PART
V

293

Co-funded by the
Erasmus+ Programme
of the European Union

Electrical Stimulation for Re-Innervated Muscles

The European Commission's support for the production of this publication does not constitute an endorsement of the contents, which reflect the views only of the authors, and the Commission and Turkish National Agency cannot be held responsible for any use which may be made of the information contained therein.

CK4Stim

Co-funded by the Erasmus+ Programme of the European Union

With the Presence of Atrophy

CEYHUN TURKMEN • ESRA DOGRU HUZMELI

Introduction

Electrical stimulation (ES) is a frequent and effective therapy for re-innervated atrophic muscles. These approaches employ ES to activate and strengthen muscles to restore function and improve the quality of life. The application of ES methods can be beneficial for a range of patient groups, including those who have suffered spinal cord injuries, peripheral nerve injuries, and other neuromuscular illnesses. In this brief introduction, we will discuss the basic concepts underpinning ES methods for re-innervated atrophic muscles as well as their potential benefits for patients undergoing rehabilitation.[1]

Treatments with ES are necessary to re-innervate atrophied muscles and restore them. It is essential for muscles that have undergone denervation and re-innervation to be stimulated, encouraged to develop, and strengthened by the application of these methods by ES. Functional Electrical Stimulation (FES), Neuromuscular Electrical Stimulation (NMES), and Transcutaneous Electrical Nerve Stimulation (TENS) are ES approaches that can help patients with a range of neuromuscular illnesses by providing their muscles to grow and perform better.[2]

The importance of ES treatments in re-innervated atrophic muscles can be attributed to their ability to improve patient's quality of life and overall function. It may be challenging for patient with atrophied muscles as a result of denervation and re-innervation to carry out daily tasks and participate in social and recreational activities. ES therapies can aid in reversing these impairments by promoting muscle development and function, boosting general strength, and enhancing the patient's ability to do daily chores. In the rehabilitation, ES are regularly used and recognized as an effective, non-invasive form of muscle rehabilitation. Physiotherapists, occupational therapists, and other rehabilitation specialists routinely use ES treatments to treat patients with neuromuscular problems, including re-innervated atrophic muscles.[3]

Anatomy and Physiology of Re-innervation and Muscle Atrophy

After a period of denervation (loss of nerve supply), nerve fibers re-appear and re-connect muscle fibers in a process known as re-innervation. The process of re-innervation, which necessitates a complex interaction between the neurological and muscular systems, is crucial for restoring muscle strength and function. On the other hand, muscular atrophy is the wasting or loss of muscle tissue as a result of several conditions, such as inactivity, immobility, aging, and neurological illnesses. When muscle fibers are not sufficiently activated, muscular atrophy can occur, resulting in a decline in muscle size, strength, and function. Since denervation can cause muscle atrophy and re-innervation is required for muscle recovery, the processes of re-innervation and atrophy are inextricably linked.[4]

Anatomy of Re-Innervation

Due to a lack of nerve stimulation (damaged or severed motor neuron), muscle fibers are denervated and this process may cause atrophy. The neuron might be able to regrow its axon and re-attach to the muscle fibers if the damage is limited to that area. Re-innervation involves several stages:

1. Axonal sprouting: To re-attach muscle fibers, the injured motor neuron's axon starts to grow new branches.
2. Target recognition: To link with the right muscle fibers, the sprouting axons look for and identify them.
3. Synapse formation: To transmit nerve impulses and cause muscular contractions, the axon terminals create new synapses with the muscle fibers.[5]

Physiology of Re-Innervation

Neurological and muscle systems interact intricately during the re-innervation process. The following things occur after the axons have grown and re-connected with the muscle fibers:

1. Retrograde signaling: The re-joined axon communicates with the cell body via retrograde signals, which activate the gene expression and protein synthesis required for nerve fiber's upkeep and expansion.
2. Remodeling of muscle fibers: The rejoined muscle fibers alter in size, shape, and contractile characteristics to accommodate the new nerve supply.
3. Motor unit recruitment: The re-energized muscle fibers are absorbed into the already-existing motor units, resulting in an improvement in strength and functionality.[4,6,7]

When an injury occurs in the peripheral nervous system, the portion of the axon distal to the injury undergoes Wallerian Degeneration, which is the degeneration of the axon and myelin sheath. Following this, an axonal stump is formed. In response to the injury, Schwann cells in the area proliferate and begin to produce new Schwann cells, which align and form a tube-like structure known as the bands of Bungner. These bands guide the axonal stump to its original target. Macrophages are also recruited to the area to help remove debris and remnants of the degenerated axon. This clears the path for the regenerating axon to grow through the tube of Schwann cells. The axonal stump begins to grow and elongate, following the guidance of Bungner's bands. Schwann cells also begin to produce a new myelin sheath to surround the regenerating axon. With time, the axon grows and eventually reaches its original target, completing the process of axon regeneration. While the process of nerve regeneration in the peripheral nervous system can be slow and may not always result in full recovery of function, it is a remarkable process that demonstrates the regenerative capacity of the nervous system.[5,7,8]

Peripheral nerve injury is followed by muscular atrophy, depending on the type of injury and treatment condition.

The Anatomy of Muscle Atrophy

Muscle atrophy can occur due to numerous factors, including disuse, immobilization, aging, and neurological disorders (Figure 33.1).

Some of the anatomical alterations that result from muscular atrophy include the following:[8]

1. A loss in muscle mass is caused by a reduction in the size of the muscle fibers, which become smaller in diameter.
2. Myofibril loss is another factor that affects muscle size and strength. Myofibrils are the contractile units of muscle fibers.
3. Alterations in fiber type: Type II fast-twitch fibers, which are more prone to atrophy, may replace type I slow-twitch fibers in muscle tissue.

The Physiology of Muscle Atrophy

Muscle atrophy is caused by several complicated and poorly understood physiological processes, including:[6,8,9]

1. Protein deterioration: There is an increase in the breakdown of muscle proteins (proteolysis), which results in a loss of muscle mass.
2. Decreased protein synthesis: This results in a reduction in the production of new muscle

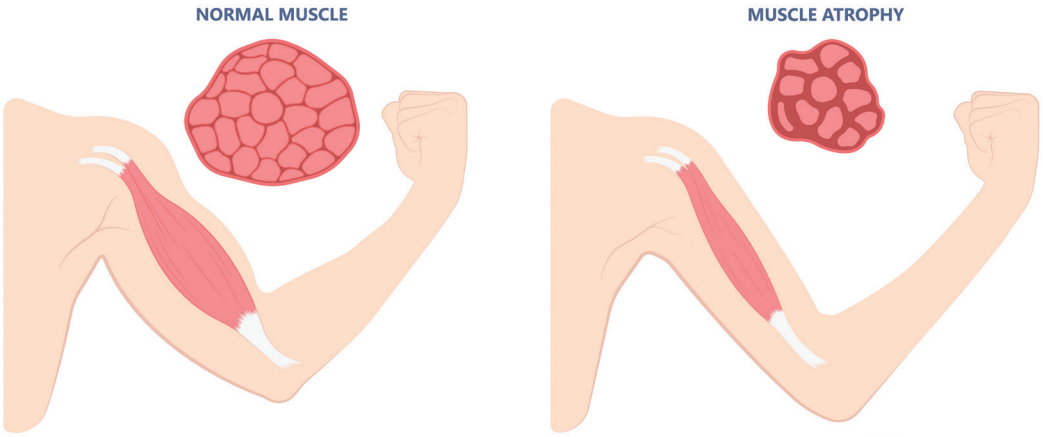

Figure 33.1 Muscle atrophy.

proteins, which accelerates the loss of muscle mass.

3. Mitochondrial dysfunction: The energy-producing mitochondria starts to malfunction, which contributes to the loss of muscle function.

In conclusion, the interaction between the neurological and muscular systems is a key factor in the processes of re-innervation and muscle atrophy. For muscle function and strength to be recovered, re-innervation is necessary.[6,9]

Overview of Electrical Stimulation for Re-Innervation

ES is a type of therapy that strengthens and improves the function of muscles by stimulating nerves and muscles. In the rehabilitation of re-innervated muscles that have atrophy owing to denervation, especially ES techniques can be helpful. Some ES techniques can be applied when re-innervated muscles exhibit atrophy.[10]

ES can lead to the regeneration of all motor axons within 3 weeks, rather than the typical 8-10 weeks that it takes without stimulation. Additionally, this stimulation has a similar effect on sensory nerve regeneration. This finding is significant because it suggests that ES may be a useful technique for promoting nerve regeneration and accelerating the recovery of motor and sensory function following nerve injury. By accelerating axon outgrowth and promoting nerve regeneration, ES could potentially lead to faster and more complete recovery from nerve injuries in humans as well.[11]

Marqueste et al. discussed the use of ES for muscle re-innervation and nerve regeneration in the Tibialis Anterior muscle.[12] The study included four groups of animals: the first group (C) was a control group with no surgical intervention, the second group (LS) had Peroneal nerve sectioned and self-anastomosed without any chronic electrostimulation, the third group (LSEm) had Tibialis Anterior muscle electrically stimulated with a monophasic current following nerve sectioning and self-anastomosis, and the fourth group (LSEb) had muscle electrically stimulated with a biphasic modulated current following nerve sectioning and self-anastomosis. All animals were kept under controlled environmental conditions with free access to food and water. The LSEm group received a monophasic rectangular single shock current with a voltage of 10 V delivered for 300 millisecond (ms) once a minute using a stimulator. The LSEb group, on the other hand, was stimulated with a biphasic current modulated in frequency and shock duration, with a stimulation frequency increasing from 4 Hertz (Hz) [200 microseconds (μs)] to 75 Hz (150 μs) during 3 second (s), followed by a 1.5 s plateau at 75 Hz, and then a decrease back to 4 Hz (200 μs) during 2 s. The intensity of stimulation was adjusted daily for each animal to achieve the maximal but non-painful contraction during the stimulation period. Both groups were stimulated

for 10 consecutive weeks, 5 hours per day, 5 days per week. The use of chronic muscle electrostimulation with biphasic currents modulated in both frequency and pulse duration has been shown to have several beneficial effects on denervated muscles. LSEb can help to prevent muscle atrophy, maintain muscle strength and endurance, and preserve the biochemical and histochemical properties of muscle. In particular, LSEb has been found to help keep the muscle closer to its control phenotype, which refers to the normal state of the muscle before denervation. This means that the muscle maintains its normal biochemical and histochemical properties, such as the levels of certain enzymes and the composition of its fibers. According to their findings, the use of an electrical current modulated at high frequency and pulse duration, as opposed to a non-modulated current, was found to improve sensory re-innervation and muscle re-innervation. In another study, the authors also found that biphasic modulated stimulation was recommended for better re-innervation and that muscle electrostimulation following denervation and re-innervation tended to restore size and functional and histochemical properties better than in unstimulated muscle.[12,13]

Bowman et al. conducted a study to compare three different stimulation parameters: pulse duration (50 and 300 μs), waveform symmetry (asymmetrical and symmetrical biphasic waveforms), and source regulation (current and voltage source regulation).[14] The results of the study showed that regardless of waveform or source regulation, participants overwhelmingly preferred the 300 μs pulse duration. They also strongly preferred the symmetrical biphasic waveform. However, there was an inconsistent preference for either regulated voltage or regulated current sources. This study highlights the importance of considering patient comfort when selecting stimulation parameters for surface stimulation. They suggested that using longer pulse durations and symmetrical biphasic waveforms may help to improve patient comfort during surface stimulation.

It is important to note that further research is needed to determine the optimal methods for ES during muscle re-innervation and nerve regeneration.

Transcutaneous Electrical Nerve Stimulation

Electrical impulses are used in TENS, which is a non-invasive therapy, to reduce pain and encourage muscular activity. TENS can be used to enhance muscle function, lessen pain, and promote muscle growth in re-innervated atrophic muscles.[15]

The Purpose of Usage

Pain reduction: Re-innervated atrophic muscles with nerve loss or muscle atrophy may experience pain relief from TENS. The TENS unit's electrical impulses can prevent pain signals from reaching the brain, thus lessening the perception of pain.[16,17]

Muscular activation: Re-innervated atrophic muscles can also benefit from TENS to stimulate muscular activation. Muscle contractions brought on by the TENS unit's electrical impulses might enhance muscle function and strength.[16,17]

Muscular growth: TENS can be applied to re-innervated atrophic muscles to encourage muscular growth. The TENS unit's electrical impulses can encourage the creation of growth factors, which can aid in promoting muscle growth and repair.[16,17]

The Recommended Parameters

Electrodes are applied to the skin over the targeted muscle or nerves using TENS techniques for re-innervated atrophic muscles. The electrodes are attached to a TENS machine, which stimulates the muscle or nerve with electrical impulses. Depending on the patient's particular needs and tolerance, the electrical impulses' frequency, intensity, and pulse width can be changed. Usually, atrophic re-innervated muscles are treated with low-frequency TENS. It is typical to use a frequency of 2 to 4 Hz to encourage muscle growth and healing. Current intensity should be adjusted to provide muscular activation while still being comfortable for the patient. As the patient's tolerance increases, the intensity can be gradually increased. For atrophic re-innervated muscles, a longer pulse width is often employed to encourage muscular activation

and development. Common pulse durations range from 100 to 200 μs.[17]

Russian Electrical Stimulation

Russian Electrical Stimulation (RES) is a form of NMES that stimulates motor neurons and causes muscular contractions by using high-frequency electrical impulses. The process of re-connecting nerve and muscle fibers that have been severed or damaged by illness or injury is known as re-innervation of muscles. It is possible to accelerate this process naturally or with the use of equipment such as ES. RES can be used in conjunction with muscle re-innervation techniques to hasten the process of nerve fiber re-innervation and muscle fiber activation. More research is needed to determine the effectiveness and safety of these methods for re-innervated muscles.[18,19]

The Purpose of Usage

RES can be utilized to re-innervate atrophic muscles, activate them, promote muscular development, and increase blood flow. By causing muscular contractions, electrical impulses from the RES can improve muscle function and strength. RES can also boost the synthesis of growth factors to aid in muscle development and repair. Increased blood flow to damaged muscles can also hasten their recovery and improve their functionality.[20,21]

The Recommended Parameters

Electrodes are applied to the skin above the targeted muscle as part of the RES procedures for re-innervating atrophic muscles. The electrodes are attached to a Russian stimulator, which stimulates the muscle with electrical impulses. Depending on the patient's particular needs and tolerance, the electrical impulses' frequency, intensity, and pulse duration can be changed. The RES current is a medium frequency current with a frequency of 2500 Hz. This current is delivered in bursts with pulse lengths of 0.2 ms and is broken up by pauses of 10 ms. This produces 50 bursts of low frequency Faradic current every second.[21]

Frequency: For RES, a frequency of 2500 Hz is frequently employed. In atrophic, re-innervated muscles, this frequency is beneficial in stimulating muscle development and healing.[21]

Curent intensity: While still causing muscle activation, the intensity of RES should be set at a level that is comfortable for the patient. As the patient's tolerance increases, the intensity can be gradually increased.[21]

Pulse duration: RES often uses a longer pulse length to encourage muscle activation and development. Common pulse durations range from 200 to 400 μs.[21]

If RES is not used carefully, it can interfere with re-innervation and damage muscle fibers. Therefore, in the acute phase of the post-surgical process RES is not recommended.

Modified Galvanic Stimulation

Direct current is used in Modified Galvanic Stimulation to excite muscles and nerves. To stop muscle wasting and enhance muscular function in the context of atrophy, Galvanic Stimulation may be applied.[22]

The purpose of Usage

Muscle activation: Atrophic muscles that have been re-innervated can be activated with Modified Galvanic Stimulation. Muscle contractions brought on by the Galvanic Stimulator's electrical current can enhance muscular function and strength. Modified Galvanic Stimulation should be stopped as soon as the muscle starts to contract voluntarily.

Muscle growth: Modified Galvanic Stimulation is effective in promoting muscle growth in atrophic re-innervated muscles. The electrical current from the Galvanic Stimulator can help stimulate the production of growth factors, which can promote muscle growth and repair.[20]

Pain relief: Atrophic, re-innervated muscles can also benefit from Modified Galvanic Stimulation for pain alleviation. The Galvanic Stimulator's electrical current can lessen pain by decreasing swelling and enhancing blood flow to the injured region.[23]

The Recommended Parameters

Electrodes are placed to the skin above the targeted muscle as part of the procedures for employing

Modified Galvanic Stimulation in re-innervated atrophic muscles. Depending on the patient and their unique needs, the Modified Galvanic Stimulation settings used in atrophic re-innervated muscles can be changed.[24]

Frequency: Direct current, which is used in Modified Galvanic Stimulation, has a frequency of 0 Hz. The frequency setting for Galvanic Stimulation is therefore irrelevant.[24]

Current intensity: The intensity of Modified Galvanic Stimulation should be adjusted to the patient's comfort level while still causing muscles to contract. As the patient's tolerance increases, the intensity can be gradually increased.[24]

Pulse duration: For Modified Galvanic Stimulation, the pulse width can be anywhere between 30 and 150 ms. To encourage muscular activation and growth, longer pulse durations may be used.[24]

It is crucial to remember that only qualified specialists with experience using the technique and the ability to guaranty the safety and efficacy of the therapy should carry out any ES procedures. A personalized treatment plan should be created based on the requirements of every patient and conditions because these therapies may not be appropriate for all people.[24]

Low Frequency Current Electrical Stimulation

The aim of using low frequency current ES is to stimulate the muscles individually or in groups for diagnostic or therapeutic purposes. It is accepted that the most suitable current type for this purpose is quadrangular currents with a frequency up to about 100 Hz. In the treatment, generally 1-100 Hz are used.[25]

The Purpose of Usage

Accelerating axon outgrowth: Brief low-frequency ES has been shown to accelerate axon outgrowth across injury sites and enhance nerve regeneration and target re-innervation in animal models and patients. This is due to the elevation of neuronal cyclic adenosine monophosphate and increased expression of neurotrophic factors and other growth-associated genes, including cytoskeletal proteins. Furthermore, ES of denervated muscles accelerates muscle re-innervation immediately after nerve transection and surgical repair also.[26]

Accelerating axonal regeneration and target re-innervation: Gordon et al. conducted a randomized control trial to investigate the effect of low frequency ES on axonal regeneration in patients with median nerve compression in the carpal tunnel.[27] Patients underwent carpel tunnel release surgery (CTRS), and those in the stimulation group received 1 hour of 20 Hz bipolar ES immediately after surgery. The researchers used surface electrodes to stimulate the thenar eminence muscle and connected these electrodes to an Electromyography (EMG) machine. The stimulation intensity was gradually increased to the maximum tolerated limit of 4-6 Volts (V) with a duration of 0.1-0.8 ms, delivered as a continuous 20 Hz train for 1 hour. This level of intensity was sufficient to produce a fused tetanic contraction but not so high as to cause excessive discomfort to the subjects. The protocol used in the study was designed to mimic that used in previous animal studies conducted by the researchers. Patients were followed up for a year, and their axonal regeneration was quantified using motor unit number estimation (MUNE) and sensory and motor nerve conduction studies. Functional recovery was assessed using various tests. The study found that the ES group had a significant improvement in axonal regeneration, with MUNE increasing from 150±62 motor units (MU) at baseline to 290±140 MU 6-8 months after CTRS. In contrast, there was no significant improvement in the control group. Terminal motor latency also significantly accelerated in the stimulation group but not in the control group. Sensory nerve conduction values also significantly improved in the stimulation group earlier than in the control group. Other outcome measures showed significant improvement in both patient groups. In conclusion, the study suggests that low frequency ES can accelerate axonal regeneration and target re-innervation in humans. The increase in MUNE observed in the ES group suggests that there was an increase in the number of motor units re-innervating the thenar muscles, indicating suc-

cessful axonal regeneration. Additionally, the acceleration in terminal motor latency and improvement in sensory nerve conduction suggests that the ES group experienced earlier re-innervation of the median nerve compared to the control group. These findings suggest that low frequency ES is a promising therapeutic approach to enhance nerve regeneration and functional recovery in patients with nerve injuries.

