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Reconstructive

Achieving Functional Outcomes after Surgical Management of Catastrophic Vasopressor-induced Limb Ischemia

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Background: Vasopressor-induced limb ischemia is an unfortunate complication that can occur in patients treated for septic shock. Current literature lacks surgical treatment recommendations for this condition, besides amputation. We describe various reconstructive surgeries and functional outcomes in patients treated surgically for vasopressor-induced limb ischemia.

Methods: We retrospectively reviewed patients who were treated for septic shock and developed vasopressor-induced limb ischemia at our tertiary referral academic medical center. We reviewed presentation, treatment, surgical outcomes, and long-term functional outcomes.

Results: We present three previously healthy patients who developed gangrene of multiple limbs following the use of vasopressors to treat septic shock. Each patient underwent amputations or limb salvage procedures.

Conclusions: Limb ischemia is a devastating complication that can occur after prolonged vasopressor use. The decision to proceed with limb salvage versus amputation of ischemic extremities should be tailored to the individual patient. The main objective should be for the patient to obtain optimal function and quality of life, regardless of the type of surgery. *(Plast Reconstr Surg Glob Open 2022;10:e4175; doi: 10.1097/GOX.0000000000004175; Published online 7 March 2022.)*

INTRODUCTION

Severe sepsis and septic shock affect millions of individuals around the world each year, and are leading causes of death in the intensive care unit (ICU).[1] Current guidelines to treat septic shock recommend fluid replacement and vasopressor infusion to maintain a mean arterial pressure above 65 mm Hg.[1] Although these strategies can be life-saving, the use of vasopressors is not benign. Vasoactive medications cause significant vasospasm that may lead to irreversible ischemia to multiple areas of the body, including the upper and lower extremities.[2–4]

In reference to the old adage "life over limb," acute limb ischemia (ALI) is often regarded as a tolerable adverse effect of life-saving vasopressor support in ICU patients.[4] Yet, distal necrosis is a limb-threatening condition and can cause a significant morbidity and impact on a person's quality of life. Peripheral gangrene is associated with poor survival in patients, with 30-day amputation rates ranging from 10% to 30% and mortality rates of 15%.[5] In this case series, we present three patients treated in the ICU for septic shock, which resulted in vasopressor-induced ALI (VIALI). We report their initial presentation of limb ischemia, management, and subsequent surgical outcomes. The aim of our study was to review cases of vasopressor-induced limb ischemia and provide recommendations on surgical management that offer the best functional outcomes.

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CASE SERIES

Case 1

A previously healthy 52-year-old woman presented with septic shock secondary to obstructive urolithiasis. She was transferred to our institution for limb salvage after

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developing necrotic bilateral upper and lower limbs following administration of three vasopressors. Preoperative angiogram demonstrated occluded left anterior tibial and posterior tibial arteries, moderate right anterior tibial artery stenosis that occluded at the ankle, and an occluded proximal right posterior tibial artery. She received 32 sessions of hyperbaric oxygen therapy (HBOT). Despite this management, her bilateral feet and hands were irreversibly necrotic and she eventually underwent four-extremity amputation.

For the gangrenous lower extremities, she underwent bilateral Ertl below-knee amputations (BKA) with targeted muscle reinnervation (TMR).[6] Ertl amputation involves creation of a tibiofibular bridge to provide a more stable residual limb; we performed it in this patient because we anticipated she would be fairly active postamputation. Skin necrosis had demarcated at the level of the ankle creases bilaterally. Viable anterior leg tissue distal to the planned BKA incision was used as a free flap to cover the salvageable portions of the bilateral hands (Fig. 1). The gangrenous hands underwent amputation at the metacarpophalangeal (MCP) joints. The myocutaneous free flap from the leg was then transferred to the hand for soft tissue coverage. Two arterial end-to-side anastomoses were performed into the radial artery in the distal forearm via the anterior and posterior tibial arteries. Four venous anastomoses (end-to-end posterior tibial veins to radial venae comitantes, anterior tibial veins to superficial veins in the forearm) were performed.

Two months later, the patient underwent radical debulking and webspace deepening of the bilateral hands. The time from initial presentation to final operation was 11 months. Functionally, the patient is ambulatory using lower limb prostheses. She has some intrinsic hand muscle weakness, but can perform daily tasks using bilateral upper limb prostheses. She is able to flex and extend her wrists to assist with transfers and to don/doff her prostheses.

