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Hand/Peripheral Nerve

# Targeted Muscle Reinnervation Combined with a Vascularized Pedicled Regenerative Peripheral Nerve Interface

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**Summary:** Symptomatic neuromas and pain caused by nerve transection injuries can adversely impact a patient's recovery, while also contributing to increased dependence on opioid and other pharmacotherapy. These sources of pain are magnified following amputation surgeries, inhibiting optimal prosthetic wear and function. Targeted muscle reinnervation (TMR) and regenerative peripheral nerve interfaces (RPNI) represent modern advances in addressing amputated peripheral nerves. These techniques offer solutions by essentially providing neuromuscular targets for transected peripheral nerves "to grow into and reinnervate." Recent described benefits of these techniques include reports on pain reduction or ablation (eg, phantom limb pain, residual limb pain, and/or neuroma pain).[1–6] We describe a technical adaptation combining TMR with a "pedicled vascularized RPNI (vRPNI)." The TMR with the vRPNI surgical technique described offers the advantage of having a distal target nerve and a target muscle possessing deinnervated motor end plates which may potentially enhance nerve regeneration and muscle reinnervation, while also decreasing amputated nerve-related pain. *(Plast Reconstr Surg Glob Open 2020;8:e2689; doi: 10.1097/GOX.0000000000002689; Published online 24 March 2020.)*

## INTRODUCTION

Neuroma-related residual limb pain and phantom limb pain (PLP) following amputation remain a challenge.[7] Neuromas represent a cut nerve's attempt at regeneration, which without a receptive end organ results in disorganized axonal sprouting.[8] PLP is the perception that the missing limb is still present and is experiencing various painful sensations. These painful sensations may be driven in part by ectopic firing from a transected nerve end and coupled with the lack of afferent feedback from the nerve's distal target that may contribute to symptomatic neuroma.[1,2]

Whereas previous surgical treatment of symptomatic neuromas has relied on excision combined with burying and/or implantation of the nerve ends, recent strategies including targeted muscle reinnervation (TMR) and regenerative peripheral nerve interfaces (RPNI) have been described.[1–6,9–14] These strategies have recognized the need to provide a physiologic end organ to satisfy the nerve ending to prevent or reduce symptomatic neuroma formation. The physiologic end organs allow neuronal regenerative signals to effectively close their feedback loop and quell ectopic charges that contribute to symptomatic neuropathic pain, while also providing sensory feedback to the sensorimotor cortex. As a result, contemporary surgical strategies for symptomatic neuromas include active management of the nerve stump to "give the nerve somewhere to go, and something to do."[1–3,5] In both the procedures, ie, TMR and RPNI surgery, neuromuscular endplates in the denervated muscles are functionally made "empty" and, thus, made more receptive to neurotization from the regenerating peripheral nerve.

TMR consists of nerve transfer from the transected peripheral nerve to a nearby motor nerve branch.[1–3] The regenerating axons from the proximal nerve stump grow through existing endoneurial tubes to reinnervate the motor endplates of the freshly deinnervated target muscle. TMR has been shown to result in a physiologic synaptic input.[13] During TMR surgery, a common experience seen with this technique involves a noted size mismatch

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between the proximal peripheral nerve to be transferred which is often larger than the distal target motor nerve during coaptation. This size mismatch is rather variable and, often, the proximal peripheral nerve can be upwards of 5-10x the size of the distal target motor nerve. Thus, some concerns have been raised, in that this size mismatch as evident with the nerve coaptation could contribute to: 1) potential neuromas-in-continuity, 2) increased rates of axonal escape due to a reduced number of downrange endoneurial tubules available for optimal axon regeneration, and 3) loss of maximal axonal reinnveration of the distal target muscle due to axonal losses or ablation of axons from the regenerating proximal peripheral nerve stump.