Providing neuroprotective effect on sensory neurons: Vivo et al. investigated whether immediate ES after sciatic nerve injury could improve axonal regeneration in rats.[28] Two groups of rats were studied, with one group receiving ES (3 V, 0.1 ms at 20 Hz) for one hour after nerve injury and the other group serving as a control. Various tests were performed to assess muscle re-innervation and changes in spinal cord circuitry excitability at different time points after surgery. The results showed that the group receiving ES had higher levels of re-innervation and a significantly higher number of regenerated myelinated fibers in the distal tibial nerve compared to the control group. Immunohistochemical labeling of sensory afferents in the spinal cord dorsal horn showed that the expression of substance P, a neuropeptide involved in pain transmission, was preserved in the group receiving ES. This suggests that ES may have a neuroprotective effect on sensory neurons. In summary, the study suggests that brief ES applied immediately after sciatic nerve injury can promote axonal regeneration and reduce spinal reflex excitability in rats.[28]

The Recommended Parameters

Electrodes are placed to the skin above the targeted muscle as part of the procedures for employing low frequency ES in re-innervated atrophic muscles.

Frequency: Low frequency ES is generally used between 10-30 Hz, but the most recommended frequency is 20 Hz.[26-28]

Current intensity: The intensity of low frequency ES should be adjusted to the patient's comfort level while still causing muscles to contract. As the patient's tolerance increases, the intensity can be gradually increased.[26-28]

Reasons for Use of ES for Re-innervated Muscles

1. ES restores muscle function: Muscles that have atrophy can be stimulated with ES techniques such as NMES and FES, increasing muscular contractions and enhancing muscle function. When voluntary muscle activation is compromised, such as in patients with spinal cord injuries or nerve loss, these techniques can be especially helpful.[29]
2. ES prevents further muscle wasting: By supplying consistent ES that helps to maintain muscular mass and strength, ES techniques can help stop further muscle wasting in atrophied, re-innervated muscles.[30]
3. ES provides pain management: In atrophied, re-innervated muscles, ES techniques like TENS and Modified Galvanic Stimulation can be used to relieve pain. These treatments relieve pain and suffering by activating the nerves that provide pain signals.[31]
4. ES improves muscle endurance: Muscle endurance can be increased in atrophied, re-innervated muscles using ES techniques such as NMES and RES. These techniques can assist in boosting the number of muscle fibers that are activated by routine ES, which will eventually improve endurance.[32]
5. ES enhances physiotherapy and rehabilitation outcomes: To improve results in the rehabilitation of atrophied re-innervated muscles, ES approaches can be employed in conjunction with other rehabilitation procedures, including exercise and physiotherapy. To promote muscular activation and boost muscle strength, for instance, NMES or FES may be used to stimulate the muscles during exercise.[33]
6. ES increases Brain-Derived Neurotrophic Factor (BDNF): Neurotrophins, in particular BDNF, have been identified as key regulators of axon regeneration. According to the studies short ES promotes the expression of BDNF in motoneurons that are renewing.[34,35]
7. ES reduces muscle atrophy: Willand et al. used ES for 5 days a week for 1 hour for 1 month

with electrodes implanted in the Gastrocnemius muscle immediately after Tibial nerve transection and immediate repair with the Fibular nerve to examine the effect of short-term muscle stimulation on increasing re-innervation and preventing muscle atrophy.[36] Two months after repair, it was discovered that stimulated animals had significantly higher muscle weights, twitch strengths, and type I fibers than repaired controls with no stimulation.

8. ES speeds up muscle re-innervation: Gordon et al. evaluated whether ES promotes axon regeneration and muscle re-innervation in carpal tunnel syndrome patients with severe axon degeneration following surgery.[37] ES speeds up axon outgrowth and targets muscle re-innervation. After chronic axotomy, chronic Schwann cell denervation, and after immediate nerve repair with and without trains of 20 Hz ES for 1 hour to 2 weeks in rats and in patients with carpal tunnel syndrome, the number of regenerating motor units and neurons was counted electrophysiologically and with dye-labeling. In contrast to a non-significant increase in the number of motor units in the control group, ES (1 hour) facilitated the entire re-innervation of thenar muscles in patients and accelerated axon outgrowth across the suture site in connection with enhanced neuronal neurotrophic factor and receptors. They concluded that both in humans and animals short ES expedites target muscle re-innervation and axon sprouting.

Overall, ES methods have a range of clinical applications in the rehabilitation of atrophied re-innervated muscles and can be used in combination with other rehabilitation techniques to achieve optimal outcomes. However, it is important to work with a healthcare professional to determine the most appropriate treatment plan for each individual patient.

Udina et al. reported that a single session of ES for one hour of an intact peripheral nerve can enhance the growth of nerve cell processes in vitro and in vivo.[38] Specifically, the study found that ES increased neurite outgrowth of dorsal root ganglion (DRG) neurons in vitro and promoted outgrowth of central sensory axons into the lesion site in vivo. Additionally, the study showed that ES increased the levels of cyclic adenosine monophosphate in DRG neurons. The ES of an intact peripheral nerve for 1 hour at 20 Hz promotes the sensory neurite outgrowth in vitro and in the spinal cord in vivo. They concluded that the number of regenerated axons was better when 20 Hz was given than 200 Hz.

In a study, the effects of low-intensity electric current at 20 Hz and Schwann-like cells on peripheral nerve damage were investigated. They found that nerve conduction velocity measurements which made at the 6th week after ES with a 1 hour 20 Hz 3V intensity the conduction velocity was recorded as 19.26 ± 4.54 m/s in the continuous neuroma damage model, while the conduction velocity with ES was 25.48 ± 4.95 m/s. Although an increase in transmission speed was detected between these two groups, this difference was not statistically significant. ES nerve conduction velocity, axon diameter, and myelin sheath thickness increased in the continuous neuroma model after ES; however, it was not found to be as effective as shown in the literature in their experimental conditions.[39]

Conclusion

In conclusion, the rehabilitation of atrophied re-innervated muscles has shown promise when using ES techniques. Biphasic modulated and low frequency stimulation (20 Hz) has been found to be successful in restoring muscular function, stopping additional muscle wasting, and improving the results of physiotherapy and rehabilitation. In order to improve treatment protocols, to identify the most suitable patient populations for these therapies, and to understand better the mechanisms underlying the success of these approaches, further study is still required.

One of the goals of future studies in this area may be to apply ES approaches to cure various forms of muscular atrophy, including age-related and disuse atrophy. There may be opportunities to examine the use of cutting-edge ES techniques, such as low-frequency and patterned stimulation,

to further increase the efficacy of these treatments. Therefore, with continued research and improvement, ES methods have the potential to play a significant role in the rehabilitation of atrophied re-innervated muscles, thereby improving patient outcomes and quality of life.

References

1. Vafadar AK, Côté JN, Archambault PS. Effectiveness of functional electrical stimulation in improving clinical outcomes in the upper arm following stroke: A systematic review and meta-analysis. Biomed Res Int. 2015;2015:729768. doi:10.1155/2015/729768.
2. Gondin J, Cozzone PJ, Bendahan D. Is high-frequency neuromuscular electrical stimulation a suitable tool for muscle performance improvement in both healthy humans and athletes? Eur J Appl Physiol. 2011;111:2473-87. doi:10.1007/s00421-011-2101-2.
3. Peurala SH, Tarkka IM, Pitkänen K, Sivenius J. The effectiveness of body weight-supported gait training and floor walking in patients with chronic stroke. Arch Phys Med Rehabil. 2005;86: 1557-64. doi:10.1016/j.apmr.2005.02.005.
4. Gordon T. Peripheral nerve regeneration and muscle reinnervation. Int J Mol Sci. 2020;21 20201117. doi:10.3390/ijms21228652.
5. Marshall KL, Farah MH. Axonal regeneration and sprouting as a potential therapeutic target for nervous system disorders. Neural Regen Res. 2021;16:1901-10. doi:10.4103/1673-5374.308077.
6. Lee B, Cho Y. Experimental model systems for understanding human axonal injury responses. Int J Mol Sci. 2021;22:474. doi:10.3390/ijms22020474.
7. Fu SY, Gordon T. The cellular and molecular basis of peripheral nerve regeneration. Mol Neurobiol. 1997;14:67-116. doi:10.1007/bf02740621.
8. Wilkinson DJ, Piasecki M, Atherton PJ. The age-related loss of skeletal muscle mass and function: Measurement and physiology of muscle fibre atrophy and muscle fibre loss in humans. Ageing Res Rev. 2018;47:123-32. doi:10.1016/j.arr.2018.07.005.
9. Sandri M. Protein breakdown in muscle wasting: Role of autophagy-lysosome and ubiquitin-proteasome. Int J Biochem Cell Biol. 2013;45:2121-9. doi:10.1016/j.biocel.2013.04.023.
10. Bersch I, Fridén J. Electrical stimulation alters muscle morphological properties in denervated upper limb muscles. EBioMedicine. 2021;74:103737. doi:10.1016/j.ebiom.2021.103737.
11. Al-Majed AA, Neumann CM, Brushart TM, Gordon T. Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. J Neurosci. 2000;20:2602-8. doi:10.1523/jneurosci.20-07-02602.2000.
12. Marqueste T, Decherchi P, Dousset E, Berthelin F, Jammes Y. Effect of muscle electrostimulation on afferent activities from tibialis anterior muscle after nerve repair by self-anastomosis. Neuroscience. 2002;113:257-71. doi:10.1016/s0306-4522(02)00187-2.
13. Marqueste T, Decherchi P, Desplanches D, Favier R, Grelot L, Jammes Y. Chronic electrostimulation after nerve repair by self-anastomosis: Effects on the size, the mechanical, histochemical and biochemical muscle properties. Acta Neuropathol. 2006;111:589-600. doi:10.1007/s00401-006-0035-2.
14. Bowman BR, Baker LL. Effects of waveform parameters on comfort during transcutaneous neuromuscular electrical stimulation. Ann Biomed Eng. 1985;13:59-74. doi:10.1007/bf02371250.
15. Dailey DL, Rakel BA, Vance CGT, Liebano RE, Amrit AS, Bush HM, Lee KS, Lee JE, Sluka KA. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. Pain. 2013;154:2554-62. doi:10.1016/j.pain.2013.07.043.
16. Gibson W, Wand BM, Meads C, Catley MJ, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for chronic pain - An overview of Cochrane Reviews. Cochrane Database Syst Rev. 2019;4:CD011890. doi:10.1002/14651858.CD011890.pub3.
17. Johnson M. Transcutaneous electrical nerve stimulation: mechanisms, clinical application and evidence. Rev Pain. 2007;1:7-11. doi:10.1177/204946370700100103.
18. Knutson JS, Fu MJ, Sheffler LR, Chae J. Neuromuscular electrical stimulation for motor restoration in hemiplegia. Phys Med Rehabil Clin N Am. 2015;26:729-45. doi:10.1016/j.pmr.2015.06.002.
19. Wang TJ, Sung K, Wilburn M, Allbright J. Russian stimulation/functional electrical stimulation in the treatment of foot drop resulting from lumbar radiculopathy: A case series. Innov Clin Neurosci. 2019;16(5-6):46-9. PMID:31440402.
20. Hamid S, Hayek R. Role of electrical stimulation for rehabilitation and regeneration after spinal cord injury: An overview. Eur Spine J. 2008;17(9):1256-69. doi:10.1007/s00586-008-0729-3.
21. Ward AR, Shkuratova N. Russian electrical stimulation: The early experiments. Phys Ther. 2002;82(10):1019-30. PMID:12350217.
22. Fridman GY, Della Santina CC. Safe direct current stimulator 2: Concept and design. Annu Int Conf IEEE Eng Med Biol Soc. 2013;2013:3126-9. doi:10.1109/embc.2013.6610203.
23. Alshahrani MS, Tedla JS, Reddy RS, Asiri F. Effectiveness of hydrogalvanic bath on improving pain, disability, and quality of life in individuals with chronic nonspecific neck pain: A randomized controlled trial. Evid Based Complement Alternat Med. 2020;2020:7974816. doi:10.1155/2020/7974816.
24. Chandrasekaran S, Davis J, Bersch I, Goldberg G, Gorgey AS. Electrical stimulation and denervated muscles after spinal cord injury. Neural Regen Res. 2020;15(8):1397-407. doi:10.4103/1673-5374.274326.
25. Şimşek N, Kırdı N, Meriç A, Savcı S, Çetişli Korkmaz N, Fırat T, et al. (2015), Elektroterapide temel prensipler ve klinik uygulamalar. Ankara: Pelikan Yayincilik. ISSN:978-605-9160-03-2.
26. Gordon T. Electrical stimulation to enhance axon regeneration after peripheral nerve injuries in animal models and humans. Neurotherapeutics. 2016;13(12):295-310. doi:10.1007/s13311-015-0415-1.
27. Gordon T, Amirjani N, Edwards DC, Chan KM. Brief post-surgical electrical stimulation accelerates axon regeneration and muscle reinnervation without affecting the functional measures in carpal tunnel syndrome patients. Exp Neurol. 2010;223(1):192-202. doi:10.1016/j.expneurol.2009.09.020.
28. Vivó M, Puigdemasa A, Casals L, Asensio E, Udina E, Navarro X. Immediate electrical stimulation enhances regeneration and reinnervation and modulates spinal plastic changes after sciatic nerve injury and repair. Exp Neurol. 2008;211(1):180-93. doi:10.1016/j.expneurol.2008.01.020.
29. Schils S, Ober T. Functional electrical stimulation (FES) in the diagnosis and treatment of musculoskeletal and neuromuscular control abnormalities in horses - Selected case studies. J Equine Vet Sci. 2022;117:104078. doi:10.1016/j.jevs.2022.104078.

30. Graham ZA, Lavin KM, O'Bryan SM, Thalacker-Mercer AE, Buford TW, Ford KM, et al. Mechanisms of exercise as a preventative measure to muscle wasting. Am J Physiol Cell Physiol. 2021;321(1):C40-57. doi:10.1152/ajpcell.00056.2021.
31. Vance CG, Dailey DL, Rakel BA, Sluka KA. Using TENS for pain control: The state of the evidence. Pain Manag. 2014;4(3):197-209. doi:10.2217/pmt.14.13.
32. Doucet BM, Lam A, Griffin L. Neuromuscular electrical stimulation for skeletal muscle function. Yale J Biol Med. 2012;85(2):201-15. PMID:22737049.
33. Gobbo M, Lazzarini S, Vacchi L, Gaffurini P, Bissolotti L, Padovani A, et al. Exercise combined with electrotherapy enhances motor function in an adolescent with spinal muscular atrophy type III. Case Rep Neurol Med. 2019;2019:4839793. doi:10.1155/2019/4839793.
34. Al-Majed AA, Brushart TM, Gordon T. Electrical stimulation accelerates and increases expression of BDNF and trkB mRNA in regenerating rat femoral motoneurons. Eur J Neurosci. 2000;12(12):4381-90. PMID:11122348.
35. McGregor CE, English AW. The Role of BDNF in peripheral nerve regeneration: activity-Dependent treatments and val66met. Front Cell Neurosci. 2018;12:522. doi:10.3389/fncel.2018.00522.
36. Willand MP, Holmes M, Bain JR, Fahnestock M, De Bruin H. Electrical muscle stimulation after immediate nerve repair reduces muscle atrophy without affecting reinnervation. Muscle Nerve. 2013;48(2):219-25. doi:10.1002/mus.23726.
37. Gordon T, Brushart TM, Chan KM. Augmenting nerve regeneration with electrical stimulation. Neurol Res. 2008;30(10):1012-22. doi:10.1179/174313208x362488.
38. Udina E, Furey M, Busch S, Silver J, Gordon T, Fouad K. Electrical stimulation of intact peripheral sensory axons in rats promotes outgrowth of their central projections. Exp Neurol. 2008; 210(1):238-47. doi:10.1016/j.expneurol.2007.11.007.
39. Kiliç MA. (2020), Electrical stimulation and the effects of schwann-like cells on peripheral nerve damage. Ankara; Phd Thesis.

