reconstruction is an arduous course, often requiring many surgeries, but may hope to restore function to a limb. A lengthy discussion must be had with patients when discussing flaps and reconstructive surgery and expectations assessed. Coverage options include the groin flap (superficial circumflex iliac artery perforator flap),⁴¹ paraumbilical perforator flap (PUP),⁴² and first dorsal metacarpal artery flap (FDMA).⁴³ However, a detailed discussion of each flap is beyond the scope of this manuscript. Once adequate coverage has been obtained, web space deepening and digital lengthening may be considered.

Phase IV is the latest phase and can be utilized as the last stage with the ultimate goal of improving function.

In cases where an appendage cannot be salvaged, there are still options for maintaining the function of a patient's limb. Various prostheses have been developed and may be personalized to the patient.^{44,45} In select cases, hand transplant may successfully restore function to a limb,^{46,47} as was the case in 2 of our patients.

Our study has several limitations, which are inherent to the nature of a retrospective case series. Inconsistent quality of documentation limited our ability to definitively track every phase of management; however, to our knowledge this is the largest series of patients who underwent management of vasopressor-induced necrosis. In addition, this study was performed in a specialized level I trauma center with fellowship-trained upper extremity and microvascular surgeons, which

may limit the ability to obtain replicable results. However, phase 1 and 2 of our management algorithm can be utilized to manage patients in the great majority of centers who manage patients necessitating vasopressors.

Life-saving vasopressors risk digital ischemia and necrosis. In order to minimize morbidity, it is critical that providers and nurses in the ICU are attentive to this potential risk and report findings of ischemia early on in the hospital course. A thorough understanding of sequential management is necessary so that this problem may be efficiently and effectively addressed, minimizing morbidity and maximizing the potential function of a patient's limb.

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