RPNIs are created by wrapping transected nerve fascicular units with free muscle grafts.[4,12,14] These free muscle grafts are transferred and wrapped circumferentially around the amputated nerve stump must undergo the following sequence of events: (1) initial immediate devascularization and deinnervation, (2) early period of graft atrophy and degeneration, then (3) delayed revascularization via neo-vascularization from the surrounding wound bed, and finally (4) neurotization of the new accepted graft.[4,12] After the aforementioned sequence of events, these muscle grafts regenerate to form specific re-neurotized muscle units.[4,12] This neurotization procedure thus allows regenerating axons from the transected nerves to create new connections to created neuromuscular units. Besides the above required steps for RPNIs to become established over time, one common identified issue surrounds the fact that we do not precisely know how large a muscle graft is necessary for a given size of nerve to provide optimal re-innervation of the graft construct. Specifically, there is a limit to the size one can take as a free muscle graft. If the graft is "too large and bulky," it will revascularize and thus not take. This situation leads to an increased likelihood of necrotic tissue formation and ultimately failure of the RPNI. Conversely, if the graft is "too small," then the regenerating nerve may not have optimal available motor end plates for re-innervation and the RPNI may fail.

Although both TMR and RPNI techniques have demonstrated efficacy for the management of symptomatic neuroma pain, they have previously been performed independently and without fundamental overlap. We sought to combine the optimal components and concepts of each technique into a single procedure to harness the most efficacious aspects of each procedure. This adaptation combines the theoretical benefits of both TMR and RPNI by providing a distal nerve target to provide for a direct nerve coaptation in combination with denervated but vascularized muscle cuff possessing denervated motor endplates. This pedicled vascularized RPNI (vRPNI) acts similar to an RPNI in that it is a denervated cerclaged muscle cuff seeking to be reinnverated and neurotized yet does not have to go through the same series of steps outlined previously for the isolated, free RPNI technique. Additionally, the devoid motor end plates will seek to capture any axon regeneration from the sprouting TMR nerve coaptation mismatch.

## TECHNIQUE

TMR as performed by both senior authors (I.V. and K.R.E) involves a series of nerve transfers from proximal nerve endings that are coapted to motor nerve targets in adjacent muscles. Typically, the major proximal mixed nerve is sharply truncated at a level proximal to the distal level of amputation. A nearby motor nerve target is identified with the assistance of a nerve stimulator, which increases the speed of identification and efficiency of the operation. Motor nerve targets are visible within the muscle and, under stimulation, will result in a significant, defined muscular contraction. This motor nerve target is then transected, and the proximal mixed nerve is then coapted to the distal transected motor target nerve using a series of 8-0 to 10-0 nylon microsutures for a direct neurorrhaphy (Fig. 1).

To combine this TMR with the vRPNI technique, the neurorrhaphy is wrapped with a pedicled, vascularized surrounding muscle cuff from the freshly denervated muscle (Fig. 2). This denervated muscle cuff, which corresponds to muscle supplied by the transected motor nerve target, provides freshly denervated muscle containing motor endplates that become unoccupied and thus receptive to the transferred peripheral nerve as it regenerates. The coaptation can then be tested since it is freshly denervated, via stimulating the proximal peripheral nerve to assess for distal motor contraction and signal transmission across the transferred nerve repair and coaptation. (**See Video 1 [online]**, which displays a completed fresh TMR with vRPNI coaptation with intraoperative nerve stimulation showing stimulation of distal freshly deinnervated motor nerve and target muscle supplied via the proximal nerve transfer.) (**See Video 2 [online]**, which displays a combined TMR with vRPNI technique with intraoperative nerve stimulation showing stimulation of distal freshly deinnervated motor nerve and target muscle.)

## PATIENTS AND METHODS

After IRB approval, those patients who had undergone TMR in combination with vRPNI since 2015 were queried and included in this study.