Takeaways

Question: Vasopressor-induced acute limb ischemia (VIALI) is an unfortunate complication following treatment of septic shock. Treatment has been largely anecdotal and mainly involves amputation of gangrenous limbs. We present our center's surgical algorithm with a focus on limb salvage and return to function.

Findings: We present three patients who developed VIALI following treatment for septic shock. We review their presentations, treatments, and functional outcomes.

Meaning: VIALI can be treated with limb salvage surgery with good functional outcomes. The decision to proceed with limb salvage versus amputation should be individualized to each patient.

Case 2

A 50-year-old woman with no medical history developed four-extremity dry gangrene after being treated for septic shock with three vasopressors for 4 weeks. Both lower limbs underwent serial debridements with amputation of all of her toes in both feet. Preoperative angiogram revealed three-vessel runoff in both legs. She then underwent left transmetatarsal amputations (TMA), which were covered with a free anterolateral thigh (ALT) flap via end-to-side anastomosis to posterior tibial artery and two venous anastomoses. A few days later, she underwent right Chopart's amputation with local flap coverage. Two weeks later, attention was turned toward her upper limbs. A left transradial amputation was covered with a local pronator quadratus flap.

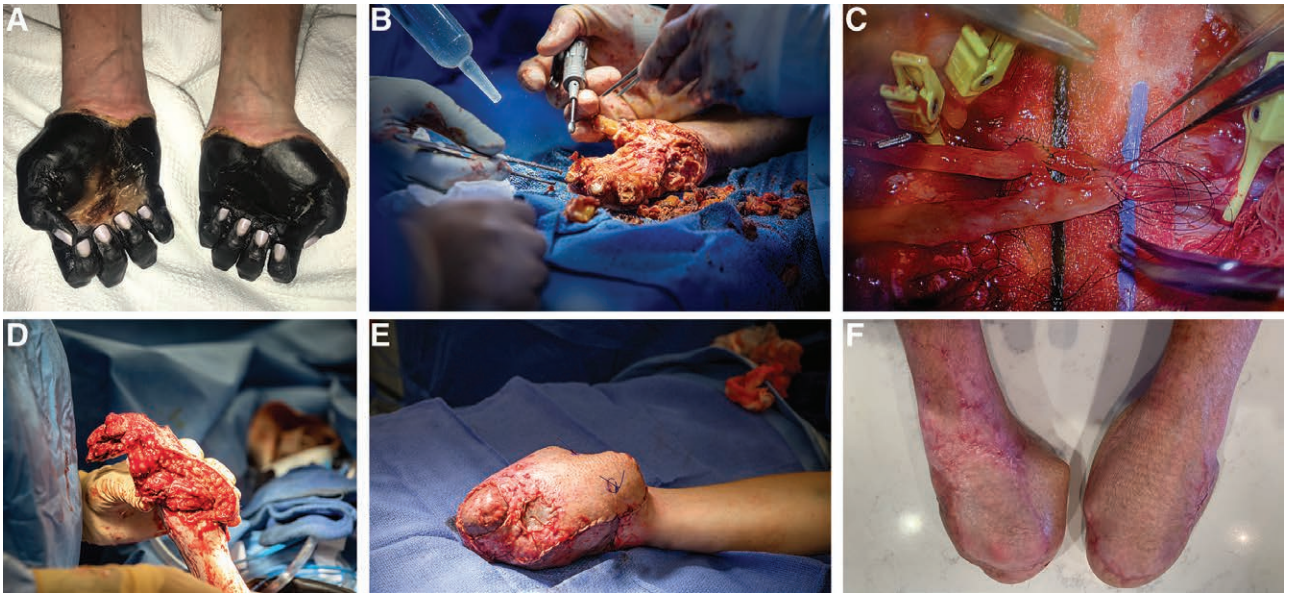

Fig. 1. Case 1: Upper extremity reconstruction. A, irreversibly necrotic bilateral hands. B, amputation at the metacarpophalangeal joints and debridement of necrotic tissue. C, End-to-side arterial anastomoses of the myocutaneous free flap from the leg that was transferred to the hand, an example of a "spare-parts" surgery. D, E, Flap inset into the hand. F, healed bilateral upper extremities.

