Reinventing Extremity Amputation in the Era of Functional Limb Restoration

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Background: Recent progress in biomechatronics and vascularized composite allotransplantation have occurred in the absence of congruent advancements in the surgical approaches generally utilized for limb amputation. Consideration of these advances, as well as of both novel and time-honored reconstructive surgical techniques, argues for a fundamental reframing of the way in which amputation procedures should be performed.

Methods: We review sentinel developments in external prosthetic limb technology and limb transplantation, in addition to standard and emerging reconstructive surgical techniques relevant to limb modification, and then propose a new paradigm for limb amputation.

Results: An approach to limb amputation based on the availability of native tissues is proposed, with the intent of maximizing limb function, limiting neuropathic pain, restoring limb perception/proprioception and mitigating limb atrophy.

Conclusions: We propose a reinvention of the manner in which limb amputations are performed, framed in the context of time-tested reconstructive techniques, as well as novel, state-of-the-art surgical procedures. Implementation of the proposed techniques in the acute setting has the potential to elevate advanced limb replacement strategies to a clinical solution that perhaps exceeds what is possible through traditional surgical approaches to limb salvage. We therefore argue that amputation, performed with the intent of optimizing the residuum for interaction with either a bionic or a transplanted limb, should be viewed not as a surgical failure, but as an alternative form of limb reconstruction.

Keywords: amputation, limb reconstruction, vascularized composite allotransplantation, targeted muscle reinnervation, regenerative peripheral nerve interface, agonist-antagonist myoneural interface, functional limb restoration

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Limb amputation is generally regarded as a therapy of last resort for patients suffering from severe injuries to the extremities—in essence, a surgical failure in the context of a limb deemed to be unsalvageable. Little of the technical expertise, creativity, and innovation that are typically applied to limb salvage are brought to bear on the everyday approach to limb amputation; indeed, amputation technique has undergone minimal modification for over a century.

We have entered an age, however, in which technological, medical, and surgical advances are introducing a new wave of treatment options for patients with severe extremity injuries. Profound improvements in biomechatronics, for example, have enabled the creation of increasingly sophisticated, computer-controlled prosthetic systems capable of bidirectional neural communication between the peripheral nervous system and the external synthetic limb.[1–3] In addition, advances in immunomodulation, rehabilitation, and surgical science have ushered in an era in which vascularized composite allotransplantation (VCA) has become a clinical reality.[4–6] A deepened understanding of limb neurovascular anatomy and function has led to the development of novel operative techniques that preserve and reconfigure soft tissues to enhance volitional motor control of an advanced limb replacement, as well as provide sensory feedback from the limb replacement.[7–18] Collectively, these advances offer remarkable promise to provide persons undergoing limb amputation with a level of function that enables uninterrupted participation in many activities relevant to their daily lives, thereby optimizing their functional restoration.

Unfortunately, the surgical approaches most commonly pursued for acute limb amputation have not evolved in pace with developments in biomechatronics and surgery. In this article, we advocate a fundamental reinvention of the manner in which acute limb amputation is performed and frame this new approach in the context of these multidisciplinary scientific advances. Of note, we do not specifically address surgical interventions such as osseointegration that are typically performed subsequent to the acute amputation stage, but rather specifically propose a reinvention of acute surgical technique. In so doing, we propose that acute limb amputation, carried out with the intent of optimizing the residuum for interaction with either a synthetic prosthesis or a transplanted biological limb, may be viewed not as a surgical failure, but as an *alternative form of limb reconstruction*. This position represents a philosophical shift in the clinical care of patients with limb compromise away from a model that emphasizes limb preservation and toward one that espouses functional limb restoration (FLR).

HISTORICAL CONTEXT

Extremity amputation is amongst the oldest known surgical procedures in medical history, with many of its technical principles having first been elucidated by Hippocrates over 2500 years ago.[19,20] Despite the passage of over 2 millennia; however, relatively little has changed in the standard-of-care operative approach. The limb amputation procedure typically consists of bony transection, vascular ligation, traction neurectomies, and myodesis creation, followed by a layered closure of the surrounding soft tissues and skin envelope.[21,22]

The relative simplicity of the standard approach to acute limb amputation is a reflection of its simple aims: to preserve ideal limb length, to provide stable residual limb coverage, and to offer, when possible, a padded platform for an appropriately fitted prosthetic

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socket.[23] Several pioneers have espoused modifications to the standard amputation technique with the intent of expanding the ability of surgeons to better meet not only these simple aims, but also to create neuromuscular interfaces for improving neural control over the external mechatronic prosthesis. These modifications have followed the evolution of increasingly sophisticated techniques in reconstructive surgery, but have largely been seated in the age-old surgical principle of utilizing "spare parts"—tissues that would otherwise be discarded at the time of amputation. The simplest execution of the spare parts principle for limb amputation was manifest in the procurement of nonvascularized bone, nerve, and/or skin from the amputated limb to preserve limb length, bridge nerve gaps, and provide distal limb coverage, respectively, beginning in the early 1900s.[24–26] More sophisticated attempts to modify the standard amputation technique were proposed in the 1950s, including the Van Nes pedicled rotationplasty, which permitted patients with isolated compromise of the distal femur and/or proximal tibia to undergo a modified amputation that resulted in preservation of a functional neo-knee joint via utilization of the uninjured distal leg, ankle, and foot.[27] Thereafter, increased knowledge regarding the neurovascular anatomy of the distal extremities over the ensuing decades enabled the development of techniques to use the sensate skin of the palmar surface of the hand or the plantar surface of the foot to resurface the distal residual limb via pedicled neurovascular island flaps.[28] Such "fillet of sole" flaps were first described as a reliable means of salvaging maximal length in amputated limbs beginning in the early 1980s,[29,30] and were revolutionary in their ability to provide sensate skin on the end of the residual limb, as well as more durable coverage; however, they required that enough of the distal limb's native anatomy remained intact to enable pedicled transfer. With the advent of microsurgical techniques, the notion of utilizing the fully amputated limb as a reservoir for free tissue transfer became a clinical reality.[31] Free tissue microvascular transfers derived from the amputated limb have been described as variably innervated fasciocutaneous, myocutaneous, osteomyocutaneous, and muscular/osseous only options for optimization of reconstruction of the residual limb,[32–34] as have those obtained from other sites (eg, rectus abdominis, latissimus dorsi, parascapular, and anterolateral thigh flaps)[35] (Fig. 1).