## RESULTS

From November 2015 to September 2019, 119 patients (123 limbs) underwent TMR/vRPNI at our institutions. The vast majority were performed at the time of major limb amputation (76% primary TMR/vRPNI) with the remaining 24% performed as part of a symptomatic neuroma excision with the stump revision procedure (ie, 24% secondary TMR/vRPNI). The level of amputations for the entire cohort consisted of 6 shoulder disarticulations, 11 transhumeral amputations, 9 transradial amputations, 46 above knee amputations, and 47 below knee amputations. A total of 478 nerves were transferred as TMR/vRPNI units, with the mean number of 3.9 TMR/vRPNI units per limb amputation site. All primary TMR/vRPNI units were coded as pedicle nerve transfers (CPT code 64905), and secondary TMR/vRPNI cases coded as excision of major

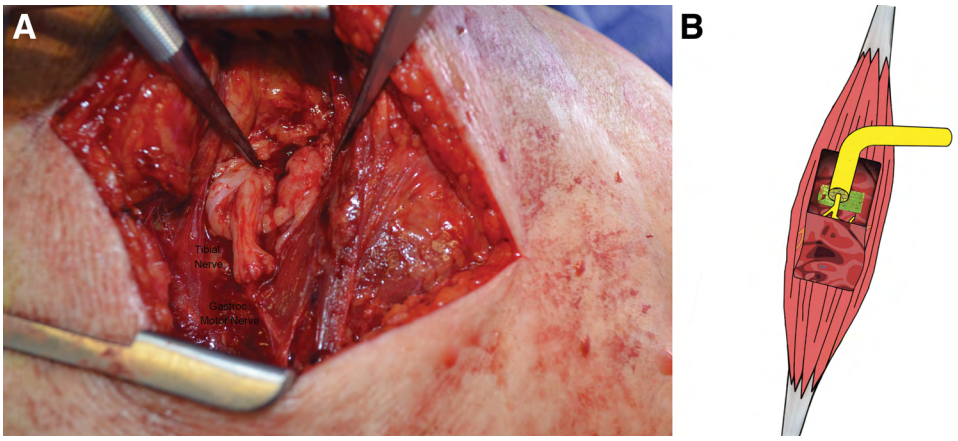


**Fig. 1.** A clinical example of the TMR with vRPNI technique. A, Immediate TMR nerve coaptation illustrating the size mismatch of the larger proximal mixed nerve and smaller distal motor target nerve within surrounding target muscle. Clinical intraoperative example. B, Illustrated rending of TMR concept for the clinical example provided in (A).

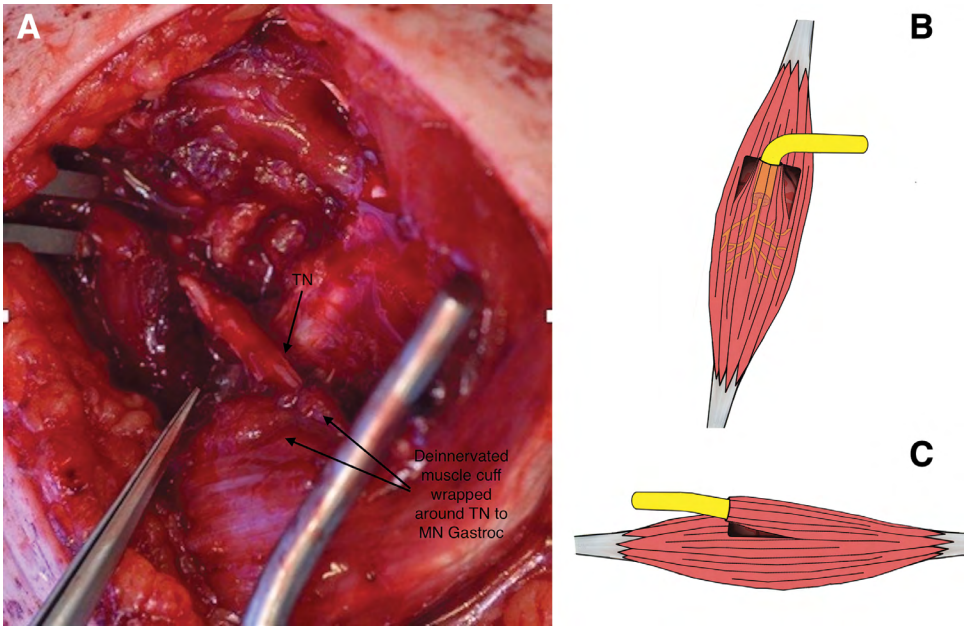


**Fig. 2.** A clinical example of the TMR with vRPNI technique. A, The transferred nerve coaptation is seen wrapped with a surrounding vascularized but freshly deinnervated muscle cuff (vRPNI) to completely cover the prior performed nerve coaptation illustrated in Figure 1A. Clinical intraoperative example. B and C, Illustrated rending of TMR vRPNI concept for the clinical example provided in (A).

peripheral neuroma (CPT code 64784) if the neuroma is resected along with the aforementioned pedicle nerve transfer code.