TMR was performed to prevent painful neuroma formation. Her right hand underwent transmetacarpal amputation using a free groin flap to preserve as much length as possible. Thus, she was able to maintain right wrist extension and flexion.

Unfortunately, the patient developed chronic osteomyelitis at the left TMA site. Over the next year, this wound was serially debrided, and eventually a left TMA revision was performed. One year after her final surgery, the patient can ambulate short distances with bilateral feet orthoses. She reports difficulty using her hand prostheses, but is able to perform light activities around her house. (**See Video 1 [online],** which displays extension and flexion at the wrist level.) She is motivated to become more independent and require less assistance.

Case 3

A previously healthy 57-year-old man presented with four-extremity gangrene after being treated with a prolonged course of three vasopressors for COVID-induced septic shock. He received 10 sessions of HBOT and 3 weeks later, underwent bilateral BKAs with Ertl technique and TMR. The right hand demonstrated stable dry gangrene at the level of the wrist crease. The left hand exhibited full-thickness necrosis of all digits with dry gangrene at the MCP joint level. The distal aspect of his left thumb was gangrenous; however, the left first webspace and thumb MCP joint were spared. Because of the bilateral nature of the injury and the importance of the hand for assistance with ambulation, all efforts were focused on preserving left hand length. The right upper limb underwent transradial amputation. In the left upper limb, necrotic tissue was removed from all digits, which required degloving of the digital skin and preserving any viable bone and flexor tendons. The left proximal phalanges were thus preserved for all digits, but soft tissue was deficient.

To provide coverage of the exposed digits on the left hand, the viable tissue from the right volar forearm (proximal to the line of necrosis and distal to the planned level of transradial amputation) was used as two separate fasciocutaneous flaps. A right radial forearm free flap was used to cover his left thumb. A right ulnar artery flap was used to cover the four nonthumb digits on the left hand that had been surgically syndactylized. Because of the relatively subnormal perfusion of the surrounding tissue, separation of the digits was performed in a lengthy staged fashion. Ten weeks after flap surgery, division of the flap was performed in the third webspace. The patient returned to the OR 14 weeks from the flap surgery for division of his second and fourth web spaces (Fig. 2). Overall, the duration of time from initial presentation to healing was 5 months. The patient is currently ambulatory with use of lower extremity prostheses. The patient reports improvement in activities with his left hand, such as eating, brushing his teeth, and removing his glasses. (**See Video 2 [online],** which displays movement of digits in the hand.) He is considering myoelectric prosthetic options for his right arm. Table 1 summarizes the three cases presented in this series.

DISCUSSION

Multiple limb ischemia is a devastating complication that can occur after prolonged use of vasoactive medications during treatment of septic shock. Vasopressors cause significant vasospasm in peripheral arteries, which may lead to irreversible ischemia in multiple areas of the body, including the upper and lower limbs.[7,8] In patients who survive their ICU stay, VIALI is associated with a significant morbidity and a high risk of amputation.[4]

Ionotropic and adrenergic medications are commonly used to maintain blood pressure in critically ill patients. Several cases of VIALI have been reported after use of norepinephrine, a commonly used first-line vasopressor to treat septic shock.[9–12] Other reports have implicated alpha-adrenergic agonists or inotropes (ie, dopamine) as causative factors.[4,13] Table 2 describes the mechanisms and effective half-lives of common vasopressors. Current guidelines recommend that vasopressor therapy be withdrawn as early as possible to minimize risk of peripheral necrosis.[10] Early recognition of VIALI has a profound impact on the management of the condition and its final outcome.[14] A recent systematic review published by Newbury et al outlined a medical treatment algorithm in cases of vasopressor-induced limb gangrene.[4] However, the surgical management of limb ischemia has been largely anecdotal, mainly involving amputation of necrotic limbs.

Before surgical management of multiple extremity ischemia, patients should be medically optimized. The wounds should be addressed with local wound care while awaiting tissue demarcation. HBOT has been shown to be a valuable adjunct to standard wound care by increasing oxygen supply to wounds.[15,16] All of our patients were treated with HBOT to allow for any viable tissue under the gangrene to recover. Any signs of infection or conversion to wet gangrene should prompt earlier surgical debridement. Once complete tissue demarcation in a gangrenous limb has occurred, serial surgical debridements are performed until negative cultures in the wound bed are achieved. Excisional debridement removes necrotic tissue and promotes granulation tissue formation, both of which are important before consideration of soft tissue coverage. Surgeons must then consider which patients will benefit from limb salvage versus BKA.