Concurrent with these advancements, cineplastic techniques emerged as an alternative approach to acute amputation.[36–46] The cineplastic procedure sought to expand the standard amputation aims to also include the creation of neuromuscular interfaces designed to improve the controllability over the external mechatronic prosthesis. In the approach, skin-lined tendon or muscle tunnels were created during the amputation procedure, and then postamputation, the tunnels were mechanically connected to an external prosthetic joint via a chain, cable, or strap. Such a direct muscle to prosthesis mechanical coupling enabled patients to exert muscular forces directly onto the external prosthesis. Although some clinical benefits were reported, cineplasty fell out of practice due to the challenges of tunnel skin irritation, infections, and muscle fatigue.

FIGURE 1. Historic surgical approaches to residual limb management. A, Split thickness skin graft closure. B, Van Nes rotationplasty. C, Pedicled filet flap. D, Microsurgical free tissue transfer to distal limb.

Despite the development and publication of these myriad potential improvements to standard amputation technique, their incorporation into everyday clinical practice has been limited, at best. By way of example, the osteomyoplastic approach to limb amputation espoused by Ertl is a technically straightforward modification that has been reported to result in improved patient-reported outcomes, load bearing capacity, and restoration of function in both upper and lower extremity subjects,[47] yet has not achieved widespread adoption among surgeons performing limb amputations. Although lackluster adoption of the Ertl procedure may be due in part to reasonable debate as to the validity of these claims, it may also be attributable to a perception that it is a procedure in search of an indication. This entrenchment in the static view of limb amputation is likely due to the fact that there has not been a compelling enough case for change made to date to justify an alteration in clinical practice. We propose, however, that such a case can now be made.

CASE FOR CHANGE IN LIGHT OF RECENT ADVANCES

In light of recent technological and scientific advances, the static notion of residual limb function is no longer appropriate. With the development of new technologies, a concomitant need for a more dynamic vision of the residual limb has emerged; indeed, consideration of advances made over the past 2 decades in prosthetic development and VCA reveals a discordant evolution in the progress of limb restoration options versus acute management strategies for patients suffering from limb loss.

In the realm of prosthetic device development, dramatic advancements in robotic technology have enabled the emergence of a new generation of bionic limbs with capabilities that far surpass what was previously thought possible. Increasingly miniaturized electronics, wireless communications, improved battery design, lighter materials, refined sensors, enhanced feedback emulators, more powerful actuators, and the advent of osseointegration have collectively enabled prosthesis developers to create next-generation bionic limbs with markedly enhanced function over standard commercial devices. Devices including the Luke Arm (Mobius Bionics, Manchester, NH), the modular prosthetic limb (Johns Hopkins Applied Physics Laboratory, Baltimore, MD), the emPOWER (Ottobock, Germany),[48,49] the Clutchable Series Elastic Actuator (CSEA) knee,[50] and the Vanderbilt Leg[51] are cutting-edge robotic extremity systems that provide markedly expanded degrees of freedom, variably integrated pressure sensors capable of providing touch information, as well as joint angle and torque sensors that collect and stream real-time data about joint movement and loading.[52,53] Such prostheses have been associated with dramatically improved manipulative and gait function in amputees who used the appropriate (Fig. 2)

For next-generation prostheses to offer persons with limb amputation maximal motor control and sensory feedback, however,

FIGURE 2. State of the art prosthetic devices. A, Johns Hopkins Applied Physics Laboratory modular prosthetic limb (MPL). B, Ottobock Empower lower limb prosthesis. Examples of bilateral upper (C) and lower (D) extremity vascularized allotransplantation.

a stable and robust mechanism for neural communication between patient and device must be established. Unfortunately, standard amputation techniques do not provide such a platform, due primarily to the treatment of peripheral nerves and muscles at the time of amputation. Traditional traction neurectomies typically result in disorganized distal nerve endings that, without a definitive end organ, produce disorganized efferent firing with very low signal-to-noise ratios,[54,55] and low polarization potentials for afferents that are all too often interpreted as pain.[56,57] Such pain may be experienced as limited to the residual limb and/or extending to the phantom limb that was previously amputated. Among major limb amputees, the frequency of residual limb pain has been reported to range from 10% to 76%, whereas that of phantom limb pain has been estimated to be as high as 85%.[58] Both residual limb pain and phantom limb pain have been associated with impaired prosthesis utilization, diminished productivity, and decreased quality of life.[56,59]

As a result, researchers working with patients who have undergone a traditional amputation are forced to design peripheral nerve interfaces within this suboptimal paradigm—most of which depend on direct contact between synthetic materials and compromised nerves. The clinical potential of intraneural electrodes (eg, penetrating electrodes and regenerative sieves/microchannel arrays) has been limited by signal resolution and low signal-to-noise ratios, as well as progressive signal degradation due to fibrosis and ongoing nerve injury.[54] Although extraneural electrodes (eg, nerve cuffs) have shown clinical promise in direct nerve stimulation for the provision of cutaneous sensory feedback,[3,60] they are subject to the same limitations as intraneural electrodes when used for recording efferent neural signals. To circumvent these invasive approaches, researchers have explored purely noninvasive techniques for achieving sensory feedback that substitute one sensation for another (eg, force on the prosthetic fingers mapped to vibration intensity somewhere on the external surface of the residuum); unfortunately, although these methods have demonstrated utility in controlled laboratory settings, they have not been successful in clinical translation or long-term usage.[61–63] Therefore, traditional acute amputation techniques do not provide the tissue environment necessary to establish the stable, long-term peripheral nerve interfaces required for persons with amputation to take full advantage of the capabilities offered by next-generation bionic devices.