Symptomatic neuromas have occurred in 3 patients in nerves that were not addressed during their initial TMR/vRPNI index surgery. One patient required a secondary intervention and revision TMR/vRPNI for recurrent neuromas x2 which were treated with a revision allograft TMR procedure with improvement and significant reduction in neuropathic pain. Only 8 patients were lost to follow-up in this reported series, with 111 patients still being active participants in this study at the time of data query.

## DISCUSSION

In the contemporary management of amputees with symptomatic neuromas, many factors should be considered by the primary treating surgeon including the prevention and treatment of neuropathic pain.[1–6,14] Recent technological advancements with TMR and RPNI have changed the landscape of amputee management and have resulted in significant progress in the management of these patients. Both TMR and RPNI were developed initially to provide interfaces for prosthetic control from efferent motor signals to allow for functional prosthetics, and both techniques have been shown to have the added benefit of reduction in pain.

The ideal interface for nerve regeneration should provide amplification and stable transmission of nerve signals to provide fine motor control, promote integration with surrounding tissues, and avoid iatrogenic axonal damage within the peripheral nerve.[10] In addition, they should have the potential to prevent and treat neuropathic pain related to symptomatic neuromas.

We have combined the benefits of the two most accepted techniques to address amputated nerves, thus combining the distinct, unique advantages of both TMR and RPNI. These main advantages include provision of a biologic, neuromuscular target for stimulation and signal generation for electrode transmission in thought-controlled and improved functional prosthetics. An end-to-end nerve coaptation, as done in TMR, serves as the foundation for this nerve transfer and repair technique—as opposed to blindly burying the terminal amputated nerve end into an indiscriminate adjacent muscle, which has shown to be less effective.[1,2] Importantly, the TMR with vRPNI technique also provides a vascularized, denervated muscle cuff (1) to function as a buffer for axonal escape and (2) possesses the potential for additional focal muscle target available for reinnervation and hence muscle stimulation in functional prosthetics. Given the inherent size mismatch of the nerve transfers in TMR, we believe that this is an important aspect of our technique in directly addressing axonal escape issues, while also permitting newly created yet unoccupied motor end plates within the target muscle for acceptance of regenerating transferred peripheral nerve. This reinnervated target muscle construct can effectively become a viable, functional signal generator as long as an identifiable muscle twitch or contraction can be picked up via pattern recognition technology.

While functional prosthetics are an admirable goal, the main goal of peripheral nerve management at the time of amputation should be to limit, improve, or eliminate the potential for neuropathic and PLP. The proposed combined technique adds minimal operative time as the surrounding muscle cuff is directly adjacent to the motor target coaptation by utilizing the adjacent vascularized and now deinnervated muscle. Given that a named vascular pedicle is not dissected, a nerve transfer code only is utilized for billing purposes by the primary authors who have utilized this technique. This easily reproduced technique may combine the optimal benefits of both TMR and RPNI, both of which have become popular techniques for management of symptomatic neuromas, both in the acute and secondary settings of amputation as well as in the management of certain symptomatic neuromas located throughout all areas of the body. TMR and RPNI surgeries have both been shown to decrease the incidence of PLP, while providing a vascularized muscle interface for advanced functional prosthetics. The vascularized nature of this modified RPNI technique may confer additional benefit as the muscle does not require revascularization and thus may be more easily innervated.

By combining the advances of nerve regeneration via direct nerve transfer with a local vascularized but denervated muscle cuff, this evolution in surgical technique represents a refinement of two promising and increasingly applied methods to treat transected nerves and amputees.

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