Surgical management should be tailored to the individual patient, accounting for his/her baseline functional status, underlying comorbidities, and wound characteristics. A multidisciplinary team approach is imperative to optimize surgical outcomes. Vascular surgeons should perform a preoperative angiogram if there is concern for peripheral vascular disease. If limb salvage is to be performed, podiatric or orthopedic surgeons must perform a biomechanical gait analysis to address any bony instability that could negatively impact a flap's durability and long-term success (Fig. 3). When only one extremity is injured, amputation may be the obvious surgery to perform. Alternatively, in cases of multiple limb ischemia, it is reasonable to consider complex limb salvage reconstruction in at least one extremity to preserve some native function in that limb and mitigate the disability that will occur following amputation of other limbs.

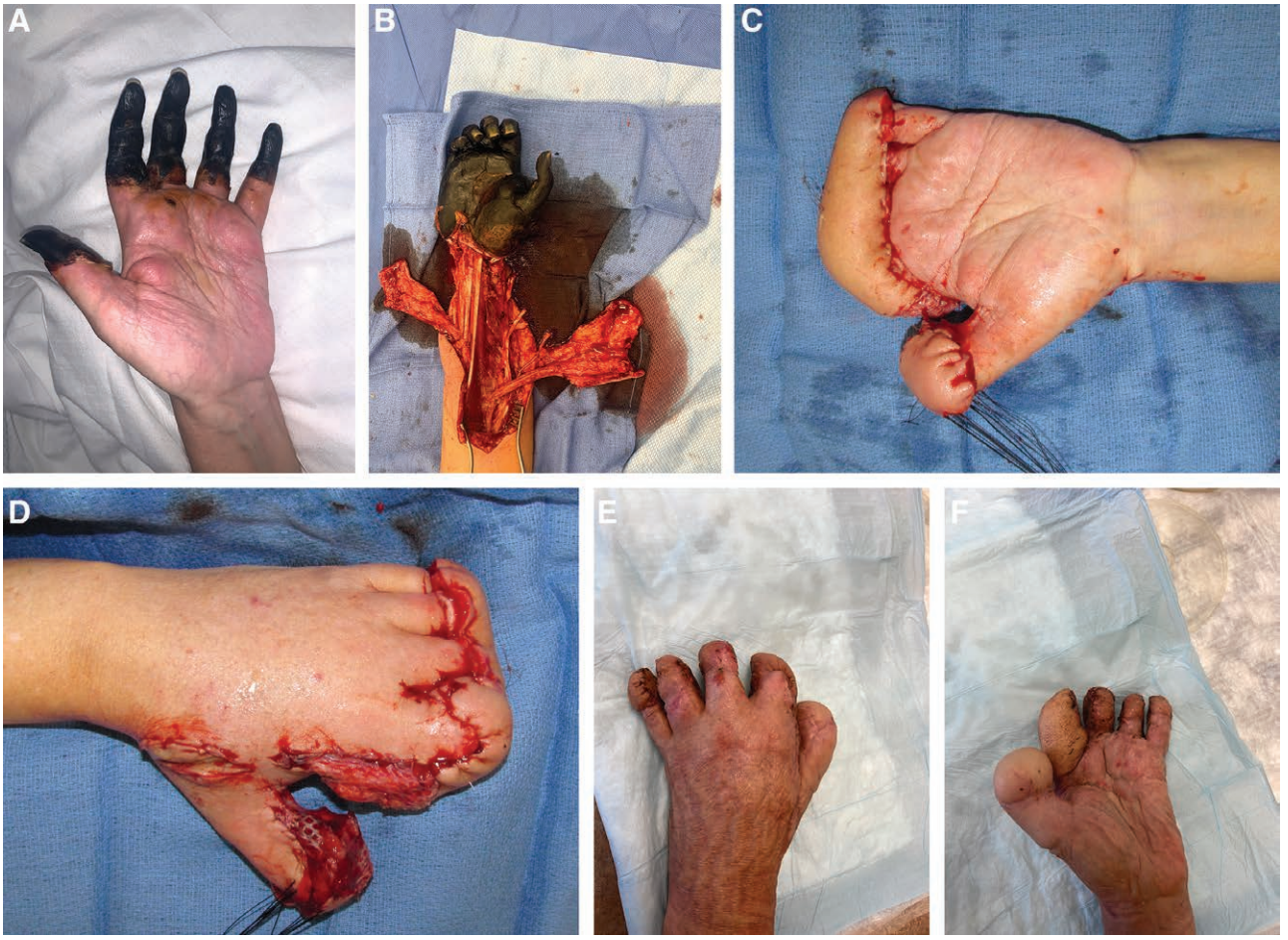

Fig. 2. Case 3 – Left hand. A, necrosis of all digits and distal aspect of the thumb, with sparing of the first webspace and metacarpophalangeal joints. B, Before right transradial amputation, two fasciocutaneous free flaps from the right forearm were harvested to cover the left thumb and digits, an example of a "spare-parts" surgery. C, D, right ulnar forearm free flap provided soft tissue coverage of left thumb, and right radial forearm free flap covered digits 2, 3, 4, 5 of left hand, with split-thickness skin graft from left thigh to left hand. E, F, healing of bilateral hands.

In recent years, advancements in amputation technique and prosthetic design have improved survival rates in amputees who walk with prostheses.[17–20] In our practice, we consider a limb that is biomechanically nonfunctional with an unsalvageable bony framework to be the primary indication for major amputation.[21] While not the focus of this series, multiple reports have cited various benefits and disadvantages of major and minor amputations.[22,23] Preoperatively, patients should be informed that undergoing primary amputation will likely shorten the treatment duration compared with limb salvage surgery. Additionally, select patients may achieve similar or better functional outcomes than salvaging a nonfunctional limb.

TMR is a relatively new surgical technique that has proven effective in preventing pain following limb amputation. Primary TMR involves transferring transected ends of sensory nerves in the amputated limb to motor nerve branches of residual target muscles, allowing the transected axons a pathway for antegrade growth. This has proven effective in preventing symptomatic neuroma and phantom limb pain, and in improving myoelectric prosthesis use.[17,24,25] TMR has been described in the setting of BKAs, shoulder disarticulations, transhumeral, and transradial amputations.[26–28] At our institution, our plastic surgeons perform amputations with TMR. If vascular or orthopedic surgeons are performing the amputations, plastic surgery should be consulted to perform TMR at the time of amputation.