Co-funded by the Erasmus+ Programme of the European Union

In Initial Phase

GUZIN KARA CAKICI • NILUFER CETISLI-KORKMAZ

Introduction

Peripheral nerve injury (PNI) is a complex condition in which different signs and symptoms such as numbness, tingling, throbbing, burning, and sharp pain are seen together.[1] Although peripheral nerves have self-renewal and healing mechanisms, they are inherently vulnerable to factors such as acute pressure or trauma, and their recovery is usually slow and partial (Figure 34.1).[1,2] This is because healing depends on axon terminations and access to intracellular substances. Therefore, the rate of recovery is 1-3 mm per day, similar to the transport rate of the axon.[2] There are many factors that affect the rate of recovery after PNI. The severity of the nerve injury, time elapsed between injury and surgical repair, distance from the injury site to the target muscle or organ, age of the patient, and appropriately guided axonal re-innervation are some of these factors.[3]

Functional recovery is directly related to the severity of nerve injury. While level 1 neuropraxia injuries require only medical treatment, recovery can be achieved in axonotmesis injuries between level 2 and 4 when no significant functional gain is observed in electrodiagnostic tests within 3 to 6

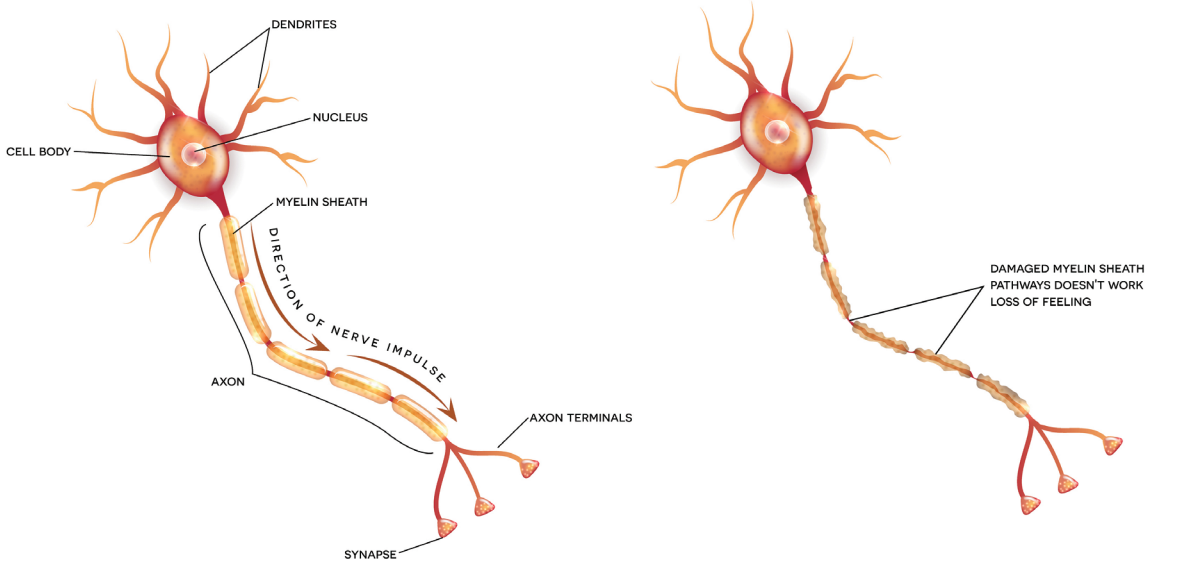

Figure 34.1 Changes after peripheral nerve injury.

months. Severe level 5 neurotmesis injury typically requires surgical repair. Nerve early re-innervation is critical to prevent atrophy of both nerve and muscle.[3]

Electrical stimulation (ES) is a non-invasive technique that enhances and regulates healing-related gene release in healing neurons, similar to crush injuries. The ES technique applied before or after surgery is seen as a conditioning strategy.[4] Daily applied ES upregulates intramuscular neurotrophic factors and stimulates terminal branching. However, it has been reported in the literature that its application alone has a small contribution in terms of long-term functional re-innervation.[5] ES applied without exercise can result in misdirection of motor axon regeneration to reinnervate different muscle groups.[6] For this reason, it is crucial to maintain the ES technique to be applied by the physiotherapist under the guidance of a protocol that is appropriate for the patient's injury condition and will contribute to the healing of the axon for a long time.

Electrical Stimulation Methods

In the literature, it is stated that there is a need to determine the optimum parameters for an effective ES method in the initial phases of the re-innervation period after ES. Most studies have used short intraoperative ES of 20 Hertz (Hz) for 1 hour as standard immediately after nerve repair.[3-5,7-10] However, it has not yet been determined whether this 1-hour application has the optimum efficiency.[3]

There are different ES methods applied in the initial phases of the re-innervation period as a result of PNI. Among these methods, there are methods such as Neuromuscular Electrical Stimulation (NMES), Functional Electrical Stimulation (FES), High Voltage Pulsed Galvanic Stimulation (HVPGS), and Transcutaneous Electrical Nerve Stimulation (TENS).

Neuromuscular Electrical Stimulation

Brief Low Frequency Electrical Stimulation

Although there are short intraoperative low frequency stimulation methods applied in different protocols in the literature, 20-50 Hz applications that will reveal muscle contraction are generally preferred for restoring sensorimotor function.[9,11] It is thought that this method of 20 Hz applied for 1-hour increases the production of neurotrophic factors and increases the functional recovery or nerve regeneration as a result of the increased regulation of these substances in their receptors.[11]

In a study, acute brief low frequency ES was applied to patients who had undergone surgery for carpal tunnel syndrome. The parameters of the current were 20 Hz, 4-6 Volts (V), 0.1-0.8 milliseconds (ms) and 1-hour application. It has been determined that this method improved axonal regeneration and accelerated muscle nerve regeneration. In another study, it was found that the application to patients with cubital tunnel syndrome who had undergone surgery with 20 Hz, balanced biphasic pulsed, 30 V, and 0.1 ms current for 1-hour was effective in muscle and nerve regeneration. These effects were also demonstrated by functional evaluations, and it was determined that it continued in the next 3-year follow-up evaluations. Significant differences in sensory and motor functions were found in the 6-month follow-up after the protocol was applied to the patients who underwent surgery after digital nerve rupture at 20 Hz, balanced biphasic beat, 30 V, and 0.1-0.4 ms for 1-hour compared to the control group.[9]

In a study, a NMES program was planned for the patients with traumatic brachial plexus injury. The current characteristics were a continuous pulse of 20 Hz for 40 minutes (min). The Biceps Brachii muscle was stimulated with double-channel electrodes from the origo and insertio of the muscle. The ES program was supported with exercise. After the first 10 days of physiotherapy and rehabilitation program was implemented with this protocol, the program was continued 3 days a week for 6 months. It has been shown that there are significant returns in the functional results of the patients after rehabilitation, and that this NMES method applied together with the exercise program also affects the cortical representation in the motor area of the upper extremity.[12]

Different studies have been carried out to find the most suitable ES parameters. Comparisons were made by applying both short and long stimulation periods to the Quadriceps Femoris muscle in older adults. Electrodes are placed in the origo and insertion of the muscle. In the NMES method, 100 Hz, symmetrical biphasic square wave, and 400 microseconds (μs) parameters were preferred. In the short period, 5 min, 4 sets of application were conducted, and in the long period, 10 min, 2 sets of it were done. There was no significant difference in functional recovery between the two groups.[9]

In another study, the NMES application was performed using four different parameters and the results were compared. Narrow pulse (200 μs), wide pulse (500 μs), 500 μs phase duration and low transport frequency (500/1 kiloHz/Aussie current - modified pulse series biphasic current) and high transport frequency (200/2, 200 μs) phase duration 5 kiloHz/Russian currents are preferred. It was observed that ES had similar effects in wide and narrow pulsed current groups and low and high-frequency current groups in the same phase duration. Higher muscle torque and efficiency were found in patients at currents of 500 μs; however, patient tolerance was lower.[9] It has been shown that 100 Hz ready high frequency ES significantly increases the release of neurotrophic factors. Another study reported that 200 Hz high frequency ES had a better effect on myelination than 20 Hz low frequency stimulation.[1]

The effects of low intensity ES have been widely investigated in vitro and in vivo. It has been shown to increase nerve regeneration with the development of brain-derived neurotrophic factor, neuron growth factor, and thus myelin production. A study investigated the effects of low intensity ES on olfactory sheath cells. The characteristic of this group of cells is that they are special glial cells that support the axons emerging from the olfactory epithelium and extend throughout the olfactory nervous system in the olfactory bulb of the central nervous system. These cells can differentiate into separate types of somatic cells having characteristics similar to Schwann cells and astrocytes. They can phagocytize degenerated axons, create channels to guide new axon regeneration, and produce many types of neurotrophic factors such as nerve growth factor, brain-derived neurotrophic factor, platelet-derived growth factor, and neuropeptide Y, which increase the survival of injured axons. After the injury of this cell group, low intensity ES was applied for re-innervation, and as a result of the studies, promising developments were observed in nerve regeneration.[13]

Faradic Current

Faradic current, an asymmetrical alternating current, has a duration of 0.01-1 ms and a frequency of 50-100 Hz.[14] Studies are showing that its application after PNI and during the re-innervation period is safe, effective in terms of functional returns, and increases the speed of recovery by maintaining the tone in the affected area.[15,16] It provides a more comprehensive functional recovery in a shorter time compared to some pharmacological treatments, for example in peripheral Facial paralysis.[17] Although the application parameters for the re-innervation period vary according to the purpose, the number of muscle groups to be used, and the application method. Applications can be made with monopolar or bipolar techniques.[18] The applied methodologies in the literature are quite different from each other.[14,19] In a literature review, the pulse duration of the current parameters was 0.1-1000 ms, the stimulation time was 5-15 min per muscle, and the treatment lasted 1-4 months due to the combined application of Galvanic and Faradic current in a study.[19]

The physiotherapy and rehabilitation program included Faradic current stimulation after decompression due to musculocutaneous nerve entrapment in children with obstetric brachial plexus. The application protocol was adjusted to Biceps Brachii and Brachialis muscles for 10 min with 1 ms duration, 20 ms interval, and 25 intermittent intervals per minute. The intensity was set due to a visible contraction without any sign of pain. The rehabilitation program, including the exercise program, was continued 3 days a week for 8 weeks. Children in rehabilitation were followed up monthly for 12 months after surgery. Children

were re-evaluated at 3 and 12 months. As a result, the functional gains of the children and the Faradic Excitability Test results they obtained continued 3 months after the treatment.[20]

In another study applied to individuals with Facial paralysis, Faradic current parameters with surge were set as 0.1 ms duration, 50 Hz frequency, and surge duration/interval time ratio of 5/5. The intensity was set according to a slight contraction and the application continued for 4 weeks. The study protocol included heat modality, exercise program, and patient education. The control group did not receive ES. At the end of rehabilitation, there was a significant difference in functional outcomes.[21] In a study conducted with individuals with Bell's Palsy, the participants were divided into 4 groups. Group A received conventional therapy, group B TENS, group C Faradic current stimulation, and group D TENS and Faradic current stimulation. Evaluations were made before treatment initiation, after 1 month, and at the end of treatment 2 months later. The Faradic stimulation treatment protocol applied in the study was planned to be 100 Hz, stimulation time 10 s, + polarity, ramp up and down times 3 s, pulse duration 100 μs, and rest time 1 ms. The study results showed that Faradic current and TENS are safe methods for Bell's Palsy, since they particularly reduce the severity of symptoms in the early stages.[16] In another study on Bell's Palsy, the participants received 12 sessions of the Faradic current for the trunk of the Facial nerve for 2 weeks. The Faradic current protocol was set to 50 Hz, pulse duration 0.7 ms, 30 contractions, 3 sets, and for 45 min. Massage, exercise, and daily living activities recommendations were also included in the rehabilitation program. As a result of the treatment, significant results were obtained in facial functions, disability indices, and classification systems.[22]

Functional Electrical Stimulation

Firstly, the target muscle is stimulated by focusing on a functional movement, and then the patient is directed to a specific function, such as reaching and grasping (for the upper extremity), standing, balance, posture, and walking (for the lower extremity).[9] These applications improve cortical excitability and stimulate cortical reorganization with its transport effect.[23] FES can be applied through three methods, as fully-implanted, percutaneous, and surface stimulation.[9] Although intraneural electrodes are more advantageous for selectivity at the target site due to the short distance,[24] they are more frequently preferred because it is not an extra-neural interventional method used with conventional electrodes and gel intermediate.[9] However, it has less selectivity properties than intraneural electrodes.[24]

FES, preferred in motor rehabilitation due to its adaptive or curative effect, performs its function by supporting or performing the movement by releasing contraction in goal-directed tasks, such as walking. In one study, FES was applied to the Common Peroneus nerve for drop foot. With an application of 20-60 Hz above the motor threshold, the activation of both sensory and motor axons was provided by supporting the function for a specific task. In the study, FES supported revealing the dorsiflexion movement required for heel strike and swing phase during walking. This effect was due to increasing the intrinsic functional capacity, supporting neural changes and providing recovery.[25] In another study in which FES was applied to the lower extremity for walking function, a current of 50 Hz and 300 ms was preferred. The anode was placed on the Gastrocnemius muscle. The study results showed that FES application had a significant effect on the contraction and activation patterns of the ankle and knee muscle groups. In another study, FES was applied during walking for 30 min, and it was found that there was an increase in the half-maximum peak-peak motor evoked potentials of the Tibial nerve, and this effect continued for at least 30 min after the application. In addition, the results of the study emphasize that the application provides an increase in corticospinal excitability without cortical inhibition only in combination with FES and exercise, and it also causes improvement in the afferent pathways of the central nervous system.[9]

In another study, after targeted muscle surgery for the Median nerve, the cases were divided into

two groups, and the functional results of one group were followed, while the other group also received FES. In the group, low frequency ES was applied with bipolar technique, 5 channels, and intramuscular electrodes. Bi-directional symmetrical waveform frequency was 20 Hz, pulse width was 200 μs, current intensity was 3-5 mA, duration-rest ratio was 10 s/10 s, 30-min sessions, and once a day for 4 weeks. The study showed that motor function and nerve recovery in targeted muscles improved significantly.[26]

It is well-known that the Ulnar, Radial, and Median nerves are effective in upper extremity functions. In another study, FES was set at 30 Hz by placing 3 anode electrodes on the proximal segment of the Inferior Radial nerve. The aim of the study was to stimulate and coordinate different finger and wrist movements. In another study, non-transcutaneous FES was applied to the proximal part of the Ulnar and Median nerves. The results of the application showed that applications made to proximal different parts of the nerves provided grasping in various patterns and coordinated finger and wrist movements.[9] Hybrid methods are preferred in FES studies conducted in recent years. Home-based systems, robotic systems, systems used with myoelectric prostheses, or systems adapted with a brain-computer interface are also effective in improving the functional results of FES use and expanding its usage area.[23,27-29]

High Voltage Pulsed Galvanic Stimulation

Studies are showing that HVPGS, which has been shown in many studies to increase circulation and regenerative effects on the healing of decubitus ulcers, also increases peripheral nerve regeneration.[30] HVPGS applied above the stimulation threshold evokes action potentials in nerve fibers. Evoked action potentials propagate along nerve fibers. If the motor fibers are stimulated, muscle contraction will occur and muscle activity can be recorded.[31] It is widely used for muscle retraining and stimulation of muscle fibers. The force-time curve of HVPGS includes short pulses of high intensity that selectively stimulate motor nerves rather than sensory fibers of pain. Therefore, HVPGS is used in the first phases after re-innervation to strengthen the muscle and reduce atrophy of the innervated muscle.[32] HVPGS application is advantageous in peripheral nerve stimulation in terms of being easily tolerated by patients and stimulating sensory and motor fibers. It provides functional recovery by accelerating the recovery of maturation of nerve fibers.[30]

Bell's palsy is one of the most common diagnoses in which HVPGS is applied together with other physiotherapy and rehabilitation methods in the first phases of re-innervation after Facial nerve injury.[33] In a study, the HVPGS and FES were applied together after PNI. The ES parameters were biphasic pulses, 120 ms, 160 V amplitude, long pulse duration, and 80 mA during 1-month. There was a significant increase at the end of 1-month application. The stimulation threshold for target muscles decreased after one month of ES.[34]

Transcutaneous Electrical Nerve Stimulation

TENS applications after PNI have been applied for sensory stimulation as neuropathic pain.[1,9,35,36] Sherrington observed that 1/3 and 1/2 of the myelinated fibers of peripheral nerves do not degenerate after cuttings on the ventral, that is, motor spinal cord roots. He applied ES to these remaining fibers for motor innervation, but when he could not get any results, he thought the fibers provided sensory innervation. As a result, the presence of both sensory and motor axons in the mixed-type nerve fiber bundle revealed that sensation should also deserve priority in ES.[25] Sensory impairments due to PNI can be between early-period cutaneous sensory loss and late-period hyperpathia. ES significantly increases tactile discrimination and pressure sensing. It also provides cutaneous regeneration of dorsal root ganglion neurons. However, it has been determined that TENS application after PNI reduces local inflammatory mediators and increases the pain threshold.[9,35] The application method may vary according to the electrode type. While superficial electrodes can be used, some studies have included percutaneous electrodes.[1]

In some studies, a medium frequency alternating current of 10 kHz, 0.3 s has been developed and applied with superficial electrodes for Median nerve injury. The results showed that this medium-frequency alternating current can be used to inhibit unwanted sensory and motor activities and accelerate nerve repair.[9] Another study showed that application of High- and Low-Frequency TENS to the Sciatic nerve, 5 days a week for 5 weeks, led to inhibition. In contrast, 2 Hz TENS applied for 2 hours immediately after the lesion increased the regeneration findings. Therefore, it was determined that the indicated application time was sufficient to support peripheral nerve regeneration and was independent of the electrode type. Studies acknowledge TENS as a low-risk, low-cost, and promising option for stimulating peripheral nerve regeneration.[37]

Considerations in Electrical Stimulation Applications at Initial Phases of Re-innervation

During the re-innervation period after PNI, stimulation parameters should be chosen not only to prevent electrode corrosion and tissue damage caused by the passage of electrical charges but also by considering physiological considerations such as stimulation efficiency and tolerance to treatment.[24] The ES program during the re-innervation period should ensure the nerve healing can continue correctly. Studies have shown that NMES methods, which cause extreme fatigue, slow down the development of nerve healing. In studies aimed at reducing muscle fatigue, the results of NMES applications with muscle and nerve stimulation were compared. The study showed that NMES with nerve stimulation can make patients feel more comfortable and cause less muscle fatigue than those with muscle stimulation.[9]

Extraneural electrodes have been proven to be safe for chronic applications and have high tolerance and clinical preference because they are easy to apply.[24] The effects of electrode number in FES with muscle stimulation for nerve recovery has been demonstrated previously. This kind of the application can cause excessive muscle fatigue. The Ultrasonic Echogenicity Measurements were performed to measure the state in some studies, and the results showed a strong linear relationship between Ultrasonic Echogenicity and FES-induced muscle fatigue. The use of intramuscular FES controllers was recommended for preventing excessive fatigue during FES.[9] Another measure taken to prevent fatigue while stimulating large muscle groups in FES is, the use of multiple electrodes. Studies have shown that the use of 4 electrodes for muscle helps muscle contraction and endurance more than using a single electrode. It is thought that this is because the motor synapses of the muscle, which remain intact, cannot be activated in a single electrode application.[9]

When the studies are examined in terms of pulse width and amplitude, it was seen that short pulses require lower electrical charges to reveal action potentials. Therefore, it is more appropriate to prefer short pulses when it is necessary to obtain higher current amplitudes.[24] For example, in a cross-sectional study, FES was applied to the Extensor Digitorum Communis and Tibialis Anterior muscles with different duration and pole combinations to prevent fatigue. Triangular wave pulsed 1 Hz application was applied with increasing intensity from 0.1 mA. It was found that the application with triangular pulsed, 200 ms duration, and the active pole was statistically more effective on the Tibialis Anterior muscle.[9]

One review reported that 50 Hz is the maximum frequency limit in chronic peripheral nerve stimulation. However, it has been stated that higher frequencies may also be safe, with a reduced percentage of effective stimulation time.[24] In another study conducted in this direction, 10, 35, and 50 Hz FES applications were applied to the Vastus Lateralis and Abductor Pollicis Brevis muscles. In high-frequency stimulation, the Vastus Lateralis muscle with more fast-twitch muscle fibers revealed more fatigue than the Abductor Pollicis Brevis muscle with more slow-twitch muscle fibers. The study also states that the duration of treatment should not exceed 14-16 min.[9]

For the ES method to be efficient in motor return, it should not only stimulate the injured motor nerve but also the sensory fibers. It has been reported that the emergence of a smooth motor movement will only occur when the senses also provide feedback in this cycle and play a role in the regulation of the movement.[9,25,38] In addition, the applied ES method must be combined with exercise to reveal a proper motor skill after PNI (Figure 34.2).[6]

Electrotherapy Protocol for Initial Phases of Re-innervation: A Clinical Guide

The biggest problem in systematic review and clinical guide preparation for ES applications after ES is the lack of systematic documentation of the treatment parameters in the studies in literature. More research is required to define the optimal parameters, and it is problematic to achieve standardization among studies.[24,35,38-43] An example of a clinical guideline application for post-re-innervation ES applications is shown in Table 34.1.[1,2,8,9,11-17,21,22,24,25,28,35-38,44-48]

NMES: Neuromuscular Electrical Stimulation; BLFES: Brief Low Frequency Electrical Stimulation; FES: Functional Electrical Stimulation; HVPGS: High Voltage Pulsed Galvanic Stimulation; TENS: Transcutaneous Electrical Nerve Stimulation.