VCA of the limbs, in contrast, offers a different spectrum of potential benefits to persons with amputation, as well as a distinct set of challenges related to the standard residual limb. Since the first successful hand transplant was performed in 1998, more than 100 upper extremities and 7 lower extremities have been transplanted worldwide (Petruzzo P. Personal Communication August 14, 2017, palmina.petruzzo@chu-lyon.fr). The vast majority of reported outcomes have been in the isolated upper extremity VCA population, in which the reported patient survival rate has been 98.5% and the overall graft survival rate has been 83.1%.[6] Nearly all upper-extremity recipients have demonstrated recovery of at least protective sensibility in the limb(s) over time, with some exhibiting restoration of 2-point discrimination in the years following their procedure. Functional recovery has been reported inconsistently across various VCA centers, but most recipients have demonstrated significant improvements in DASH scores and Carroll tests relative to their pretransplantation state, as well as good recovery of their ability to perform activities of daily living including dressing, driving, picking up small objects, and returning to work.[6] Long-term outcomes for lower-extremity transplantation have been reported for only 1 case, in which a unilateral lower extremity was donated at the level of the pelvis across ischiopagus conjoined twins.[4] In this report, the patient was noted at 6 years postoperatively to have recovered good hip flexion and knee flexion/extension, but limited ankle and subtalar motion; ambulation was performed with the assistance of a brace and the patient was able to run short distances. Sensation was present throughout the limb but diminished relative to the normal side (Fig. 2).[5]

Although positive outcomes in extremity VCA are undoubtedly contingent upon a complex set of factors (eg, appropriate patient selection and expectation setting, as well as patient compliance with rehabilitation and immunosuppression), there is little doubt that a principal anatomic determinant of success is the distance required for nerve regeneration. With few exceptions, functional recovery in limb transplant recipients has been noted to improve with more distal levels of amputation—a phenomenon due primarily to the fact that distal amputations require a shorter reinnervation distance as compared to those located more proximally. For this reason, the success of limb transplantation is limited by the simplicity of the standard limb amputation procedure, in which nerve transection generally occurs either at or above the osteotomy level. Even in patients who have some or all of their distal neural tree intact at the time of amputation, traditional amputation technique dictates that this nerve reservoir be shortened in conjunction with limb sacrifice. In this way, standard extremity amputation practice neglects the relevance of nerve length preservation to positive functional outcomes in both upper- and lower-extremity VCA.

REVIEW OF NEW SURGICAL STRATEGIES

Advancements in prosthetic technology and limb transplantation have revealed the shortcomings of standardized approaches to acute limb amputation. In light of these shortcomings, there is a need to fundamentally redesign the way in which acute amputations are performed to enable downstream maximization of function in patients with significant limb compromise. The importance of redesigning the approach to amputation *at the time of limb sacrifice* is critical in that the opportunity to use distal tissues as a reservoir for reconstructive purposes is otherwise lost. The pallet of options from which such a redesign may be developed includes not only the range of reconstructive techniques described above, but also several novel surgical interventions that have been described only recently. These surgical interventions include targeted muscle/sensory reinnervation (TMR/TSR), regenerative peripheral nerve interface (RPNI) construction, and agonist-antagonist myoneural interface (AMI) construction. Like cineplasty, these interventions expand the simple aims of standard amputation technique to include the creation of neuromuscular interfaces for the improvement of prosthetic control.

Targeted Muscle/Sensory Reinnervation

TMR is a technique whereby nerve transfers are used to reinnervate specific vascularized native muscles to create additional prosthetic control sites during limb amputation.[8,9] The technique requires that a surgeon first denervate a native functional muscle, wholly or in part, that is deemed functionally noncritical by performing a motor neurotomy. Following this step, the surgeon then transfers a major nerve (eg, the tibial nerve) that necessarily is transected during the amputation and previously innervated the distal limb to the neurotomy site. After successful reinnervation, the target muscle depolarizes with the reinnervated peripheral nerve, in response to appropriate cortical signals from the brain. In this way, the muscle serves to amplify the intrinsic nerve signal for improved signal detection. This amplified signal is then measured by external muscle electrodes and used to intuitively control synthetic motors within a prosthesis.[9] Functional outcomes from more than 100 patients treated with TMR have been associated with more efficient task completion trials and more intuitive prosthetic control than previously witnessed.[8] TSR is a complementary technique in which the mixed or pure sensory nerves that previously traveled down the limb are