Surgical planning for limb salvage reconstruction should be centered on functional and aesthetic outcomes. In general, flap coverage is the reconstructive choice for wounds with exposed tendons, joints, or bones.[29] Oftentimes, local flap options are quite limited in patients with multiple limb gangrene. Furthermore, local flaps cannot usually bring enough tissue to cover the large wound defects. With continued advances in microsurgery, free tissue transfer has become a reliable reconstructive solution, with high rates of flap success and limb salvage.[30,31]

Two of our cases (1 and 3) involved "spare-parts" surgeries, in which viable skin, soft tissue, and muscle that would otherwise be discarded after an amputation were used to reconstruct another limb.[32] Both patients had a unique pattern of injury and tissue loss, and our team sought to restore as much limb length, function, and

Table 1. Summary of the Surgical Management and Functional Outcomes of Three Cases of Vasopressor-induced Limb Ischemia

Cases	Etiology of Septic Shock	ICU Course	Limb Salvage or Amputation	Reconstruction	Complications	Additional Surgeries	Duration of Treatment	Functional Outcome
Case 1: 52F	Obstructive urolithiasis	3 vasopressors	LE: Bilateral BKA + TMR UE: Bilateral amputation at MCP joints	LE: N/A UE: Spare parts surgery with free flap from anterior leg distal to BKA site	None	Debulking and webspace deepening	11 months	Ambulates with prostheses. Intrinsic hand muscle weakness but performs daily tasks with upper limb prostheses.
Case 2: 50F	Suspected toxic shock syndrome	3 vasopressors for 4 weeks	Left LE: TMA Right LE: Chopart's amputation Left UE: transradial amputation Right UE: transmetacarpal amputation	Left LE: ALT free flap coverage of TMA site Right LE: local flap Left UE: local flap Right UE: free groin flap	Osteomyelitis of left TMA site	Serial debridements, left TMA revision	12 months	Ambulates short distances with bilateral orthoses. Good right wrist extension and flexion. Difficulty using her hand prostheses but can perform light activities around her house.
Case 3: 57M	COVID-19 infection	3 vasopressors	LE: bilateral BKA + TMR Right UE: transradial amputation Left UE: excision of necrotic tissue with salvage of proximal phalanges	LE: N/A Right UE: N/A Left UE: Spare parts surgery with forearm free flap (from right UE) to cover digits	None	Division of surgically syndactylized left hand at third webspace 14 weeks later: division of flap at second and fourth web spaces	5 months	Ambulates with prostheses. Improvement in daily activities with his left hand. Considering myoelectric prosthesis for right arm.