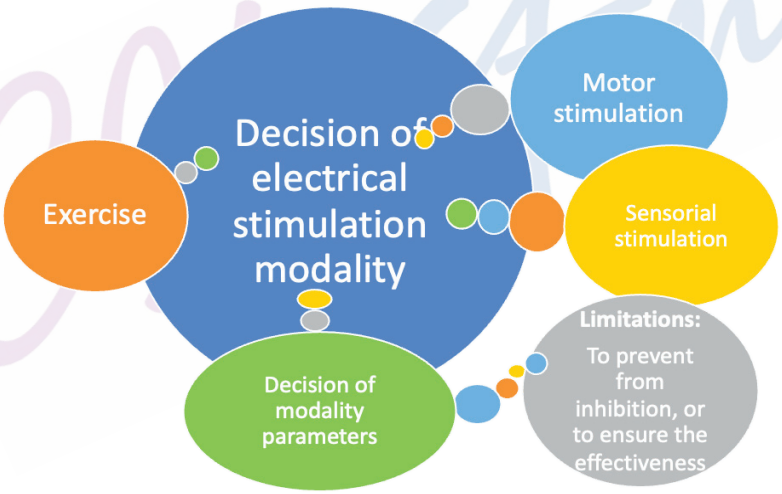

Figure 34.2 Decision-making of the electrical stimulation method in initial phases of re-innervation in peripheral nerve injury.

Table 34.1 A clinical practice guide for the re-innervation period [1,2,8,9,11-17,21,22,24,25,28,32,34-38,44-48]

Electrical Stimulation Method		Treatment Parameters	The Aims of the Application
NMES	**BLFES**	• 20 Hz, 1-hour application	• Functional improvement • Nerve regeneration
		• 100-200 Hz • Low intensity current-until minimal contraction • 4-6 V, 20-30 V • 5-10 min • Every day or every other day • Bipolar technique	• 100 Hz→ Stimulating the release of neurotrophic factors that supports nerve healing • 200 Hz→ Stimulating myelination
	Faradic Current	• 50-100 Hz • 0.1-1 msn • Surge interval 5/5 • Until minimal contraction • 45-45 or 30-30-30 contractions • 10 min stim/5 min rest/10 min stim • Total of 20-30 min • Every day or every other day • Monopolar or bipolar technique	• Functional improvement • Accelerating nerve regeneration and healing
FES		• Short-pulsed triangular wave • 20-60 Hz • 200-300 µs • 10 s stim/10 s rest • Until minimal contraction • Effective stimulation percentage should be low. • Max 14-16 min • Every day or every other day • Using surface electrode • 4 electrodes application per muscle	• Providing functional return by focusing on the target movement • Generally improving walking or upper extremity reach-grip functions • Ensuring the activation of motor and sensory axons
HVPGS		• Monophasic or biphasic pulsed • Pulse frequency 60/min • 120 ms • Pulse duration 65-75 µs • Long-pulsed duration • 160-300 V • Until strong contraction • 20-30 min • 5 days/week	• Functional improvement • Nerve regeneration • Increasing muscle strength • Reducing muscle atrophy
TENS		• 2-10 Hz • 2 hours/day • 4 days/week • Adequacy of knowledge about other current parameters related to sensory stimulation for nerve regeneration: (-)	• Provide sensory support for peripheral nerve regeneration as well as neuropathic pain inhibition • Stimulating sensory axons to reveal motor movements

NMES: Neuromuscular Electrical Stimulation; BLFES: Brief Low Frequency Electrical Stimulation; FES: Functional Electrical Stimulation; HVPGS: High Voltage Pulsed Galvanic Stimulation; TENS: Transcutaneous Electrical Nerve Stimulation.

References

1. Hussain G, Wang J, Rasul A, Anwar H, Qasim M, Zafar S, et al. Current status of therapeutic approaches against peripheral nerve injuries: A detailed story from injury to recovery. Int J Biol Sci. 2020;16(1):116-34. doi:10.7150/ijbs.35653.
2. Li Y, Ma Z, Ren Y, Lu D, Li T, Li W, et al. Tissue engineering strategies for peripheral nerve regeneration. Front Neurol. 2021;12:768267. doi:10.3389/fneur.2021.768267.
3. Javeed S, Faraji AH, Dy C, Ray WZ, MacEwan MR. Application of electrical stimulation for peripheral nerve regeneration: Stimulation parameters and future horizons. Interdiscip Neurosurg. 2021;24:101117. doi:10.1016/j.inat.2021.101117.
4. Senger JLB, Verge VMK, Macandili HSJ, Olson JL, Chan KM, Webber CA. Electrical stimulation as a conditioning strategy for promoting and accelerating peripheral nerve regeneration. Exp Neurol. 2018;302:75-84. doi:10.1016/j.expneurol.2017.12.013.
5. Willand MP. Electrical stimulation enhances reinnervation after nerve injury. Eur J Transl Myol. 2015;25(4):243-8. doi:10.4081/ejtm.2015.5243.
6. Gordon T, English AW. Strategies to promote peripheral nerve regeneration: Electrical stimulation and/or exercise. Eur J Neurosci. 2016;43(3):336-50. doi:10.1111/ejn.13005.
7. Willand MP, Nguyen M-A, Borschel GH, Gordon T. Electrical stimulation to promote peripheral nerve regeneration. Neurorehabil Neural Repair. 2016;30(5):490-6. doi:10.1177/1545968315604399.
8. Zuo KJ, Gordon T, Chan KM, Borschel GH. Electrical stimulation to enhance peripheral nerve regeneration: Update in molecular investigations and clinical translation. Exp Neurol. 2020;332:113397. doi:10.1016/j.expneurol.2020.113397.
9. Ni L, Yao Z, Zhao Y, Zhang T, Wang J, Li S, et al. Electrical stimulation therapy for peripheral nerve injury. Front Neurol. 2023;14:1081458. doi:10.3389/fneur.2023.1081458.
10. Chan KM, Curran MWT, Gordon T. The use of brief post-surgical low frequency electrical stimulation to enhance nerve regeneration in clinical practice. J Physiol. 2016;594(13):3553-9. doi:10.1113/JP270892.
11. Ransom SC, Shahrestani S, Lien BV, Tafreshi AR, Brown NJ, Hanst B, et al. Translational approaches to electrical stimulation for peripheral nerve regeneration. Neurorehabil Neural Repair. 2020;34(11):979-85. doi:0.1177/1545968320962508.
12. Trofin D, Matei D-V, Trofin DM, Onu I, Iordan DA, Stamate T. Clinic-electrophysiologic correlations in rehabilitation of adult patients with traumatic Brachial Plexus lesions. Appl Sci. 2023;13(9):5679. doi:10.3390/app13095679.
13. Panagopoulos GN, Megaloikonomos PD, Mavrogenis AF. The present and future for peripheral nerve regeneration. Orthopedics. 2017;40(1):e141-e56. doi:0.3928/01477447-20161019-01.
14. Burelo-Peregrino EG, Salas-Magaña M, Arias-Vázquez PI, Tovilla-Zarate CA, Bermudez-Ocaña DY, López-Narváez ML, et al. Efficacy of electrotherapy in Bell's palsy treatment: A systematic review. J Back Musculoskelet Rehabil. 2020;33(5):865-74. doi:10.3233/BMR-171031.
15. Oliveira C, De Sousa R, Ramos C, Cruz AL. Effect of electrostimulation applied on Bell's palsy—A systematic review. Open Access Library Journal. 2022;9(6):1-14. doi:10.4236/oalib.1108600.
16. Abdelatief EEM. Effect of transcutaneous electrical nerve stimulation and faradic current stimulation on the recovery of Bell's palsy. Int J Hum Mov Sports Sci. 2020;8(6):369-80. doi:10.13189/saj.2020.080608.
17. Quintero JE, Manotas GF, Galeano YA, Mauricio D. Design and development of transcutaneous electrical stimulation equipment for neuromuscular rehabilitation in individuals with facial palsy. Tecciencia. 2014;9(16):43-9. doi:10.18180/tecciencia.2014.16.4.
18. Tuncay F, Borman P, Taser B, Ünlü I, Samim E. Role of electrical stimulation added to conventional therapy in patients with idiopathic facial (Bell) palsy. Am J Phys Med Rehabil. 2015;94(3):222-8. doi:10.1097/PHM.0000000000000171.
19. Justice D, Awori J, Carlson S, Chang KWC, Yang LJS. Use of neuromuscular electrical stimulation in the treatment of neonatal brachial plexus palsy: A literature review. Open J Occup Ther. 2018;6(3):1-11. doi:10.15453/2168-6408.1431.
20. Fırat T, Delioğlu K, Tunç Y, Üzümcügil A, Yörübulut M, Leblebicioğlu G. The results of decompression of the musculocutaneous nerve entrapment in children with obstetric brachial plexus palsy. Childs Nerv Syst. 2020;36:2815-23. doi:10.1007/s00381-020-04828-8.
21. Sandeep SM, Jayprakash VN. Effect of electrical stimulation on facial grading system in subjects with early facial palsy. Natl J Integr Res Med. 2013;4(3):29-33. doi:(NA).
22. Javath JM, D'Souza AF, Rebello SR. Low-level laser therapy versus electrical stimulation for the management of acute Bell's palsy: A randomized clinical trial. Physical Treatments-Specific Physical Therapy Journal. 2021;11(4):261-68. doi:10.32598/ptj.11.4.508.1.
23. Popović DB. Advances in functional electrical stimulation (FES). J Electromyogr Kinesiol. 2014;24(6):795-802. doi:10.1016/j.jelekin.2014.09.008.
24. Günter C, Delbeke J, Ortiz-Catalan M. Safety of long-term electrical peripheral nerve stimulation: Review of the state of the art. J Neuroeng Rehabil. 2019;16:1-16. doi:10.1186/s12984-018-0474-8.
25. Carson RG, Buick AR. Neuromuscular electrical stimulation-promoted plasticity of the human brain. J Physiol. 2021;599(9):2375-99. doi:10.1113/JP278298.
26. Wang P, Li Y, Zhang Z, Lin Y, Jiang Z, Ding X, et al. Effects of functional electrical stimulation on neuromuscular function after targeted muscle reinnervation surgery in rats. 2020:3823-26. doi:10.1109/EMBC44109.2020.9175836.
27. Liu T, editor The application of brain-computer interface (BCI) based Functional Electrical Stimulation (FES). Journal of Physics Conference Series. 2021;2065(1):012006. doi:10.1088/1742-6596/2065/1/012006.
28. Kern H, Carraro U. Home-based Functional Electrical Stimulation for long-term denervated human muscle: History, basics, results and perspectives of the Vienna Rehabilitation Strategy. Eur J Transl Myol. 2014;24(1):27-40. doi:10.4081/ejtm.2014.3296.
29. Sajer S, Guardiero GS, Scicchitano BM. Myokines in home-based functional electrical stimulation-induced recovery of skeletal muscle in elderly and permanent denervation. Eur J Transl Myol. 2018;28(4):337-45. doi:10.4081/ejtm.2018.7905.
30. Teodori RM, Silva AM, Silva MT, Oliveira LS, Polacow MLO, Guirro ECO. High-voltage electrical stimulation improves nerve regeneration after sciatic crush injury. Braz J Phys Ther. 2011;15:325-31. doi:10.1590/S1413-35552011005000008.
31. Lienemann S, Zötterman J, Farnebo S, Tybrandt K. Stretchable gold nanowire-based cuff electrodes for low-voltage peripheral nerve stimulation. J Neural Eng. 2021;18(4):045007. doi:10.1088/1741-2552/abfebb.
32. Kaya D, Yüksel İ, Callaghan MJ, Güney H, Atay ÖA, Çitaker S, et al. High voltage pulsed galvanic stimulation adjunct to rehabilitation program for patellofemoral pain syndrome: A prospective randomized controlled trial. Turk J Physiother Rehabil. 2013;24(1):1-8.
33. Çalişgan E, Şenol D, Cay M. Physiotherapy outweighed multiple therapy methods of Bell's palsy: A review study. 2017;24(3):375-80. doi:10.5455/jtomc.2017.04.060.

34. Gera S, Gangadharan N, Navin BP, Tharion G, Chalageri PH, Thomas R, et al., editors. Electrical stimulation and assessment of the induced force in the denervated Muscle. IEEE. 2019;TENCON 2019:2046-50. doi:10.1109/TENCON.2019.8929282
35. Chu X-L, Song X-Z, Li Q, Li Y-R, He F, Gu X-S, et al. Basic mechanisms of peripheral nerve injury and treatment via electrical stimulation. Neural Regen Res. 2022;17(10):2185-93. doi:10.4103/1673-5374.335823.
36. Feldman EL, Russell JW, Löscher WN, Grisold W, Meng S, Feldman EL, et al. (2021), Principles of nerve and muscle rehabilitation. atlas of neuromuscular diseases: a practical guideline. 3rd ed. Cham: Springer Nature Switzerland AG. doi:10.1007/978-3-030-63449-0_6.
37. Oliveira JT, de Oliveira Goulart C, de Lima SVS, Mendonça HR, de Andrade KM, Baptista AF, et al. (2016), Regenerative medicine-from protocol to patient: 4 Regenerative therapies I. 3rd ed. Cham: Springer. doi:10.1007/978-3-319-28293-0_7.
38. Pasluosta C, Kiele P, Stieglitz T. Paradigms for restoration of somatosensory feedback via stimulation of the peripheral nervous system. Clin Neurophysiol. 2018;129(4):851-62. doi:10.1016/j.clinph.2017.12.027.
39. ElAbd R, Alabdulkarim A, AlSabah S, Hazan J, Alhalabi B, Thibaudeau S. Role of electrical stimulation in peripheral nerve regeneration: A systematic review. Plast Reconstr Surg Glob Open. 2022;10(3):1-8. doi:10.1097/GOX.0000000000004115.
40. Gordon T. Peripheral nerve regeneration and muscle reinnervation. Int J Mol Sci. 2020;21(22):1-24. doi:10.3390/ijms21228652.
41. Alvites R, Rita Caseiro A, Santos Pedrosa S, Vieira Branquinho M, Ronchi G, Geuna S, et al. Peripheral nerve injury and axonotmesis: State of the art and recent advances. Cogent Med. 2018;5(1):1-45. doi:10.1080/2331205X.2018.1466404.
42. Chandrasekaran S, Davis J, Bersch I, Goldberg G, Gorgey AS. Electrical stimulation and denervated muscles after spinal cord injury. Neural Regen Res. 2020;15(8):1397-407. doi:10.4103/1673-5374.274326.
43. de Mattos EDSR, Guedes A, dos Santos Viana M, Baptista AF. Influence of electrical stimulation on peripheral nerve regeneration: Protocol for a systematic review. Res Soc Dev. 2021;10(17):1-8. doi:10.33448/rsd-v10i17.24942.
44. Acheta J, Stephens SBZ, Belin S, Poitelon Y. Therapeutic low-intensity ultrasound for peripheral nerve regeneration–A schwann cell perspective. Front Cell Neurosci. 2022;15:1-10. doi:10.3389/fncel.2021.812588.
45. Fu T, Lineaweaver WC, Zhang F, Zhang J. Role of shortwave and microwave diathermy in peripheral neuropathy. J Int Med Res. 2019;47(8):3569-79. doi:10.1177/0300060519854905.
46. Hei W-H, Byun S-H, Kim J-S, Kim S, Seo Y-K, Park J-C, et al. Effects of electromagnetic field (PEMF) exposure at different frequency and duration on the peripheral nerve regeneration: In vitro and in vivo study. Int J Neurosci. 2016;126(8):739-48. doi:10.3109/00207454.2015.1054032.
47. Ito A, Wang T, Nakahara R, Kawai H, Nishitani K, Aoyama T, et al. Ultrasound therapy with optimal intensity facilitates peripheral nerve regeneration in rats through suppression of pro-inflammatory and nerve growth inhibitor gene expression. PloS one. 2020;15(6):e0234691. doi:10.1371/journal.pone.0234691.
48. Jiang W, Wang Y, Tang J, Peng J, Wang Y, Guo Q, et al. Low-intensity pulsed ultrasound treatment improved the rate of autograft peripheral nerve regeneration in rat. Sci Rep. 2016;6(1):1-13. doi:10.1038/srep22773.

