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). Current guidelines to treat septic shock recommend fluid replacement and vasopressor infusion to maintain a mean arterial pressure above 65 mm Hg. 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.

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. 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%. 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.

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...
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). 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 webspaces 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.

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 nontooth 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.
In recent years, advancements in amputation technique and prosthetic design have improved survival rates in amputees who walk with prostheses.\textsuperscript{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.\textsuperscript{21} While not the focus of this series, multiple reports have cited various benefits and disadvantages of major and minor amputations.\textsuperscript{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.\textsuperscript{17,24,25} TMR has been described in the setting of BKAs, shoulder disarticulations, transhumeral, and transradial amputations.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{32} Both patients had a unique pattern of injury and tissue loss, and our team sought to restore as much limb length, function, and

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.
### 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 | Reconstructive Surgeries | Complications | Additional Surgeries | Duration of Treatment | Functional Outcome |
|-------|--------------------------|------------|---------------------------|-------------------------|---------------|---------------------|---------------------|---------------------|
| Case 1: Obstructive urolithiasis | 52F | 3 vasopressors | LE: Bilateral BKA + TMR LE: N/A | None | Debunking and web space deepening | | 11 months | Ambulates with prostheses. Intrinsic hand muscle weakness but performs daily tasks with upper limb orthoses. |
| Case 2: Suspected toxic shock syndrome | 50F | 3 vasopressors for 4 weeks | Left LE: TMA Right LE: Chopart's amputation Left UE: transradial amputation Right UE: transmetacarpal amputation | 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: COVID-19 infection | 57M | 3 vasopressors | LE: bilateral BKA + TMR Right UE: N/A | Division of surgically syndactylized left hand | | 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
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

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.

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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