LE: lower extremity; UE: upper extremity

appearance of the patients' limbs as possible, while obviating donor-site morbidity. To our knowledge, this is the first case series to report using "spare-parts" surgery to reconstruct limbs afflicted by VIALI.

Depending on the extent of irreversible necrosis, some patients can undergo minor amputation with subsequent flap coverage. We previously reported our experience with another patient who developed limb ischemia after being treated with vasopressors for septic shock following a prostate biopsy.[33] He underwent bilateral TMA with subsequent ALT free flap coverage. After intense physical therapy, he was able to ambulate. He was highly motivated and fortunate to obtain custom-made upper and lower extremity prostheses, allowing him to function independently. Although bilateral BKAs would have abbreviated his hospital course, limb salvage efforts were extremely valuable in his case. Patients should be informed that reconstructive limb salvage can be an arduous course, often requiring multiple revision surgeries, but ultimately it may restore both form and function of their injured limb.[8] In the cases we presented, treatment duration from initial presentation to limb salvage completion lasted several months.

Multiple studies have reported limb salvage does not always yield substantially improved outcomes.[34] In some cases, patients may incur more complications, more surgeries, and higher healthcare costs.[35] The patient in case 2 underwent bilateral partial foot amputations with flap coverage to salvage her lower limbs, but then developed osteomyelitis at the TMA site. Consequently, she had to undergo several additional surgeries, and is currently only able to walk short distances with lower extremity orthoses. If she had undergone primary BKA, she would likely be functioning independently at this time.

As Brown et al stated, "life salvage" should be prioritized over "limb salvage." The surgeon's objective should be for the patient to obtain optimal function and quality of life regardless of type of surgery.[36] Amputations are currently performed with the intent of restoring a functional limb that is prosthetically optimal. With improvements in amputation technique, TMR, and prosthetic design, BKAs have more predictable functional outcomes compared with limb salvage.[36] Many amputees are able to return to most, if not all, of their preinjury activities.[37] Yet, the impact that undergoing an amputation can have on a patient's physical and psychological well-being should not be minimized.[38,39] Tekin et al compared function and quality of life of healthy patients who underwent BKA with those who received salvage surgery after severe lower limb trauma, and found that reoperation rates, quality of life, and pain scores were better in the BKA group.[40] Similarly, our patients in this series were healthy before developing septic shock and VIALI. Compared with patients with diseased lower extremities secondary to systemic illness, traumatic injuries and VIALI have fewer confounding variables to skew outcome data on BKA or limb salvage.[36]

The decision to proceed with limb salvage versus amputation of ischemic limbs should be individualized to each patient. Limb salvage should be attempted in

Table 2. Mechanism of Action and Effective Half-life of Common Vasopressors

Vasopressor	Alpha 1 Receptor	Beta 1 Receptor	Beta 2 Receptor	Dopamine Receptor	V1 Receptor	Half-life (min)
Norepinephrine	+++++	+++	++	None	None	2.5
Epinephrine	+++++	++++	+++	None	None	1.2
Phenylephrine	+++++	None	None	None	None	5
Vasopressin	None	None	None	None	++	10-35
Dopamine	++	++++	++	+++++	None	2
Dobutamine	+	+++++	+++	None	None	2

+ = level of activity on receptor.

healthy patients who understand and accept the possible risk of additional surgeries or a secondary amputation if reconstruction fails. On the other hand, patients with poor baseline health and sedentary lifestyles before injury may prefer a poorly functioning natural leg if they can perform bed-to-chair tasks without wearing a prosthesis. Moreover, in patients who were healthy preinjury, a BKA with a highly functioning prosthesis may allow them to get back to their active lifestyle.