Co-funded by the Erasmus+ Programme of the European Union

Electrical Stimulation for the Re-Innervated Muscles in The Chronic Phase

YASEMIN KARAASLAN • ESRA DOGRU HUZMELI

Introduction

Muscle re-innervation is an important clinical goal in physiotherapy and rehabilitation. Ideal re-innervation is expected 1-3 months after denervation, functional re-innervation may take up to 1 year, but re-innervation is not expected after 3 years. The re-innervation time depends on the level of the lesion and its distance from the target organ.[1] The "chronic phase" process occurs days or months after injury. The aim of the physiotherapy and rehabilitation methods should be conservative to eliminate or minimize secondary changes while waiting to see how much functional re-innervation will occur. Application of electrical stimulation (ES) methods can be beneficial for patients including spinal cord injuries, peripheral nerve injuries and other neuromuscular diseases, and gynecological problems.[2-4] ES is considered as a safe and effective treatment option for a variety of conditions. Compared to conservative approaches and surgical treatments, ES offers unique benefits and can be applied to the vast majority of patients. However, it is important to consider certain factors and eligibility criteria when determining the suitability of ES for an individual patient.[5]

Electrical Stimulation of Re-Innervated Muscles in the Chronic Phase

Although progress has been made in elucidating the many events that occur during regeneration and re-innervation of the muscle, some functional aspects of the innervation process need further investigation. ES is used as an adjunct to other physiotherapy and rehabilitation modalities to perform various tasks in physiotherapy and rehabilitation. When clinical studies were examined, it was recorded that ES was effective in axon growth and acceleration of sensorimotor recovery during nerve repair. Neuromuscular Electrical Stimulation (NMES), Transcutaneous Electrical Nerve Stimulation (TENS), and Functional Electrical Stimulation (FES) can be used for purposes such as reducing muscle atrophy and restoring muscle re-innervation. Both animal and human studies have shown that ES has positive effects on the nerve repair process.[6-13] It has been reported that when long-term stimulation is applied to intact axons of partially de-innervated muscles, muscle recovery, muscle weight, and electrically induced muscle tension increase.[14] It has been reported that accelerated locomotor recovery occurs and re-innervation is facilitated when short ES is applied.[7,12,13]

ES is a versatile approach for treating peripheral nerve injuries. It addresses various aspects of nerve injury and recovery, including synaptic preservation, pain relief, nerve regeneration, neurological function improvement, muscle atrophy reduction, and sensory function recovery. ES applied to target organs, reduces the atrophy of de-innervated skeletal muscle and improves sensory function.[5]

The application of ES to de-innervated skeletal muscle can indeed have beneficial effects on mus-

cle atrophy and fibrosis. ES has been shown to increase insulin activation by inhibiting various hydrolysis systems involved in protein breakdown in muscle fibers. By enhancing insulin activation, ES can help maintain protein balance and counteract the harmful effects of denervation-induced muscle atrophy.[5] Wang et al. stated that with low-frequency ES therapy, transplanted nerve regeneration can be achieved and the motor function of target muscles can be increased.[15] Regenerative ES has been shown to have positive effects on neuro regeneration by upregulating brain-derived neurotrophic factor (BDNF) and its receptor, promoting accurate re-innervation of muscles by motor neurons. BDNF is a crucial neurotrophic factor that supports the survival, growth, and maintenance of neurons, including motor neurons. ES can enhance the expression and release of BDNF in the injured nerve and surrounding tissues.[16]

ES is indicated to accelerate axon growth during nerve repair. ES can be divided into NMES, TENS and FES according to the mode of administration and its use.[17]

Neuromuscular Electrical Stimulation

NMES is used to stimulate motor neurons in innervating muscles and restore skeletal muscle mass and function.[18] Atrophy is prevented by the contraction of the muscles with NMES. NMES decreases muscle wasting during periods of disuse/illness and is typically applied directly on the muscle belly. Muscle strength and endurance can be increased using NMES with exercise and physiotherapy and rehabilitation methods.[19]

The Purpose of Usage

Muscles that have lost their nerve supply after an injury or illness can be activated with NMES. By doing this, it may prevent additional muscle atrophy and promote strength and muscular growth.[20,21] NMES can also be used to re-educate muscles to perform specific movements and improve motor function in patients with neurological conditions such as spinal cord injuries, stroke, or multiple sclerosis (Figure 35.1).[20,21] Despite the positive effects of ES, using ES higher than normal

Figure 35.1 Neuromuscular Electrical Stimulation device.

causes muscle fatigue and weakened nerve recovery. Vanderthommen and Duchateau stated that high-frequency currents cause early muscle fatigue and that short-range ES is a better option.[22] In another study comparing muscle ES and nerve ES, it was found that nerve ES caused less muscle fatigue and was more comfortable than muscle ES.[19]

The Recommended Parameters

Before starting NMES, the patient's muscle strength, range of motion, and sensory function should be assessed to determine the appropriate stimulation parameters.[23,24] Electrodes are placed over the muscle belly or motor points, which are areas where the motor nerve enters the muscle. The electrodes deliver electrical impulses that provide muscle contractions. NMES is applied to the neuromuscular junction and surrounding muscle fibers. To apply to these areas; surface electrodes are placed on the motor points of the treated muscle.[24] The application of NMES in the frequency range of 20-50 Hertz (Hz) is used to produce muscle contraction and improve the patient's function.[25] In re-innervated atrophic muscles, NMES can be combined with other physiotherapy and rehabilitation techniques such as resistance training, stretching, and functional training to optimize the recovery process.[17,24,26]

Acaröz Candan et al. stated that both the short stimulation period [5 minutes (min) × 4 sets] and the long stimulation period (10 min × 2 sets) of NMES (symmetrical, biphasic, squared waveform with a frequency of 100 Hz and a pulse duration of

400 microseconds (μs) can improve Quadriceps Femoris muscle function in the elderly.[27] However, they did not find a significant difference between the two groups. Toth et al. applied NMES (1 hour; 50 Hz; symmetrical biphasic pulses; 400 μs) to patients postoperatively for anterior cruciate ligament injuries.[28] In conclusion, NMES has been shown to reduce the atrophy of slow-twitch fibers. In addition, the strength of the muscle contraction and the output of fast/slow twitch fibers were preserved with NMES. Stevens-Lapsley et al. reported an increase in muscle strength and function with the application of personalized parameters based on the patient's maximum tolerance.[29]

There are also clinical applications where NMES is not effective. For example, Hyer et al., applied NMES and sham stimulation to the calf muscles during the treatment process after tendon surgery.[30] However, they found no improvement in muscle mass or muscle function in the two groups. In the study of Piccinini et al., ES treatment [triangular-rectangular stimuli with a duration of 150 milliseconds (ms) and a frequency of 1 Hz] was performed using circular shaped rubber electrodes with surface area of 4.9 cm and radius of 12.5 mm.[31] The lowest intensity required to induce the muscle contraction was above 0.5 milliamperes (mA). If there was no sensation in the stimulated area, an intensity of 1 mA was used. In this double-blind randomized clinical study, it was stated that there was no difference between the groups after traumatic peripheral nerve injuries.[31] In this context, further studies should be conducted to establish the optimum parameters in NMES application.

Transcutaneous Electrical Nerve Stimulation

The combination of stimulation mode and system created by using a small current to activate sensory axons without triggering muscle contraction is called TENS. TENS can be used to enhance muscle function, lessen pain, and promote muscle growth in re-innervated atrophic muscles. In cases with motor nerve damage, the sensory nerve temporarily innervates the muscle until the motor nerve heals, in order to prevent muscle atrophy. Sensory feedback is important in completing action, and TENS can be used to tune neural network pathways and improve sensory feedback.[32] TENS is also used in the treatment of pain, spasticity, and urinary incontinence.[17]

The Purpose of Usage

Re-innervated atrophic muscles with nerve loss or muscle atrophy may experience pain relief with TENS. The electrical impulses of the TENS unit can reduce the perception of pain by preventing pain signals from reaching the brain. Re-innervated atrophic muscles may benefit from TENS in stimulating muscle activation. Muscle contractions caused by electrical impulses of the TENS unit can increase muscle function and strength. TENS can be used to increase muscle growth in re-innervated atrophic muscles. The electrical impulses of the TENS unit can promote the formation of growth factors that can help support muscle growth and repair (Figure 35.2).[33,34]

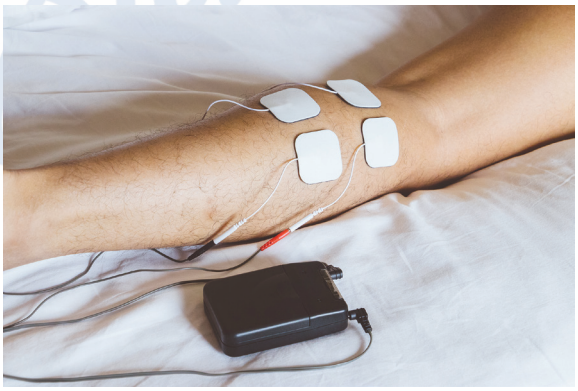

Figure 35.2 Transcutaneous Electrical Nerve Stimulation application on leg.

TENS is effective in the treatment of persistent pain resulting from peripheral nerve injuries. Non-invasive or minimally invasive TENS are the forms that patients can easily adapt to. The disadvantages are that the effect of TENS is short-term and the effect of TENS is less in the elderly with reduced sensitivity than in the young.

The Recommended Parameters

TENS is widely used in the frequency range of 1-150 Hz in the clinic.[35] It is generally used at low fre-

quencies such as 2-10 Hz or ultra-high frequencies for pain relief. While no visible muscle contraction occurs with low-frequency TENS (the transmission of pulsed currents of 10 Hz or less), it is usually targeted at sensory nerves. High-frequency TENS is used for frequencies higher than 10 Hz.[36]

Functional Electrical Stimulation

FES is a specific type of NMES that is used to activate muscles functionally in situations such as walking or holding objects. FES applications include restoring upper and lower extremity functions. FES can help restore normal movement patterns and stop additional muscle wasting, making it particularly helpful in the rehabilitation of re-innervated muscles that have become atrophied. FES is a method for stimulating muscles and nerves with an electrical current to produce a functioning movement or task. It can be used in physiotherapy and rehabilitation in various ways, including re-innervating atrophic muscles in areas where the nerve is healthy.[37]

The Purpose of Usage

FES can be used to improve muscle strength and function in patients with neurological diseases such as spinal cord injuries, stroke, or multiple sclerosis. FES can also be used to retrain muscles to perform certain movements and improve motor function in patients with muscle atrophy due to disuse, denervation, or other reasons.[38] If the ES device is worn for a long time, it can cause muscle fatigue and reduce sensitivity (Figure 35.3).[32]

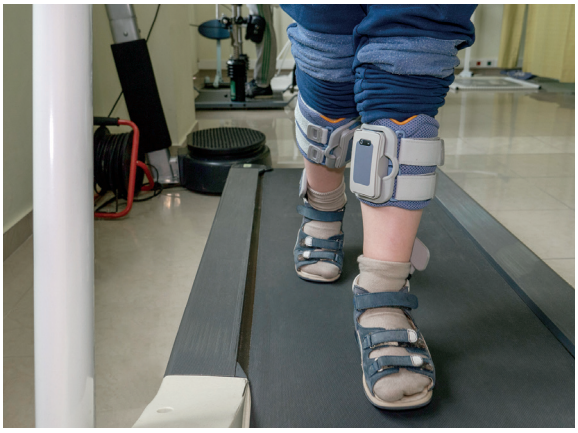

Figure 35.3 Treatment with Functional Electrical Stimulation.

The Recommended Parameters

Before starting FES, the patient's muscle strength, range of motion, and sensory function should be evaluated to determine appropriate stimulation parameters.[39] There are 3 types of stimulation methods in FES application (fully implanted, percutaneous stimulation, and surface stimulation). The FES instruments are mostly small portable devices.[32] In the innervation of large muscles, surface electrodes are applied with biocompatible gels.[40]

The waveform used is a triangular wave, and the intensity is set to be in the range of 20 to 30 mA. The frequency of the stimulation ranges from 50 to 100 Hz and the pulse duration is 10 ms. The FES device is typically programed to deliver an electrical impulse pattern that mimics the muscle's natural motor activation pattern, allowing the patient to perform functional movements such as walking, cycling, or grasping.[41] In re-innervated atrophic muscles, FES can be combined with other physiotherapy and rehabilitation techniques such as resistance training, stretching, and functional training to optimize the healing process.[41] Kapadia et al. stated that FES applied for 39 hours for 13-16 weeks in individuals with chronic incomplete tetraplegia resulted in great improvements in voluntary hand functions.[42]

Pulsed Galvanic Stimulation

Pulsed Galvanic stimulation is used in the form of direct current modalities that provide a unidirectional, uninterrupted current, both according to the patient's tolerance and without damaging the tissue. It can be applied directly to stimulate muscles, reduce edema, create ionic changes in tissues, and administer drugs to the skin following nerve injury.[43]

Superficial skin burns and irritation may occur through direct uninterrupted electrical current. Therefore, a modification called High-Voltage Pulsed Galvanic Stimulation (HVPGS) was developed in which the current is applied in an alternating or "pulsed" manner. ES of the muscle is performed either by direct current or alternating current or a combination of both. The reason why

alternating current is preferred over direct current is more patient comfort.[44]

The Purpose of Usage

The clinical use of HVPGS is similar to that of low-voltage NMES. It has purposes such as strengthening atrophied muscles or minimizing disuse atrophy, facilitating muscle re-education, protecting joint movement and reducing joint limitations, providing orthotic support to the joint, and reducing joint effusion and interstitial edema.[43]

The Recommended Parameters

General principles of ES should be followed during ES applied to the muscle. Good contact between the skin and electrodes are required. Since the de-innervated muscle has no motor point, the active electrode is either placed at the point of best motor response or in the form of two electrodes at either end of the muscle to allow current to flow.[45]

HVPGS is an arbitrarily adjustable frequency current with a two-peak monophasic waveform, a constant duration of up to 200 μs, and a voltage higher than 100 Volts (V). This waveform shows a sudden increase and then a sudden decrease. The pulse duration of HVPGS includes the phase duration of both peak pulses. The pulses of this current are characteristically very short transitions (100-200 μs). This provides selective stimulation of motor nerves rather than sensory nerves. Therefore, HVPGS is used in disuse-induced atrophy and muscle strengthening.[46] In HVPGS applications, less tissue resistance is encountered than in low-voltage applications. This feature theoretically makes HVPGS current more effective and tolerable.

The effectiveness of ES in preserving the muscle's properties during the re-innervation process is still debated and no consensus has been reached.[47-51] In a group of studies, results were reported that ES slows down re-innervation, decreases regeneration, or does not make a significant difference, while in a group of studies, there are findings that ES has an increasing and accelerating effect on nerve regeneration.[47-51] Therefore, it is stated that there is a need for future studies evaluating the therapeutic indications.[30]

Literature Review of Electrical Stimulation for the Re-Innervated Muscles in the Chronic Phase

Marqueste et al., have discussed the use of ES to assist muscle re-innervation and nerve regeneration in the Tibialis Anterior muscle.[52] The use of chronic muscle electrostimulation with modulated biphasic currents has been shown to have several beneficial effects on de-innervated muscles. ES can help prevent muscle atrophy, preserve muscle strength and endurance, and preserve the biochemical and histochemical properties of muscles. According to their findings, the use of modulated ES at high-frequency and pulse duration, as opposed to an unmodulated current, was found to improve sensory re-innervation during muscle re-innervation. The authors also found that biphasic modulated stimulation is recommended for better re-innervation and that muscle ES following denervation and re-innervation tends to restore size, functional, and histochemical properties better than unstimulated muscle. It has been reported that further research is required to confirm these findings and to determine the most appropriate modalities for ES during muscle re-innervation and nerve regeneration.[11,52] To the best of our knowledge, the amount of stimulation, the interval between stimulations, appropriate frequency, ES characteristics, session duration, and type of stimulation are not standardized.[53] In addition, these features may alter the response to treatment based on the time interval after nerve injury, severity of nerve damage, and stage of muscle atrophy/degeneration.

In the study of El Abd et al., it was reported that ES applied in peripheral nerve regeneration is beneficial in increasing and accelerating recovery.[54] It was reported that the meta-analysis could not be performed due to heterogeneity, and positive findings and low complications were mentioned in all studies. With the application of ES to the injured peripheral nerves after surgical repair, both senso-

ry and motor functions are greatly improved. Some animal studies have evaluated the role of exercise or electrical effects applied early in the nerve repair process (immediately after nerve injuries), up to 3 weeks after denervation, and before or during the re-innervation period. These studies supported positive effects after both ES and physical exercise.[9,50,55-57] Other studies have evaluated the effects of exercise or ES during late re-innervation. Also, studies have reported late-term positive effects after ES.[55,58,59]

Wang et al., introduced a miniature device made of fully biodegradable, self-electric, and soluble galvanic cells.[60] The other is a small, disposable (24-hour), internally powered, wireless, and portable neuromuscular stimulation device. As the device adapts, it can be used by patients during the day and even during sleep. With a shelf life of 2 years, this device has 7 stimulation modes with a frequency not exceeding 1 Hz and variable pulse widths.[61]

Asensio-Pinilla et al., conducted a study to investigate the role of the ES and exercise-induced neuronal activity in promoting axonal regeneration and modulating plasticity in the spinal cord injury.[62] ES (3 V, 0.1 ms at 20 Hz) was applied to both groups for 1 hour. The third group was applied ES for 1 hour and run on the treadmill for 4 weeks (5 m/min, 2 hours per day). The fourth group was given only exercise, another untreated group became the control group. The researchers found that the group that received both ES and treadmill training had the highest levels of muscle re-innervation compared to the other groups. In addition to muscle re-innervation, the study also investigated changes in the excitability of spinal cord circuitry using nerve conduction, H reflex, and algesimeter tests. These tests were performed at various time points (1, 3, 5, 7, and 9 weeks after surgery) to assess the effects of ES and exercise on neuronal activity. The groups that received acute ES and/or treadmill training showed a higher number of regenerated myelinated axons, indicating enhanced axonal regeneration compared to the control group or the group that received chronic ES. The combination of ES and exercise appears to have synergistic effects, leading to improved muscle re-innervation and increased numbers of regenerated myelinated axons, particularly during the initial phase of the study.