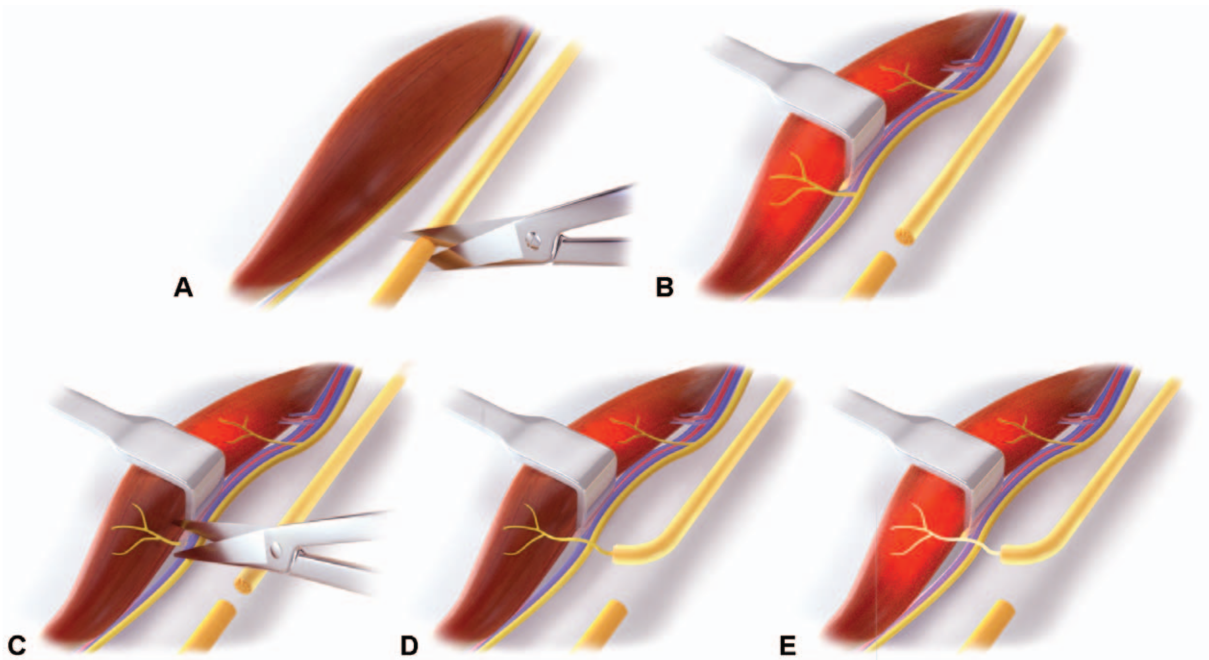

FIGURE 3. Targeted muscle reinnervation. A, Transection of primary nerve. B, Isolation of neurovascular supply to neighboring muscle. C, Transection of 1 discrete motor branch supplying neighboring muscle, leading to selective muscle deinnervation. D, Primary nerve to muscle motor nerve coaptation. E, Eventual reinnervation of neighboring muscle with fascicles from primary nerve.

coapted to newly divided sensory nerves that previously innervated the skin of a distinct anatomical site. Progressive reinnervation of the targeted skin patch located at the distinct anatomical site allows the patient to once again receive sensory feedback from the hand or the sole into the appropriate cortical area of the brain when actuators apply forces upon the targeted skin patch.[63] Because TMR and TSR each require denervating functional muscle and/or skin, respectively, only a modest number of nerve transfers for each amputation is possible for prosthetic control and feedback (Fig. 3).

Regenerative Peripheral Nerve Interface

An RPNI is a surgical construct that consists of a nonvascularized segment of muscle coapted to a distal motor, sensory, or mixed nerve ending.[7,11] Unlike TMR, RPNI construction does not require sacrifice of a vascularized innervated native muscle; instead, it is constructed as a free graft from orthotopically sourced donor tissue. The muscle segment is gradually reinnervated by the redirected nerve ending, which then promotes volitional activation of the muscle segment when triggered by the central nervous system. In a motor RPNI, intuitive control occurs because the reinnervated muscle is controlled by the same nerve that innervated a native muscle once responsible for movement of the amputated portion of the limb. In the case of a sensory RPNI, the neural directionality is reversed; stimulation of the reinnervated muscle leads to activation of the associated sensory nerve, with resultant sensory feedback transmitted via native pathways to the central nervous system.[64,65] Unlike TMR, there are few limitations on the number of buildable anatomic sites and control signals which can be generated with RPNIs[10] (Fig. 4).

Agonist-antagonist Myoneural Interface

The AMI is a more recent surgical approach that offers the possibility of restoration of both efferent motor control and afferent proprioceptive muscle-tendon feedback from both spindle fibers and Golgi tendon organs. The key advancement in this architecture is the surgical coaptation of agonist-antagonist muscle pairs within the residuum.[13–18,66,67] Preservation of the mechanical coupling between agonist contraction and antagonist stretch allows activation of native mechanoreceptors within these linked muscles. In conjunction with a bionic limb, at least 1 AMI is surgically constructed in the residuum for each prosthetic joint to be controlled, either by (1) rerouting native agonist-antagonist musculature, (2) connecting agonist-antagonist neurovascular island muscle flaps, or (3) creating and connecting muscle units (either via TMR or RPNI construction) on the nerves that once innervated agonist-antagonist muscle pairs. When distal tissues are still available, these agonist-antagonist muscle pairs are linked by using the tarsal tunnels or extensor compartments from the discarded limb to create functional pulley systems with the residual limb; when such structures are not available, they may be created de novo using either fascial slips or strips of acellular dermal matrix. This diversity of surgical approach enables the AMI technique to be employed as either a native model[15,17,66,67] or a regenerative model.[16,18] Early results indicate that the AMI is capable of providing graded proprioceptive muscle-tendon feedback along native physiological afferent pathways,[15,16] as well as improved efferent control of joint position and impedance.[17] By applying functional electrical stimulation to the agonist muscle of the AMI muscle pair, the force or position of its antagonist muscle partner can be controlled (or vice versa). Thus, the AMI has been shown to provide natural force feedback from the external prosthesis, enabling closed-loop neural control of robotic prostheses[17] (Fig. 5).

PROPOSED APPROACH TO REINVENTING LIMB AMPUTATION

Drawing on the above-described arsenal of both established and novel reconstructive techniques, we propose a new paradigm in the surgical approach to acute limb amputation. This paradigm is informed by the demands imposed by new therapeutic options for