Limitations in this study are inherent to retrospective case series. This study was performed in a specialized tertiary limb-salvage center with microvascular surgeons; thus, our results may not be replicable at other centers. If feasible, patients with multiple limb ischemia should be

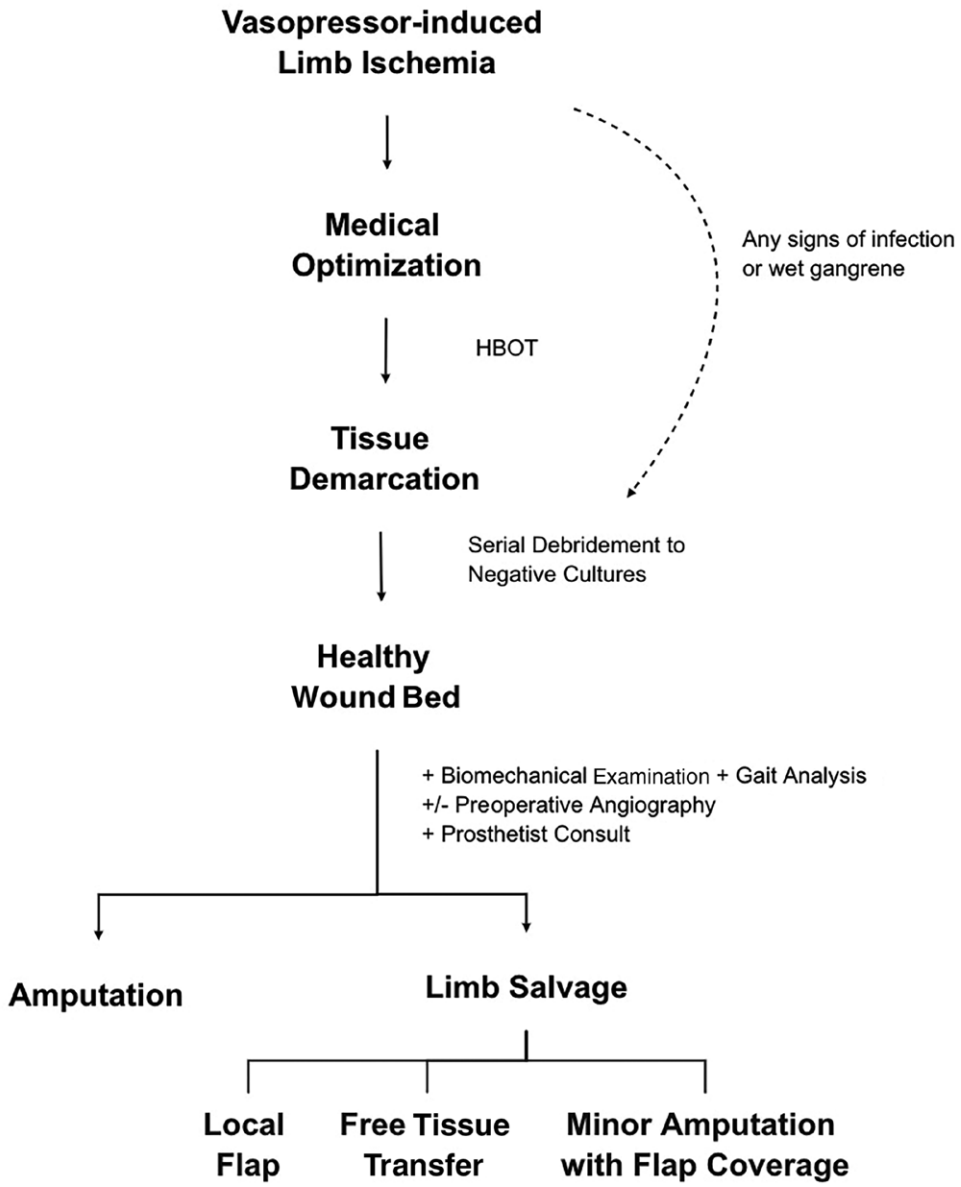

Fig. 3. Surgical management algorithm for vasopressor-induced limb ischemia.

transferred to tertiary hospitals with experienced reconstructive microsurgeons. Before this study, there have been no reports on utilizing "spare-parts" surgery to reconstruct limbs afflicted by VIALI. We conclude that in patients who have suffered irreversible limb ischemia, the best surgery is the one that will yield the most function, and thereby improve their quality of life.

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