A cuff electrode (250 Hz, 5 μs) was placed around the Median or Radial nerves 25 cm above the elbow of 8 tetraplegic patients. They evaluated the flexion range (thumb, finger, wrist) and functional movements of the patients. In conclusion, this minimally invasive ES was shown to increase the patient's grasping function.[63]

Southwell review the improvement in symptoms of neurogenic bowel dysfunction when various ES modalities were applied. However, the number of high-quality studies supporting the effects of ES is insufficient.[64] Lim et al., introduced a case who had difficulty defecating because of cauda equina syndrome, which developed after a cesarean section under spinal anesthesia 12 years ago.[4] Neurophysiological effects were evaluated using the bulbocavernosus reflex and electromyography. Interferential current therapy and TENS have been applied to stimulate the bowel and external anal sphincter. It has been reported that after the treatment, the patient had better perianal sensation, had less difficulty in defecation than before, and was satisfied with the duration of defecation and bowel condition. In electrodiagnostic tests, it has been shown that there is a decrease in the abnormal spontaneous activities of the bulbocavernosus muscles and the re-innervation of this muscle.[4]

Recent studies have indeed focused on the ES of a proximal nerve at the site of injury to enhance re-innervation after peripheral nerve injury. However, the specific cellular mechanisms by which ES accelerates nerve regeneration are still not fully understood. One proposed mechanism involves the initiation of an intracellular calcium (Ca^{2+}) wave at the site of axotomy induced by ES. The intracellular Ca^{+2} wave is believed to play a significant role in nerve regeneration. It can travel along the axon toward the neuronal cell body. Once it reaches the neuronal soma, the increased Ca^{+2} levels can induce the upregulation of BDNF and its receptor. BDNF is a crucial neurotrophic factor involved in

promoting neuronal survival, growth, and regeneration. The over expression of BDNF induced by the increased Ca^{+2} levels can have several effects. One notable effect is the inhibition of phosphodiesterases, which are enzymes responsible for degrading cyclic adenosine monophosphate (cAMP). By inhibiting phosphodiesterases, BDNF promotes sustained elevation of cAMP levels within the neuronal cells.[65] It is worth mentioning that these findings are based on current research and may be subjected to further refinement and discovery as more studies are conducted in this field.

Conclusion

In conclusion, in the chronic phase of ES of re-innervated muscles, agents such as NMES, TENS, and FES are effective techniques that can be used in physiotherapy and rehabilitation to restore muscle function, stop additional muscle wasting, manage pain, increase muscle endurance, and improve physical therapy results. Although there are many studies on ES, there is still a need for studies on the chronic phase re-innervation of ES.

References

1. Avcı G, Akan M, Yıldırım S, Aköz T. Nerve Repair and Grafting (Review of the Literature). T Klin J Med Sci. 2002; 22:428-37.
2. Green RJ, Laycock J. Objective methods for evaluation of interferential therapy in the treatment of incontinence. IEEE Trans Biomed Eng. 1990;37(6):615-23. doi:10.1109/10.55665.
3. Jarit GJ, Mohr KJ, Waller R, Glousman RE. The effects of home interferential therapy on post-operative pain, edema, and range of motion of the knee. Clin J Sport Med. 2003;13(1):16-20. doi:10.1097/00042752-200301000-00004.
4. Lim SK, Lee CH, Oh MK, Chun SW. Neurophysiological effects of electrical stimulation on a patient with neurogenic bowel dysfunction and cauda equina syndrome after spinal anesthesia: A case report. Medicina (Kaunas). 2023;59(3):588. doi:10.3390/medicina59030588.
5. Chu XL, Song XZ, Li Q, Li YR, He F, Gu XS, et al. Basic mechanisms of peripheral nerve injury and treatment via electrical stimulation. Neural Regen Res. 2022;17(10):2185-93. doi:10.4103/1673-5374.335823.
6. Geremia NM, Gordon T, Brushart TM, Al-Majed AA, Verge VM. Electrical stimulation promotes sensory neuron regeneration and growth-associated gene expression. Exp Neurol. 2007;205(2):347-59. doi:10.1016/j.expneurol.2007.01.040.
7. Brushart TM, Jari R, Verge V, Rohde C, Gordon T. Electrical stimulation restores the specificity of sensory axon regeneration. Exp Neurol. 2005;194(1):221-9. doi:10.1016/j.expneurol.2005.02.007.
8. Marqueste T, Alliez JR, Alluin O, Jammes Y, Decherchi P. Neuromuscular rehabilitation by treadmill running or electrical stimulation after peripheral nerve injury and repair. J Appl Physiol (1985). 2004;96(5):1988-95. doi:10.1152/japplphysiol.00775.2003.
9. Kao CH, Chen JJ, Hsu YM, Bau DT, Yao CH, Chen YS. High-frequency electrical stimulation can be a complementary therapy to promote nerve regeneration in diabetic rats. PLoS One. 2013;8(11):e79078. doi:10.1371/journal.pone.0079078.
10. English AW, Schwartz G, Meador W, Sabatier MJ, Mulligan A. Electrical stimulation promotes peripheral axon regeneration by enhanced neuronal neurotrophin signaling. Dev Neurobiol. 2007;67(2):158-72. doi:10.1002/dneu.20339.
11. Marqueste T, Decherchi P, Desplanches D, Favier R, Grelot L, Jammes Y. Chronic electrostimulation after nerve repair by self-anastomosis: Effects on the size, the mechanical, histochemical and biochemical muscle properties. Acta Neuropathol. 2006;111(6):589-600. doi:10.1007/s00401-006-0035-2.
12. Gordon T, Amirjani N, Edwards DC, Chan KM. Brief post-surgical electrical stimulation accelerates axon regeneration and muscle reinnervation without affecting the functional measures in carpal tunnel syndrome patients. Exp Neurol. 2010;223(1):192-202. doi:10.1016/j.expneurol.2009.09.020.
13. Wong JN, Olson JL, Morhart MJ, Chan KM. Electrical stimulation enhances sensory recovery: A randomized controlled trial. Ann Neurol. 2015;77(6):996-1006. doi:10.1002/ana.24397.
14. Pieber K, Herceg M, Paternostro-Sluga T, Schuhfried O. Optimizing stimulation parameters in functional electrical stimulation of denervated muscles: A cross-sectional study. J Neuroeng Rehabil. 2015;12:51. doi:10.1186/s12984-015-0046-0.
15. Wang L, Lu C, Yang S, Sun P, Wang Y, Guan Y, et al. A fully biodegradable and self-electrified device for neuroregenerative medicine. Sci Adv. 2020;6(50):eabc6686. doi:10.1126/sciadv.abc6686.
16. Balog BM, Deng K, Labhasetwar V, Jones KJ, Damaser MS. Electrical stimulation for neuroregeneration in urology: A new therapeutic paradigm. Curr Opin Urol. 2019;29(4):458-65. doi:10.1097/MOU.0000000000000632.
17. Ni L, Yao Z, Zhao Y, Zhang T, Wang J, Li S, Chen Z. Electrical stimulation therapy for peripheral nerve injury. Front Neurol. 2023;14:1081458. doi:10.3389/fneur.2023.1081458.
18. Bickel CS, Yarar-Fisher C, Mahoney ET, McCully KK. Neuromuscular electrical stimulation-induced resistance training after SCI: A review of the dudley protocol. Top Spinal Cord Inj Rehabil. 2015;21(4):294-302. doi:10.1310/sci2104-294.
19. Inns TB, McCormick D, Greig CA, Atherton PJ, Phillips BE, Piasecki M. Factors associated with electrical stimulation-induced performance fatigability are dependent upon stimulation location. Exp Physiol. 2021;106(4):828-36. doi:10.1113/EP089204.
20. Baldwin ER, Klakowicz PM, Collins DF. Wide-pulse-width, high-frequency neuromuscular stimulation: Implications for functional electrical stimulation. J Appl Physiol (1985). 2006;101(1):228-40. doi:10.1152/japplphysiol.00871.2005.
21. Lago AF, de Oliveira AS, de Souza HCD, da Silva JS, Basile-Filho A, Gastaldi AC. The effects of physical therapy with neuromuscular electrical stimulation in patients with septic shock: Study protocol for a randomized cross-over design. Medicine (Baltimore). 2018;97(6):e9736. doi:10.1097/MD.0000000000009736.
22. Vanderthommen M, Duchateau J. Electrical stimulation as a modality to improve performance of the neuromuscular system. Exerc Sport Sci Rev. 2007;35(4):180-5. doi:10.1097/jes.0b013e318156e785.
23. Lee KJ. The Effects of kinesio taping on the intestinal activation. KPTSA. 2013;20(1):37-42.

24. Nussbaum EL, Houghton P, Anthony J, Rennie S, Shay BL, Hoens AM. Neuromuscular electrical stimulation for treatment of muscle impairment: Critical review and recommendations for clinical practice. Physiother Can. 2017;69(5):1-76. doi:10.3138/ptc.2015-88.
25. Johnson MI, Claydon LS, Herbison GP, Jones G, Paley CA. Transcutaneous electrical nerve stimulation (TENS) for fibromyalgia in adults. Cochrane Database Syst Rev. 2017;10(10):CD012172. doi:10.1002/14651858.CD012172.pub2.
26. Lee B, Cho Y. Experimental model systems for understanding human axonal injury responses. Int J Mol Sci. 2021;22(2):474. doi:10.3390/ijms22020474.
27. Acaröz Candan S, Akoğlu AS, Büğüşan S, Yüksel F. Effects of neuromuscular electrical stimulation of quadriceps on the quadriceps strength and functional performance in nursing home residents: A comparison of short and long stimulation periods. Geriatr Gerontol Int. 2019;19(5):409-13. doi:10.1111/ggi.13633.
28. Toth MJ, Tourville TW, Voigt TB, Choquette RH, Anair BM, Falcone MJ, et al. Utility of neuromuscular electrical stimulation to preserve quadriceps muscle fiber size and contractility after anterior cruciate ligament injuries and reconstruction: A randomized, sham-controlled, blinded trial. Am J Sports Med. 2020;48(10):2429-37. doi:10.1177/0363546520933622.
29. Stevens-Lapsley JE, Balter JE, Wolfe P, Eckhoff DG, Kohrt WM. Early neuromuscular electrical stimulation to improve quadriceps muscle strength after total knee arthroplasty: A randomized controlled trial. Phys Ther. 2012;92(2):210-26. doi:10.2522/ptj.20110124.
30. Hyer CF, Berlet G, Philbin T, Bull P, Brandão R, Prissel M, et al. Does functional neuromuscular electrical stimulation (NMES) influence calf atrophy following achilles tendon surgery? Prospective double-blind randomized controlled trial on the use of immediate postoperative electrical muscle stimulation to preserve muscle function and volume. J Foot Ankle Surg. 2021;60(4):683-8. doi:10.1053/j.jfas.2020.12.005.
31. Piccinini G, Cuccagna C, Caliandro P, Coraci D, Germanotta M, Pecchioli C, et al. Efficacy of electrical stimulation of denervated muscle: A multicenter, double-blind, randomized clinical trial. Muscle Nerve. 2020;61(6):773-8. doi:10.1002/mus.26880.
32. Dailey DL, Rakel BA, Vance CGT, Liebano RE, Amrit AS, Bush HM, et al. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. Pain. 2013;154(11):2554-62. doi:10.1016/j.pain.2013.07.043.
33. Gibson W, Wand BM, Meads C, Catley MJ, O'Connell NE. Transcutaneous electrical nerve stimulation (TENS) for chronic pain - An overview of cochrane reviews. Cochrane Database Syst Rev. 2019;2(2):CD011890. doi:10.1002/14651858.CD011890.pub2.
34. Johnson M. Transcutaneous electrical nerve stimulation: mechanisms, clinical application and evidence. Rev Pain. 2007;1(1):7-11. doi:10.1177/204946370700100103.
35. Vance CG, Dailey DL, Rakel BA, Sluka KA. Using TENS for pain control: The state of the evidence. Pain Manag. 2014;4(3):197-209. doi:10.2217/pmt.14.13.
36. Durmuş D, Alayli G, Cantürk F. Effects of quadriceps electrical stimulation program on clinical parameters in the patients with knee osteoarthritis. Clin Rheumatol. 2007;26(5):674-8. doi:10.1007/s10067-006-0358-3.
37. Anderson KD. Targeting recovery: Priorities of the spinal cord-injured population. J Neurotrauma. 2004;21(10):1371-83. doi:10.1089/neu.2004.21.1371.
38. Scano A, Mira RM, Gabbrielli G, Molteni F, Terekhov V. Whole-body adaptive functional electrical stimulation kinesitherapy can promote the restoring of physiological muscle synergies for neurological patients. Sensors (Basel). 2022;22(4):1443. doi:10.3390/s22041443.
39. Schriwer E, Juthberg R, Flodin J, Ackermann PW. Motor point heatmap of the calf. J Neuroeng Rehabil. 2023;20(1):28. doi:10.1186/s12984-023-01152-5.
40. Miller L, McFadyen A, Lord AC, Hunter R, Paul L, Rafferty D, et al. Functional electrical stimulation for foot drop in multiple sclerosis: A systematic review and meta-analysis of the effect on gait speed. Arch Phys Med Rehabil. 2017;98(7):1435-52. doi:10.1016/j.apmr.2016.12.007.
41. Yang L, Li Y, Zhang Q, Jiang M, He J. (2021), The role of functional electrical stimulation in brachial plexus injury repair. In: Bahn J, editor. Brachial plexus injury-new techniques and ideas. Intechopen; p. 53-73. doi:10.5772/intechopen.99660.
42. Kapadia N, Zivanovic V, Popovic MR. Restoring voluntary grasping function in individuals with incomplete chronic spinal cord injury: pilot study. Top Spinal Cord Inj Rehabil. 2013;19(4):279-87. doi:10.1310/sci1904-279.
43. Press JM, Bergfeld DA. (2007), Physical modalities. In: Frontera WR, editor. Clinical sports medicine. Elsevier Inc,; 207-26. doi:10.1016/B978-141602443-9.50019-2.
44. Hillman SK, Delforge G. The use of physical agents in rehabilitation of athletic injuries. Clin Sports Med. 1985;4(3):431-8. PMID:3874709.
45. Gobbo M, Maffiuletti NA, Orizio C, Minetto MA. Muscle motor point identification is essential for optimizing neuromuscular electrical stimulation use. J Neuroeng Rehabil. 2014;11:17. doi:10.1186/1743-0003-11-17.
46. Dumitru D. High voltage stimulation: An integrated approach to clinical electrotherapy. Am J Phys Med Rehabil. 1988;67(2):89.
47. Gigo-Benato D, Russo TL, Geuna S, Domingues NR, Salvini TF, Parizotto NA. Electrical stimulation impairs early functional recovery and accentuates skeletal muscle atrophy after sciatic nerve crush injury in rats. Muscle Nerve. 2010;41(5):685-93. doi:10.1002/mus.21549.
48. Love FM, Son YJ, Thompson WJ. Activity alters muscle reinnervation and terminal sprouting by reducing the number of Schwann cell pathways that grow to link synaptic sites. J Neurobiol. 2003;54(4):566-76. doi:10.1002/neu.10191.
49. Rui B, Guo S, Zeng B, Wang J, Chen X. An implantable electrical stimulator used for peripheral nerve rehabilitation in rats. Exp Ther Med. 2013;6(1):22-8. doi:10.3892/etm.2013.1110.
50. Teodori RM, Betini J, de Oliveira LS, Sobral LL, Takeda SY, de Lima Montebelo MI. Swimming exercise in the acute or late phase after sciatic nerve crush accelerates nerve regeneration. Neural Plast. 2011;2011:783901. doi:10.1155/2011/783901.
51. Alrashdan MS, Park JC, Sung MA, Yoo SB, Jahng JW, Lee TH, et al. Thirty minutes of low intensity electrical stimulation promotes nerve regeneration after sciatic nerve crush injury in a rat model. Acta Neurol Belg. 2010;110(2):168-79.
52. Marqueste T, Decherchi P, Dousset E, Berthelin F, Jammes Y. Effect of muscle electrostimulation on afferent activities from tibialis anterior muscle after nerve repair by self-anastomosis. Neuroscience. 2002;113(2):257-71. doi:10.1016/s0306-4522(02)00187-2.

53. Midrio M. The denervated muscle: facts and hypotheses. A historical review. Eur J Appl Physiol. 2006;98(1):1-21. doi:10.1007/s00421-006-0256-z.
54. ElAbd R, Alabdulkarim A, AlSabah S, Hazan J, Alhalabi B, Thibaudeau S. Role of electrical stimulation in peripheral nerve regeneration: A systematic review. Plast Reconstr Surg Glob Open. 2022;10(3):e4115. doi:10.1097/GOX.0000000000004115.
55. Huang J, Lu L, Zhang J, Hu X, Zhang Y, Liang W, et al. Electrical stimulation to conductive scaffold promotes axonal regeneration and remyelination in a rat model of large nerve defect. PLoS One. 2012;7(6):e39526. doi:10.1371/journal.pone.0039526.
56. Herbison GJ, Jaweed MM, Ditunno JF, Scott CM. Effect of overwork during reinnervation of rat muscle. Exp Neurol. 1973;41(1):1-14. doi:10.1016/0014-4886(73)90176-3.
57. Udina E, Cobianchi S, Allodi I, Navarro X. Effects of activity-dependent strategies on regeneration and plasticity after peripheral nerve injuries. Ann Anat. 2011;193(4):347-53. doi:10.1016/j.aanat.2011.02.012.
58. Herbison GJ, Jaweed MM, Ditunno JF. Effect of swimming on reinnervation of rat skeletal muscle. J Neurol Neurosurg Psychiatry. 1974;37(11):1247-51. doi:10.1136/jnnp.37.11.1247.
59. Chiaramonte R, Pavone V, Testa G, Pesce I, Scaturro D, Musumeci G, et al. The role of physical exercise and rehabilitative implications in the process of nerve repair in peripheral neuropathies: A systematic review. Diagnostics (Basel). 2023;13(3):364. doi:10.3390/diagnostics13030364.
60. Wang P, Li Y, Zhang Z, Lin Y, Jiang Z, Ding X, et al. Effects of functional electrical stimulation on neuromuscular function after targeted muscle reinnervation surgery in rats. Annu Int Conf IEEE Eng Med Biol Soc. 2020;2020:3823-6. doi:10.1109/EMBC44109.2020.9175836.
61. Summers JA, Clinch J, Radhakrishnan M, Healy A, McMillan V, Morris E, et al. The geko™ electro-stimulation device for venous thromboembolism prophylaxis: a NICE medical technology guidance. Appl Health Econ Health Policy. 2015;13(2):135-47. doi:10.1007/s40258-014-0139-0.
62. Asensio-Pinilla E, Udina E, Jaramillo J, Navarro X. Electrical stimulation combined with exercise increase axonal regeneration after peripheral nerve injury. Exp Neurol. 2009;219(1):258-65. doi:10.1016/j.expneurol.2009.05.034.
63. Tigra W, Dali M, William L, Fattal C, Gélis A, Divoux JL, et al. Selective neural electrical stimulation restores hand and forearm movements in individuals with complete tetraplegia. J Neuroeng Rehabil. 2020;17(1):66. doi:10.1186/s12984-020-00676-4.
64. Southwell BR. Electro-neuromodulation for colonic disorders-review of meta-analyses, systematic reviews, and RCTs. Neuromodulation. 2020;23(8):1061-81. doi:10.1111/ner.13099.
65. Al-Majed AA, Brushart TM, Gordon T. Electrical stimulation accelerates and increases expression of BDNF and trkB mRNA in regenerating rat femoral motoneurons. Eur J Neurosci. 2000;12(12):4381-90. doi:10.1111/j.1460-9568.2000.01341.x.