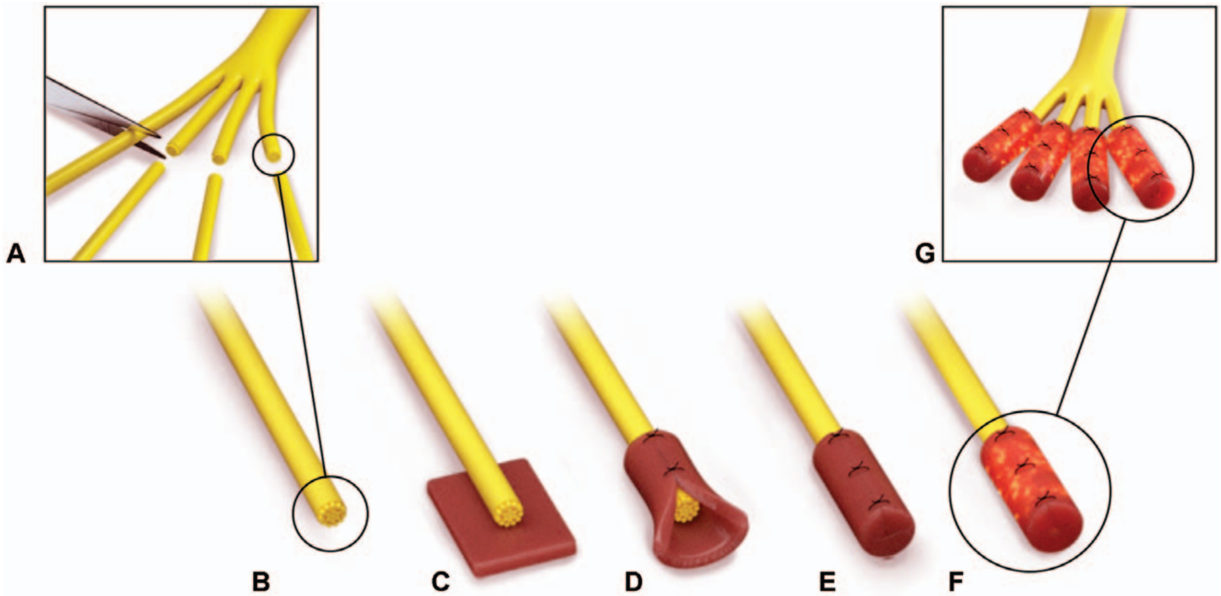

FIGURE 4. Regenerative peripheral nerve interface construction. A, Transection of primary nerve and intrafascicular split to facilitate reinnervation. B, Magnified view of individual nerve fascicle. C, Fascicle terminus is placed into deinnervated, nonvascularized free muscle graft procured from remote site. D, Suture closure of graft around distal nerve ending. E, Completed regenerative peripheral nerve interface (RPNI) construction. F, Eventual reinnervation of free muscle graft by terminal nerve fascicle. G, Collective view of primary nerve following completion of multiple RPNI construction.

patients, and in the availability of new operative techniques to promote improved peripheral nerve interfacing and sensory function. The specific clinical approach we advocate, described below, is dictated by the amount of intact distal tissues available at the time of amputation. The goals of this approach are to maximize eventual motor control, establish sensory feedback pathways, prevent neuroma development, and, when feasible, enable optimal downstream biological restoration.

Full Availability of Distal Tissues

The ideal circumstance is one in which the patient demonstrates fully intact distal soft tissues but requires amputation due to chronic pain or joint instability. Such a circumstance often occurs in the case of limited traumatic injury, advanced arthritis, or failed joint replacement. In this scenario, we advocate the utilization of natively innervated and vascularized muscles that once controlled joints contained in the amputated segment to construct AMIs in the residual limb (eg, elbow, distal radioulnar joint, and wrist for the upper extremity; knee, ankle, and subtalar joint for the lower extremity).[14] Near-anatomic length may also be preserved for both distal motor and sensory nerves through the fabrication of regenerative constructs (TMR, RPNI, or AMI), with coiling or wrapping of the excess nerve length within the confines of the residual limb soft tissue envelope. In the setting of below-elbow or below-knee level amputations, stabilization of the distal skeletal architecture may be augmented through the construction of distal tibiofibular and radioulnar bone bridges. When possible, the distal residual limb envelope may be augmented by incorporating neurovascular island flaps derived from the palmar or plantar skin to maintain fine sensory perception in these receptor-dense tissues[13] (Fig. 6).

Incomplete Availability of Distal Tissues

A less ideal but arguably more common scenario is one in which some, but not all, distal tissues are intact at the time of limb amputation, as is often the case in severe traumatic injuries or extensive oncologic processes. In this circumstance, we advocate the utilization of natively innervated and vascularized muscles to construct AMIs where possible, followed by the utilization of regenerative approaches (TMR, RPNI, or AMI) to establish relays for prosthetic joint control, prevent neuropathic pain, and achieve nerve length preservation for distal sensory and motor nerves. Consideration may also be given to the utilization of distal neurovascular island flaps for residual limb resurfacing as described in the previous case, or vascularized or nonvascularized bone grafting from the amputation segment to augment bony length and establish distal tibiofibular or radioulnar synostoses for improved socket distal loading capabilities. In this scenario, temporary coverage through means such as skin grafting and/or local tissue rearrangement may also be warranted as a bridge to optimal amputation (Fig. 6).

Minimal or No Availability of Distal Tissues

The third clinical scenario is one in which no distal tissues remain intact for recruitment at the time of amputation, as in the case of a traumatic amputation. In this circumstance, we advocate the exclusive construction of validated regenerative models (ie, TMR/TSR or RPNIs or AMI in 2-stage procedure) with the primary intent of establishing large-joint sensorimotor control and preventing neuroma formation. Grafting of nerves from the amputated limb may also be considered as a means to restore and preserve the distal nerve tree, assuming that the limb is available and the nerves demonstrate appropriate integrity; of note, successful performance of either of these efforts will be contingent on having an accurate sense of the topographical anatomy of nerves at or above the level of amputation. This scenario may also warrant consideration of free tissue transfer resurfacing of the distal residual limb—whether procured from the amputated segment or from a site on the patient remote from the zone of injury— to preserve residual limb length, assure stable padding, and protect innervated constructs created at the time of amputation (Fig. 6).