CK4STEM

Co-funded by the Erasmus+ Programme of the European Union

Electrical Stimulation After Reinnervation in Later Phases

BETUL SOYLEMEZ • FATMA NUR ALCIN • NİLUFER CETISLI-KORKMAZ

Introduction

Peripheral nerve injury (PNI) is a very common condition and is often encountered in limb trauma patients.[1] According to Sunderland (1951), PNI is divided into five degrees according to the degree of injury and loss of function.[2] The first degree describes a conduction block, which is a physiological interruption of nerve conduction along the axon at the site of injury, with an intact nerve structure and without Wallerian Degeneration. Self-repair is expected in first degree injuries. The second degree is characterized by axonal interruption, intact endoneurium, and Wallerian Degeneration. In cases with second-degree injury, self-repair of the nerve is observed at a rate of about 1 mm per day. The third, fourth, and fifth degrees include injury to the endoneural tubes, perineurium, and epineurium, respectively (Figure 36.1).

Although it is expected that the nerve will repair itself in third-degree injuries, this is usually slow and incomplete. Therefore, it may require surgical intervention. In patients with fourth and fifth degree PNI, the nerve is not expected to show the self-repairing capacity and surgical intervention is usually required.[3] Wallerian Degeneration, which occurs after acute nerve incision injury, results in axon loss and reorganization of support cells in the distal stump (Figure 36.2). In this process, cells can disappear through apoptosis and refill the wrong endoneural tubes. The fact that the nerve regenerates very slowly during this process leads to the inability to achieve functional recovery of a distant area due to irreversible changes due to denervation.[4] It is also stated in the literature that the functional recovery of peripheral nerves after PNI is generally insufficient despite the tolerant growth environment specific to the peripheral nervous system.[5]

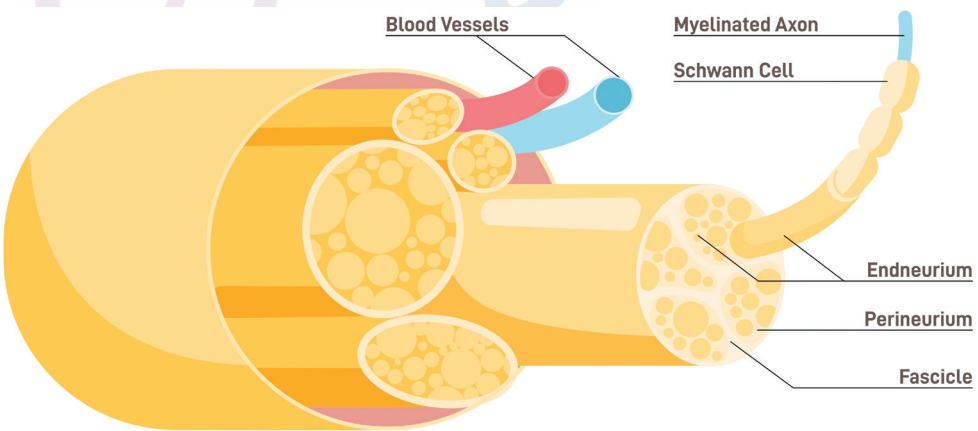

Figure 36.1 Nerve structure.

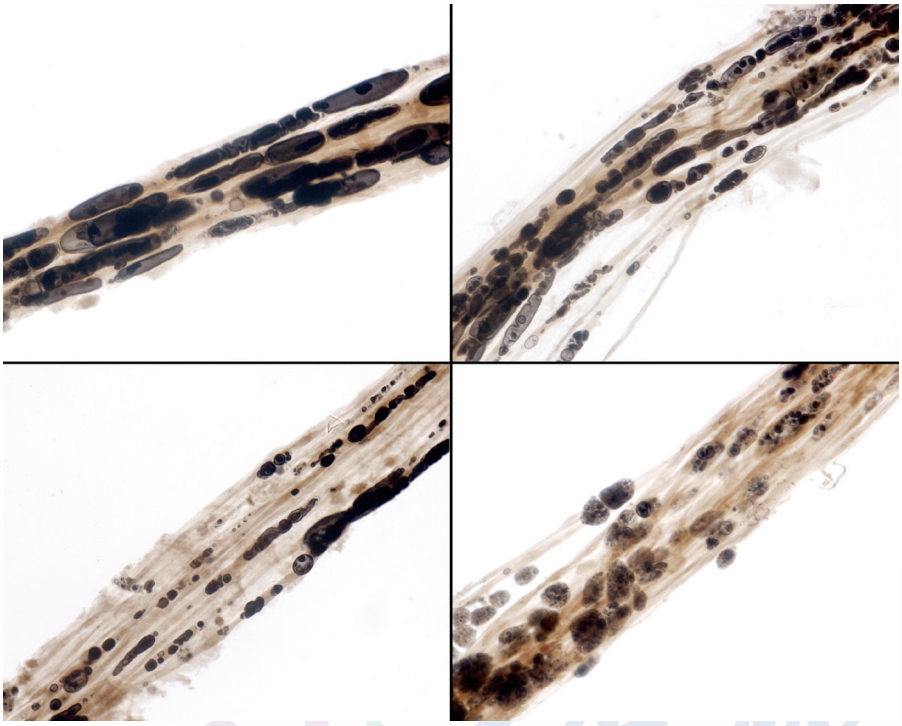

Figure 36.2 Wallerian Degeneration.

Immediately after PNI, a complex series of events begins to occur in the skeletal muscle, which is innervated by the nerve, leading to profound, short-term, largely reversible, structural, and functional changes.[6] The typical image formed after trauma includes the loss of motor control, sensory loss, and impaired vasomotor control.[7] When the peripheral nerve is injured, target muscles lose their ability to "pump" due to loss of nerve innervation. This condition leads to a relatively reduced perfusion of the target muscle and may cause skeletal muscle atrophy.[8] A previous study showed that PNI caused the cross-sectional area of skeletal muscles to decrease by 70% within 2 months.[9] PNI is a complex condition with various signs and symptoms such as numbness, tingling, throbbing, burning, or sharp pain. Sensory disorders observed after PNI could be classified as negative and positive phenomena. A condition in which there is a decrease or loss in the senses of touch, deep sensation, and stereognosis is called a negative phenomenon, while a condition characterized by increased sensation or dysesthesia is called a positive phenomenon. The pattern of sensory impairment varies with the cause and severity of injuries. PNI causes a loss of mechanical pressure due to the absence of mechanoreceptors.

The most common positive phenomena after PNI are needling, tingling, and hyperalgesia caused by compression applied directly on the injury site.[7,8] Peripheral nociceptive neurons are stimulated when initially free nerve endings (A-delta and C fibers) receive harmful stimuli or are damaged. Over time, the primary afferent A-delta and C nociceptors in the injured nerve area begin to respond in an amplified way to harmful stimulation, which leads to the development of excessive excitability and spontaneous activity. This is explained by the significantly reduced firing thresholds of A-delta fibers. Inflammatory factors may cause changes in the genetic and molecular composition of nociceptors, increasing primary nociceptor excitability.[10] In addition, decreases in the activation threshold of thermoreceptors and nociceptors gradually lead to neuropathic pain.[1] The expression of voltage-gated sodium channels is altered in the dorsal root ganglia after PNI. This change forms the basis of ectopic discharges, and then neuropathic pain

occurs due to the change. Sensory changes affect the peripheral nerves, organization of the spinal cord, and plasticity of the brain. All three factors may affect early regeneration and later neuropathic pain. The slow regeneration rate delays the speed at which the proximal tip crosses the surgical cavity. In addition, non-specific reinnervation reduces the chances of regeneration.[8] Motor and sensory disorders caused by injury significantly affect the daily life, social lives, and participation of patients.[1]

Wallerian Degeneration begins immediately after PNI at the distal nerve stump, suggesting that these axons are denatured and fragmented. Therefore, one of the goals of therapeutic treatments is to create a microenvironment conducive to axonal regrowth and reinnervation.[11] Surgical intervention is required to provide functional nerve regeneration in many PNIs (Figure 36.3).

Currently, the surgical treatment of PNI includes end-to-end repair with microsurgery, tension-free nerve epineurium suture, and autologous nerve grafting. Significant progress has been made in peripheral nerve surgery over the years, but despite advances in microsurgical techniques, recovery of nerve function remains insufficient. One third of patients show little or no improvement despite appropriate surgery.[1,5,12] The literature states that surgical approaches do not guarantee functional recovery, which can lead to neuronal atrophy and prevent accelerated regeneration.[1] Skeletal muscle reinnervation requires the resumption of axonal elongation, synaptogenesis, and contraction function. Important factors for reinnervation may be counted as the denervation interval, the path followed by axons to reach muscle fibers, the number of axons that are re-inversed according

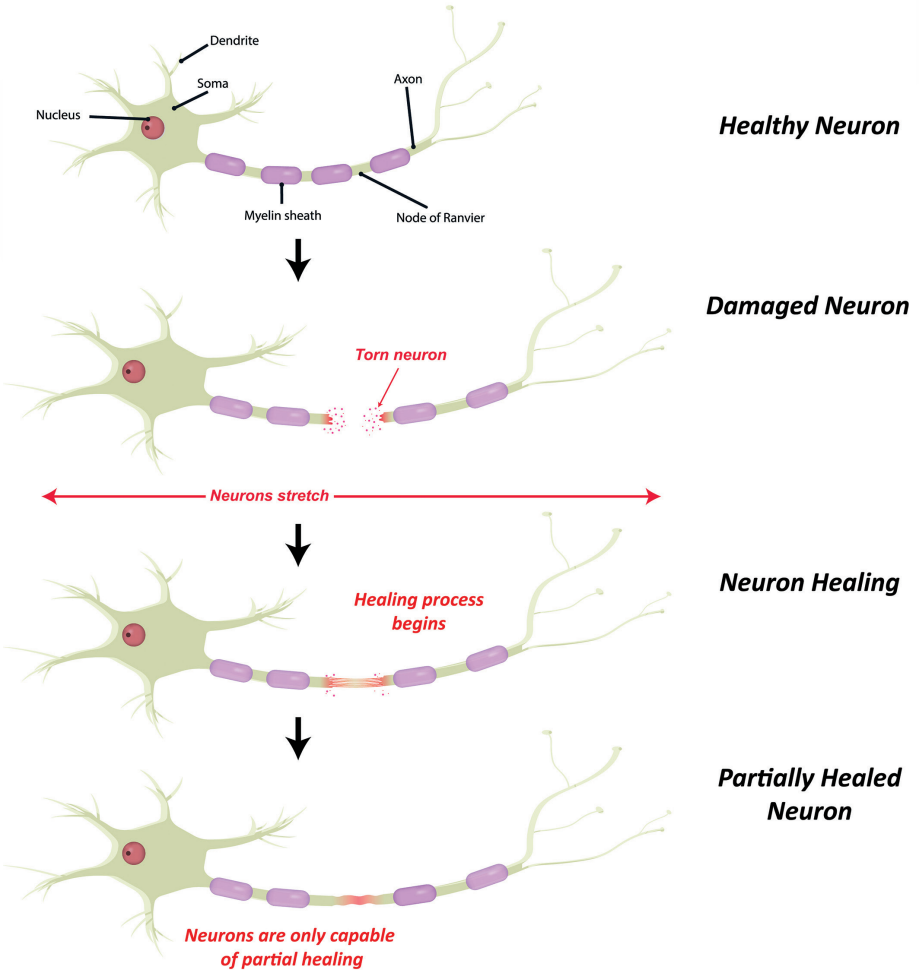

Figure 36.3 Nerve regeneration.

to the number that originally innervated the muscle, and the specificity.[6] The regeneration of axons into inappropriate pathways is an important factor contributing to this failure.[13]

The regeneration of axons into unsuitable distal nerve branches may negatively affect functional recovery after peripheral nerve suture. For example, renewed motor axons may enter Schwann cell tubes, which give rise to sensory branches and are directed to sensory end organs. Similarly, sensory axons can be directed to motor endplates. Not only do these axons fail to make functional connections but they also prevent suitable axons from entering the pathways they occupy (Figure 36.4 and Figure 36.5).[13-15]

If we sample from the hand, the skin areas of the hand will not be re-innervated by their original axons to a large extent due to axonal misdirection. Instead, they may be reinnervated by axons that originally innervated other parts of the hand. The result is significant restructuring changes in the cortical region where the Median nerve is normally represented.[16] Because of axonal misdirection in sensory nerve repair, patients experience painful sensations in hurt fingers even years after repair. As another example, following the repair of the Sciatic nerve, motor axons may be incorrectly directed to the Tibial and Peroneal nerve branches involved in the plantar and dorsiflexion of the ankle, affecting antagonistic muscles.[17] Motor neurons preferentially reinnervate the motor branch in teenagers and adults, even if the repair is intentionally misaligned or a gap has been applied between the proximal and distal decussations. Although motor axons preferentially reinnervate the motor branch, they also enter most sensory branches. An even larger proportion of the renewed sensory axons entered the motor branch, suggesting that sensory axon behavior may be more random. The definition of the mechanism of preferential motor rein-

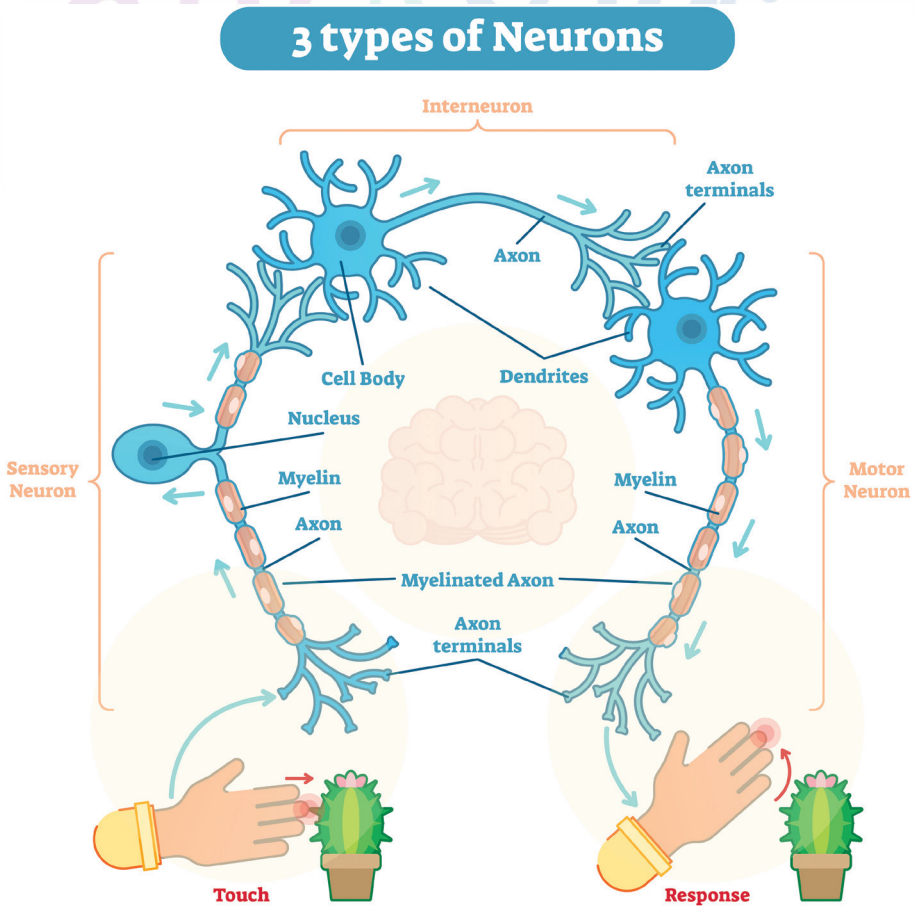

Figure 36.4 Normal nerve conduction.