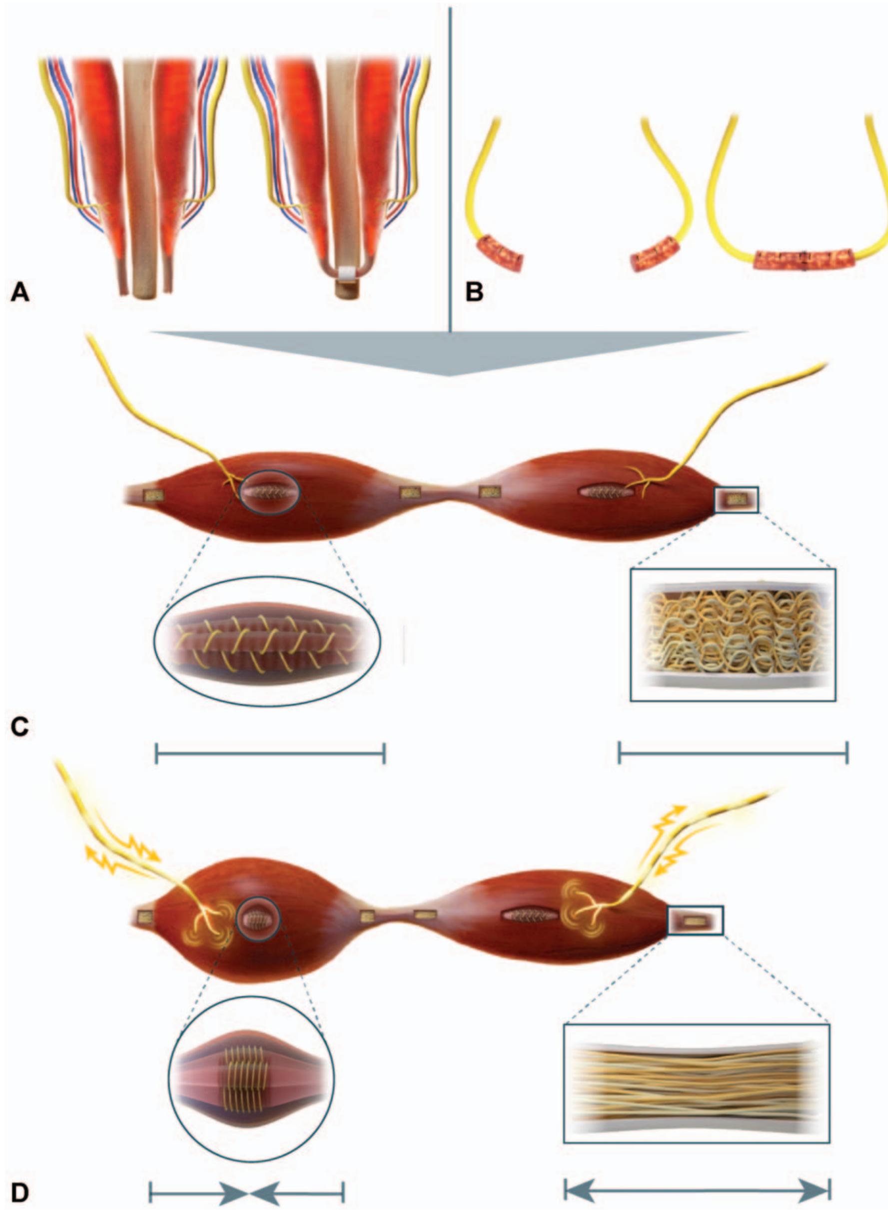

FIGURE 5. Agonist-antagonist myoneural interface construction. A, Illustration of native agonist-antagonist myoneural interface (AMI) construction including natively innervated and vascularized muscle units. B, Illustration of regenerative AMI construction using linked regenerative peripheral nerve interfaces (RPNIs). C, Biomechanical linkage of innervated agonist and antagonist muscle pair, with muscle spindle fibers and Golgi tendon organs at rest. D, Volitional contraction of agonist muscle leads to simultaneous stretch of antagonist muscle, resulting in activation of muscle spindle fibers and Golgi tendon organs.

These operative approaches represent a substantially more advanced set of surgical procedures than those reserved for traditional limb amputations; as such, it is anticipated that they will require longer operative times, more extensive utilization of operating room resources, and longer acute hospital lengths of stay. Patients undergoing such procedures will require more intensive postoperative monitoring protocols and will be at elevated risk for serious postoperative complications due to prolonged procedural lengths and more technically demanding operative interventions. Appropriate patient selection will be critical due to requirements for compliance with modified rehabilitation strategies. Collectively, these factors will demand that these modified procedures be framed in a manner more consistent with complex reconstructions than that of traditional amputations.

Following acute recovery, patients who undergo these new operative approaches should be amenable to fitting with standard extremity prostheses; however, to achieve maximal benefit from their modified amputations, they will also need to have access to biomechatronic limbs capable of taking advantage of the additional neural control afforded by their novel residual limbs. If the muscle end organs are superficially located for the TMR, RPNI, or AMI constructs, commercially available surface skin electrodes can be used to record muscle electromyographic signals for the control of prosthetic motors on the external prosthesis. However, although a few of today's commercially available prosthetic systems can be used to exploit some of the benefits of the proposed reconstructive techniques, full bionic integration will require the ongoing development of next-generation prosthetic devices capable of residual limb interfacing via bidirectional transcutaneous, percutaneous, and/or implantable wireless electrodes, sophisticated actuators to emulate cutaneous sensibility, and advanced control algorithms to integrate these systems

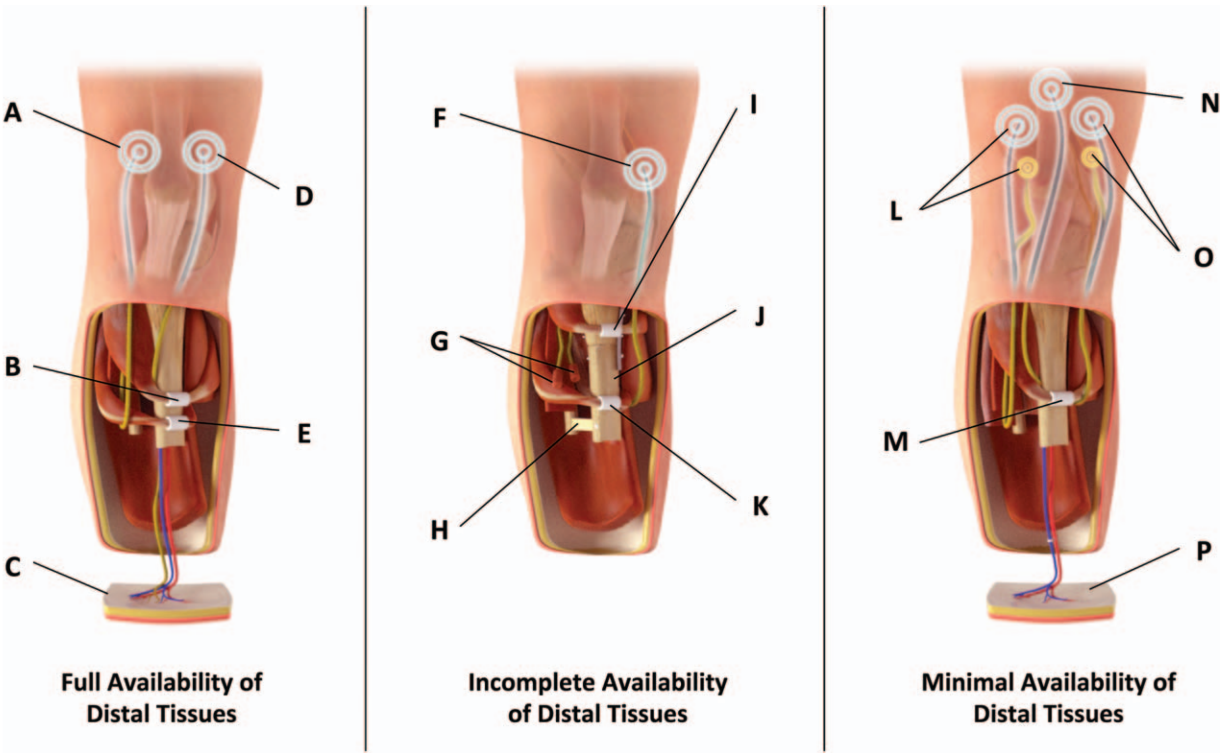

FIGURE 6. Illustrative examples of novel below knee amputation strategy under various clinical scenarios. Full availability of distal tissues: (A) superficial peroneal nerve targeted sensory reinnervation (TSR) or sensory regenerative peripheral nerve interface (RPNI); (B) native tibialis anterior/lateral gastrocnemius agonist-antagonist myoneural interface (AMI); (C) innervated heel neurovascular island flap; (D) deep peroneal nerve TSR or sensory RPNI; (E) native tibialis posterior/peroneus longus AMI. Incomplete availability of distal tissues: (F) tibial nerve TSR or sensory RPNI; (G) deep and superficial peroneal nerve RPNIs; (H) tibiofibular synostosis; (I) regenerative tibialis posterior/native lateral gastrocnemius AMI; (J) vascularized bone graft to reconstruct distal tibia; (K) native tibialis posterior/peroneus longus AMI. Minimal availability of distal tissues: (L) superficial peroneal nerve targeted muscle/sensory reinnervation (TMR) and TSR; (M) native tibialis anterior/lateral gastrocnemius AMI; (N) deep peroneal nerve TSR or sensory RPNI; (O) tibial nerve TMR and TSR; (P) free tissue transfer resurfacing of distal residual limb.

(Fig. 7). Such systems are currently being vetted in a host of biomechatronic research laboratories.

A significant concern regarding the generation of advanced technology for limb restoration is its cost and subsequent availability to members of the general public. The expense of standard extremity prostheses varies widely, depending on the level of function required; for example, a lower limb prosthesis allowing an amputee to walk on level ground may cost $5000 to $7000, whereas a microprocessor-controlled limb capable of more advanced function may cost as much as $70,000.[68] The devices capable of interacting with peripheral neural constructs such as those described above are presently valued at over $100,000 each, and are therefore presently available only under the umbrella of research grants limited largely to laboratory-based utilization only. As such technology evolves, however, its cost will assuredly reduce in a fashion similar to that witnessed in other industries. Furthermore, the functional, psychosocial, and productivity-related benefits provided by such systems should provide ample justification for such technology to be covered by insurers for patients who have the physical and psychological capacity to achieve such gains. Present policy guidelines for major insurers currently support this claim; for example, BlueCross Blue Shield of North Carolina currently provides coverage for myoelectric prostheses for patients "who have the physical strength and demonstrated need to move for long distances at variable rates of speed or over uneven terrain."[69]

Although advanced devices will be required to maximize the potential of the novel reconstructive techniques described herein, it is worth noting that many of these procedures have shown clinical benefit even in the absence of advanced prosthetic limbs. For example, recent studies have demonstrated that both TMR and RPNI construction may significantly ameliorate residual limb and phantom limb pain,[70,71] and preliminary studies indicate that the AMI may attenuate or eliminate atrophy of the residual limb.[66] Such clinical benefits argue for adoption of the proposed operative procedures in the near term, even before next-generation prosthetic devices become broadly available.

While it is unlikely that the majority of patients who undergo these modified amputation procedures will ultimately prove eligible or willing to undergo limb allotransplantation, it is anticipated that those who do will benefit from the nerve preservation strategies described above. To the extent that these techniques permit maintenance of near-anatomic length for major peripheral motor nerves with viable motor end plates, the unfurling of such nerves at the time of transplantation may, from a neural regeneration perspective, convert a proximal level transplant to a more distal one. It is expected that such a conversion will likely result in significantly improved

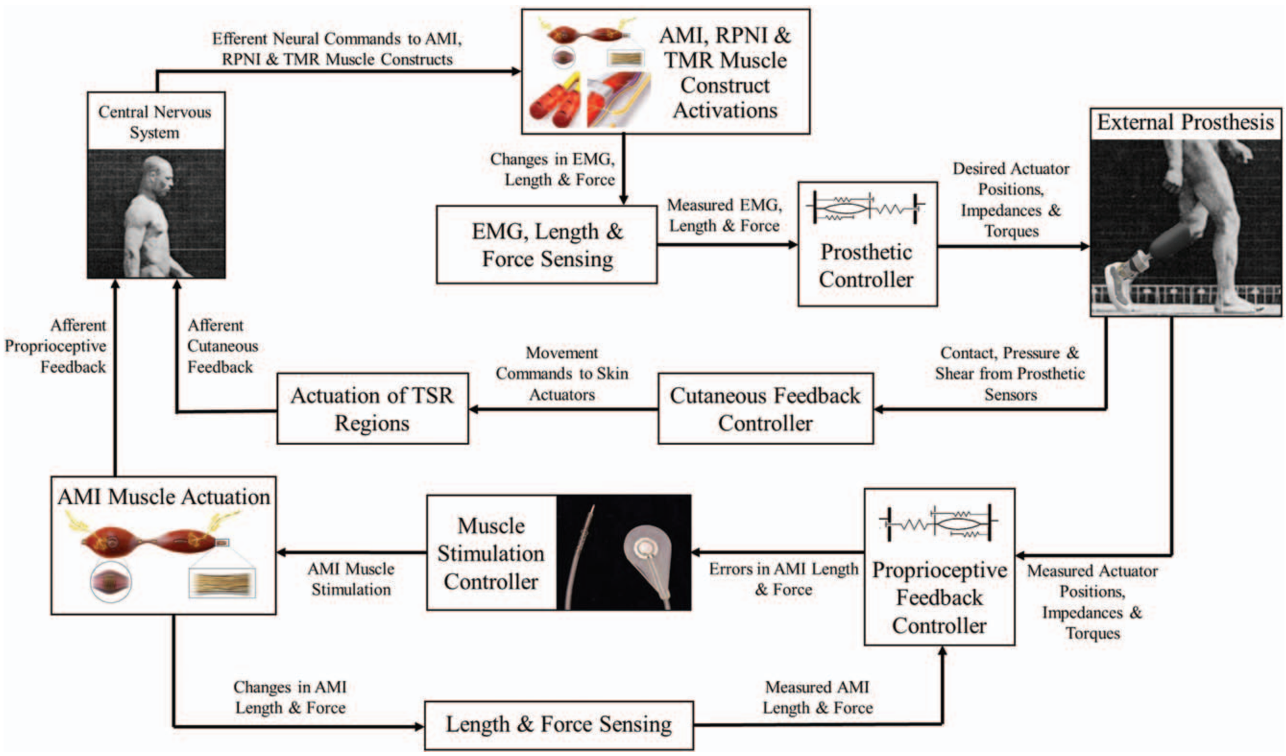

FIGURE 7. Schematic illustrating closed loop communication between agonist-antagonist myoneural interface (AMI) construct and adapted, next generation lower limb prosthesis.

motor functionality in the transplanted limb as reinnervation progresses.

It should be noted that this proposed paradigm change for extremity amputation may be controversial for patients requiring limb sacrifice due to advanced peripheral vascular disease; such patients typically demonstrate peripheral neuropathy and microvascular compromise, which may limit the potential for effective reinnervation and increase the risk of wound healing problems. At worst, however, the potential ineligibility of this population does not negate the value of our proposed paradigm change. It is estimated that approximately 54% of limb amputations performed in the United States are secondary to dysvascular disease, with the remaining 46% attributable to trauma, malignancy, and congenital anomalies.[72] Exclusion of dysvascular individuals results in an estimated potential pool of more than 85,000 patients per year who may still benefit from a renewed approach to limb amputation such as the one advocated herein.[73]

IMPLICATIONS AND FUTURE DIRECTIONS

Our intent in advocating a revised approach to acute limb amputation is to update this procedure to make it contemporaneous and congruent with other modern limb loss management strategies. The impetus for this effort is not only to maximize the long-term functional capacity and quality of life of persons with limb amputation, but also to elevate the notion of amputation from one of surgical failure to that of an *alternative form of limb reconstruction*. In so doing, we are promoting a philosophical shift in the model of limb compromise management away from one that emphasizes limb preservation, toward one that espouses FLR. The FLR model requires an increased emphasis on successfully aligning expected functional outcomes with patient goals at the time of acute management, informed by consideration of the novel technologies and surgical approaches now available to patients. It furthermore demands an increasingly multidisciplinary approach to care, in which communication and collaboration between surgical specialties (including trauma surgery, vascular surgery, orthopedic surgery, and plastic surgery), rehabilitation specialists, biomechatronic experts, and prosthetists is fluid and constant. We believe that this represents a model of care that is not only more modern but also fundamentally better than the current clinical standard.

In addition, the establishment of this new paradigm for limb amputation anticipates the development of other advances in limb restoration that are just beginning to emerge. Osseointegrated implant technology, for example, continues to gain traction as a treatment modality for amputees with short or unstable residual limbs[74]; utilization of the intramedullary component of these implants may provide an internalized means to link the neural interfaces described above to external prostheses. Similarly, the new paradigm proposed here for limb amputation may also be compatible with other internalized electromyogram systems such as implantable myoelectric sensors that could obviate the need for surface or transcutaneous electrodes.[68] Furthermore, the techniques described above may serve as the basis for developing techniques to augment the residual limbs of patients whom have already undergone amputation[16,18]; such revision strategies will likely require a combination of both native (AMI) and regenerative (TMR, RPNI, or AMI) approaches to neural relay construction, and hold the promise of providing such patients with improved volitional motor control, restored proprioception, and reversal of muscle atrophy. The development of such revision strategies is currently underway.

CONCLUSIONS

In light of present-day options to achieve maximal FLR, we advocate that the surgical approach to limb amputation be revised to incorporate modern neuromuscular techniques aimed at preservation of distal innervated tissues and more optimal management of divided nerve endings. Implementation of these techniques in the acute setting has the potential to elevate advanced limb replacement to a clinical solution with outcomes that perhaps exceed what is possible through traditional approaches to limb salvage. It furthermore demands that we reframe the model for management of limb compromise to one that emphasizes FLR.

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