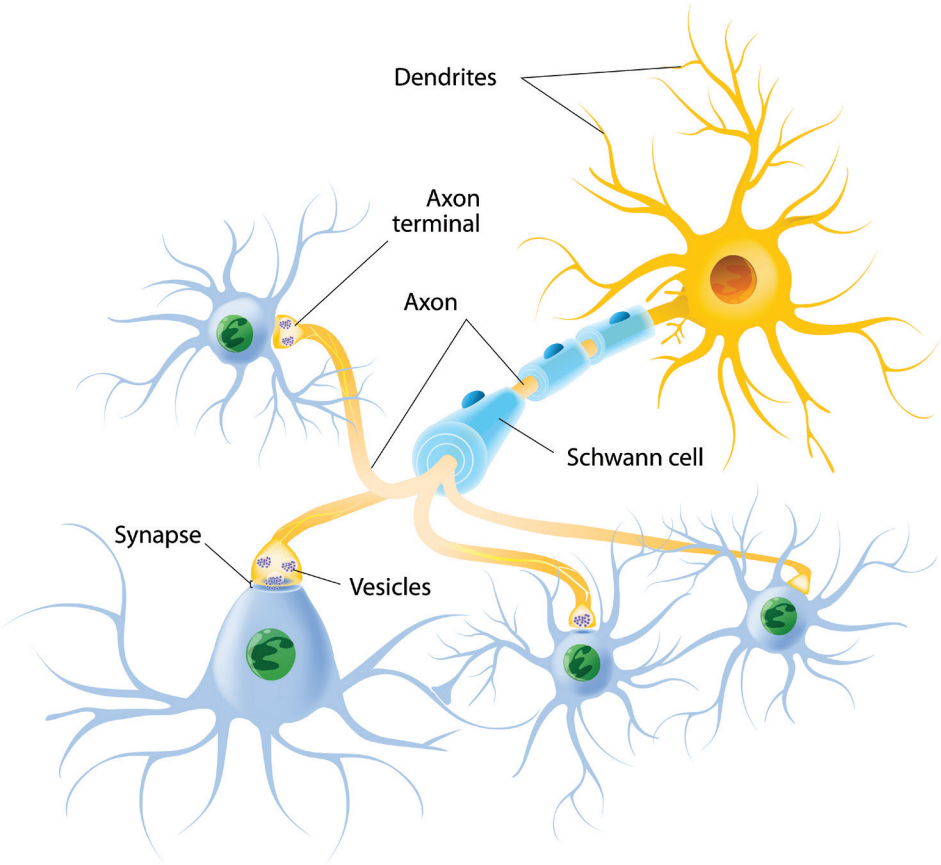

Figure 36.5 Synaptic organization.

nervation and its increase, especially in adults, can potentially improve the prognosis of damage to nerves involving both sensory and motor axons.[13,14]

A meta-analysis conducted in 2005 to determine predictors for motor and sensory recovery after microsurgical repair of Median and Ulnar nerve transection lesions revealed the same results as Sunderland's first reports on 40 years of nerve repair. According to the results of this meta-analysis, the three important determinants of successful motor recovery are patient's age, lesion site, and delay in repair.[12] The best recovery after a motor nerve injury may only be achieved when an abundant supply of motion-specific motor axons is provided to the muscles because of nerve trans-section (Figure 5).[6] After axonal injury, axons close to the injury site begin to produce new axon buds. However, gradual axonal growth may lead to a progressive prolongation of the time required for axons to pass through the injury site. This increase in time may weaken the ability of Schwann cells at the far end of the injury to promote proliferation. Cumulative narrowing of the endoneural membrane tube and non-specific reinnervation may also exacerbate the passage of injured axons.[8]

Non-surgical treatments continue to be investigated in terms of their potential to restore nerve function after PNI. Physiotherapy and rehabilitation is a necessary stage for patients to recover better. Despite this requirement, most patients who undergo surgery are not subjected to a systematic physiotherapy and rehabilitation program after surgery. This condition also leaves patients with sensorimotor disorders and chronic neuropathic pain that will last a lifetime. Electrical stimulation (ES), one of the rehabilitation strategies, has emerged as a pioneer in the rehabilitative treatment of PNI. ES plays a significant role among non-pharmacological interventions.[1,12] Compared to surgical treatment and other conservative ap-

proaches, ES is considered as a safe and effective treatment option that can be applied in most patients. ES not only treats PNI but also includes tests that show changes in the process of injury. A study has shown that the use of pulsed ES to record changes in muscle fibers of the movement and muscle speed recovery cycle on injured muscle can provide a detailed understanding of the in vivo evidence of the potential for depolarized rest after PNI.[18] In general, patients without a malignant tumor, high fever, coma, active bleeding, skin damage, or acute inflammation are eligible for ES.[8]

Practices of Electrical Stimulation

Post-therapeutic modalities could be used both directly and indirectly to increase or decrease muscle activation levels, affect skeletal muscle activity and performance, and reduce pain. Clinical studies have shown that ES increases axon growth during nerve repair and accelerates sensorimotor healing. Direct applications of therapeutic modalities used to facilitate skeletal performance include the use of ES to depolarize peripheral nerves to drive more motor units.[1,19] The diameters of the nerve fibers in the peripheral nerve and their resistance to stimulation are different. In the presence of a stimulus with sufficient strength and duration, the nerve fibers with the largest diameter and the lowest resistance depolarize earlier. The largest of the nerve fibers in a mixed peripheral nerve is A-alpha, which carries motor and proprioceptive signals; therefore, it is depolarized first. To stimulate the smaller diameter A-beta fibers carrying the sensations of touch and pressure and the even smaller diameter A-delta and C fibers carrying the sensations of pain and temperature, stimuli with increasing amplitude and duration are required.[19] Sunderland showed that the motor and sensory components of the nerve are arranged more randomly in the proximal segments of the large nerve trunks, while they are more clearly localized in the distal extremities. This situation may be a guide in the ES application.[20]

ES applications applied after PNI could be classified into 5 regions. ES of skeletal muscle (promote skeletal muscle regeneration and prevent skeletal muscle atrophy), Spinal Cord Stimulation (SCS) (inhibit apoptosis and synaptic stripping), Transcutaneous Electrical Nerve Stimulation (TENS) (mediate decreased local inflammatory mediators and elevated pain thresholds), Dorsal Root Stimulation (DRS) (suppress the excitability of the dorsal root ganglion) and Peripheral Nerve Stimulation (PNS) (promote axon regeneration and the exactness of axon growth; activated Schwann cells secrete glutamate and exosomes to enhance the ability of regeneration and inhibit apoptosis).[8] The intermittent currents are preferred for the denervated muscles and the intermittent or burst alternating currents are preferred for the innervated muscles. Currents can be applied with monophasic or biphasic features. While the current applied to the denervated muscles is 10 milliseconds (ms) or longer, the innervated muscles are usually applied for 100-200 microseconds (μs). While the current frequency is 2-4 Hertz (Hz) for denervated muscles to obtain slow fasciculation, 20-40 Hz is applied to obtain fast fasciculation in the innervated muscles. The frequency is between 35 and 75 Hz, with 10-15 submaximal or maximal contractions in each period. Superficial electrodes are used in practices performed by physiotherapists. While electrode placements are made to the most bulging point of the muscle for denervated muscles, the motor point of the muscle or peripheral nerve tracing can be preferred for the innervated muscles. ES applied to denervated muscles aims to minimize denervation atrophy, the main purpose for innervated muscles is muscle strengthening or muscle retraining.[21] ES, which modifies neuromuscular activity with electrical currents, mainly includes Neuromuscular Electrical Stimulation (NMES), TENS and Functional Electrical Stimulation (FES). NMES usually produces muscle contraction at a frequency of 20-50 Hz and is used to improve patient function. TENS is usually used to relieve pain at a frequency as low as 2-10 Hz or at an ultra-high frequency. Low-Frequency TENS usually targets sensory nerves and does not produce visible muscle contraction. FES involves a functional task in which the target muscle is initially stimulated to create

movement, and the next step is for the upper limb to grasp the object or the lower limb to walk.[1]

Electrical Stimulation of Skeletal Muscle

NMES generally implies that ES is used to increase strength in the innervated muscle, whereas Electrical Muscle Stimulation (EMS) refers to the stimulation of the denervated muscle. The main difference between NMES and EMS is the tissue that is really stimulated and depolarized to bring out the therapeutic effect.[19] While NMES is widely used to restore skeletal muscle mass and function in patients with PNI, it is also applied to activate the nervous system in healthy individuals.[22] Most studies in the literature use low-frequency ES to support nerve regeneration. Studies have revealed that low frequency ES strengthens axon growth and muscle reinnervation after sudden or delayed nerve repair.[1,5] The studies, the foundation of which was laid by Hoffman and colleagues in 1952, provided important evidence on the ES of peripheral nerves. The reports of these studies show that EMS applied early after injury accelerates nerve regeneration. It is argued that the mechanism of action contributing to this success is the increased production of neurotrophic factors caused by ES and the upregulation of its receptors. In addition, studies in the literature have revealed that ES still has therapeutic potential to stimulate functional recovery after chronic axonotmesis.[12] It has been reported in the literature that 20 Hz continuous ES of the main axons proximal to the repair site from 1 hour to 2 weeks reduces the axonal regeneration time up to 3 weeks and accelerates motor reinnervation.[13] In one of the studies in the literature, it was found that 1 hour continuous 20 Hz ES period was as effective as 1 day to 2 weeks ES periods in significantly increasing motor axonal regeneration in a severed and surgically repaired rat Femoral nerve. ES is also hypothesized to increase the regenerative capacity of sensory neurons. The observed beneficial effects of ES on motor neurons are evidenced by the increased number of sensory neurons that regenerate their axons in response to stimulation and its pronounced effect on the expression of genes associated with injury/regeneration. The study results show that this effect extends to sensory neurons.[23] A study conducted to determine the appropriate protocol for maintaining muscle mass and strength during long-term denervation periods has shown that 200 to 1200 contractions per day maintain muscle mass, average muscle fiber cross-sectional area, and maximum strength.[24] There are many studies in the literature that examine whether different parameters such as stimulation duration, the type of target muscle, and ES intensity change the effect of ES. Acaroz Candan et al. proved that the symmetric biphasic square waveform of NMES (100 Hz; 400 μs) can improve Quadriceps Femoris muscle function with both short stimulation duration [5 minutes (min) × 4 sets) and long stimulation duration (10 min × 2 sets) in elderly individuals.[25] Mani et al. used both short pulses at 50 Hz (0.26 ms) and long pulses at 100 Hz (1 ms) to improve mobility function in elderly individuals. They reported that both pulse methods improved lower limb strength and functional performance.[26]

There are studies in the literature that report that NMES is effective and studies that report that its effect is limited. Hyer et al. used NMES to treat the calf muscles of patients after Achilles tendon surgery. In the results, it was reported that muscle mass and function did not improve in the NMES group and in the sham NMES group.[27] Piccinini et al. reported that there was no significant difference between ES and the control group after traumatic PNI.[28] Peripheral nerves contain an anatomical sequence that organizes not only various types of axons but also other important cells such as Schwann cells, immune cells, and vascular structures with blood nerve barriers. Given this complexity, it may not be surprising that different evaluation parameters give different results.[29] Although in many studies in the literature, the standard ES parameter of 20 Hz is preferred, the method and frequency range of ES need to be standardized.[1]

Electrical Stimulation After Reinnervation

During re-innervation of the limb, ongoing motor and sensory rehabilitation is of critical importance.

Sensory healing is also important for motor healing. Objective measurement of sensory recovery includes the intensity test, in which mobile and static two-point discrimination are used, and the threshold test, in which Frey or Semmes-Weinstein monofilaments are used. It is clear that early re-innervation provides superior functional return.[30]

The time frame of ES in nerve regeneration is controversial. Low healing is caused by irreversible nerve degeneration. Early ES seems to be better for nerve regeneration.[31] In contrast, most nerve injuries in humans are repaired recently, sometimes days or weeks later. ES also enhances nerve regeneration following delayed nerve repair.[32-34] There is significant evidence in the literature that postoperative ES could increase nerve regeneration in chronic PNI that is considered impossible to treat.[33,35] ES has also been found to accelerate regeneration following injuries that are primarily irreparable and require alternative forms of reconstruction.[36,37] Instead of altering nerve regeneration rates, ES could accelerate axon regrowth, weaken the damaged regeneration environment, and improve sensory and motor nerve repair.[31] Neuromuscular plasticity is critical for the re-characterization of muscle properties after nerve regeneration and muscle reinnervation. ES applied to all motor nerves that normally innervate muscles can alter the properties of muscle fibers. It has been reported that the order of recovery in regaining the characteristic features of nerve and muscle properties after PNI is from small slow motor units to large fast motor units.[38] Misdirection of regenerative nerves to reinnervate several different muscles may adversely affect the normal use of re-innervated muscles.[39] If there is a serious delay in muscle re-innervation, the regenerative capacity of axotomized motor neurons and the growth support provided by denervated Schwann cells in distal nerve stumps may be compromised.[38]

Rehabilitation of Neuropathic Pain with Electrical Stimulation

After PNI, the expression of neurotrophic factor increases in the early days to support neuronal survival and axonal regeneration. Although they are involved in axonal regeneration, nerve growth factor and brain-derived neurotrophic factor are well-known pain modulators and play various roles in terms of peripheral and central synthetization in neuropathic pain. Pain is one of the most obvious complaints of patients and one of the sensory disorders that affect their daily lives the most, and it is also the most subjective sensory disorder. Since neuropathic pain is probably the most disabling condition in patients with severe nerve injury, physiotherapy and rehabilitation treatments that increase the activity of the injured limb and the possible positive or negative effects of these treatments on the patient should definitely be considered.[1,40] It has been shown in the literature that ES is associated with changes in neurotrophic factors involved in the formation of neuropathic pain.[40]

Following the introduction of stimulation-induced analgesia by Reynolds, the Gate Control Theory has been tested in both animals and humans through various experiments. These experiments led to the naming of SCS by Shealy et al.[41], cutaneous electrical nerve stimulators by Long [42] and Shealy [43], and TENS by Burton[44]. Later, both transcutaneous and spinal cord neurostimulators were applied clinically.[20] ES applications for neuropathic pain after PNI consist of SCS, DRS, PNS, Peripheral Nerve Field Stimulation (PNFS), TENS, and Interferential Current (IC) methods. In the studies conducted, ES applied with these methods has been shown to accelerate both muscular reinnervation and the initial recovery of nociceptive responses after sciatic nerve incision and repair.[40]

Spinal Cord Stimulation (SCS)/Dorsal Root Stimulation (DRS)

SCS is defined as the process of blocking the transmission of pain signals to the brain in the targeted area by injecting a low-voltage electrical current into the patient's spinal cord and stopping the pain.[45] SCS is provided by electrodes placed at different spinal cord levels depending on the location of pain, posterior to the dorsal columns of the spinal cord at epidural distance and connected to a pulse generator implanted under the skin.[46] In this method, by stimulating the large myelinated fibers

in the posterior colon with different stimulation modes, the place where the needling sensation covers the painful area of the patient is determined and the electrode is fixed under the skin according to this area. A trial stimulation is performed, and if a successful result is obtained at the end of the trial period, the permanent system placement process is initiated. For this procedure, the part placed in the intervertebral space is connected to the permanent electrode. In the first years when this treatment started to be used, the practice was called "DRS" because it was thought that ES would affect only the dorsal horn of the medulla spinalis. However, in the following years, it was revealed that ES provides inhibition in all parts of the medulla spinalis, and the name of the procedure was changed to "SCS".[45,47] Although it is currently not fully understood by which mechanisms neurostimulation blocks pain, this technique is based on the "Gate Control Theory", which is based on the idea that painless signals prevent pain sensation from reaching the central nervous system by inhibiting painful signals.[46]

For SCS practice, the pain should be chronic and related to an underlying organic cause. Currently, the most common indications for SCS are conditions such as resistant low back/limb pain, spinal cord injuries, failed low back surgery syndrome, neuropathy, and complex regional pain syndrome. In addition, recently, the use of SCS has been increasing in conditions such as reflex sympathetic dystrophy, postherpetic neuralgia, arachnoiditis, epidural fibrosis, phantom pain, malignancy pain due to vertebral metastases, and fecal and urinary incontinence. As with all neurostimulation applications, appropriate patient selection for SCS is an important marker of success.[46] In the literature, it has been observed that pain decreases by at least 50% in most patients after SCS implantation.[48]

PNI has been found to produce local inflammatory changes in the nerve. The development of allodynia after injury seems to be associated with dysfunction of the spinal Gamma-Aminobutyric Acid (GABA) system. It is thought that neuropathic pain alters the local neurochemistry of the dorsal horns, thereby decreasing the hyperexcitability of neurons. Experimental evidence is available in the literature that GABA and serotonin levels are increased and excitatory amino acid levels are suppressed. It is thought that SCS exerts its effect on neuropathic pain by restoring normal GABA levels. In one of the studies in the literature, the response to SCS was compared in allodynic and non-allodynic rats after PNI, and it was found that sensitivity thresholds to harmless stimuli decreased at the end of treatment.[41,49] Another study in the literature states that in cases with a long-standing history of painful peripheral neuropathy that is resistant to conservative treatment, SCS provides pain control and helps patients to stop medications.[50]

As with many invasive procedures, it should be known that mild or serious complications may occur during and after SCS implantation. Nerve/spinal cord injury, epidural hematoma, epidural abscess, post-dural headache, seroma, wound infection, electrode migration, and electrode fracture are some of these complications. It has been stated that the most common among these complications are electrode migration and infection.[47] Targeting SCS in paresthesia of special anatomical locations is a difficulty experienced in practice.[48]

Peripheric Nerve Stimulation (PNS)/Peripheric Nerve Field Stimulation (PNFS)

For the treatment of chronic pain, PNS uses a percutaneous approach, in contrast to implantable systems, and allows for minimally invasive approaches.[51] The concept of PNS was introduced into clinical practice by Wall and Sweet in 1967. In Wall and Sweet's study, stimulation was applied to the Infraorbital nerve via a percutaneous needle, and a condition occurred in which hypoesthesia and pain were stopped distally of the stimulation. Although the technique has experienced some ups and downs since those days, it has been electrified since 1999. Although highly irregular results and a high rate of complications were identified before 1999, various indications for the use of this neurostimulation method other than pain or apart from pain (motor stimulation of the Phrenic nerves and stimulation of the somatic nerves of the extremities

in patients with hemiplegia and paraplegia, autonomic stimulation for urinary and gastrointestinal disorders, etc.) were presented after 1999.[51,52] PNS has been applied to various nerves in the body until today, including the Occipital, Supraorbital, Infraorbital, Radial, Ulnar, Median, Tibial, Peroneal, and Sciatic nerves.[53] Published studies show that neuropathic pain responds to PNS in many patients.[54] In PNI, ectopic discharges are transmitted by injured nerves, especially low-threshold A-beta and high-threshold A-delta and C fibers. All these nerves could contribute to the formation of pain. PNS has long been used as a method of orthodromic stimulation of non-nociceptive A-beta nerve fibers. It is assumed that this method, which has direct painless ES, could change the ectopic discharge, which leads to a decrease in pain perception. Activation of the A-beta nerve fibers stimulates the corresponding dorsal horn interneurons, which are involved in the processing and transmission of nociceptive information through peripheral A-delta and C nerve fibers. Thus, painless stimulation of the peripheral nerve region results in a decrease in pain signals.[51]

PNS is applied to a specific nerve. In PNFS, another technique, stimulation is performed not on a nerve but on a group of nerve endings at the subcutaneous level. In PNFS, it is necessary to position one or more electrodes within the maximal pain zone. With this method, the small distal branches of the nerves are targeted within the subcutaneous space. PNFS produces paresthesia along a diffuse painful area that may not be associated with a specific dermatome or may not be well defined.[52,53] The purpose of PNS is always to produce paresthesia along the region innervated by the stimulated nerve, while PNFS distributes paresthesia as an electric field around the active electrodes. When PNS is selected, a unidirectional paresthesia along the stimulated nerve; when PNFS is selected, a concentric stimulation should be sought in a specific area without radiation, held exactly in the painful area of the patient. PNS should be selected if more specificity is needed depending on the location and type of pain, and PNFS should be selected if a broader paresthesia is sought. Regardless of the application technique, the purpose of both techniques is to reduce pain by creating paresthesia.[52] These techniques may also be used to complement other electrical neuromodulation procedures, such as SCS and DBS. In the literature, various names such as “hybrid” stimulation, spinal-peripheral neurostimulation, or triangular stimulation are used for the use of SCS combined with PNFS. PNS is also thought to be based on the Gate Control Theory of pain described by Melzack and Wall more than 40 years ago, similar to SCS. In terms of approved indications, SCS is much more accepted than PNS. Although PNS is considered a new technique in the continuity of treatment methods for resistant neuropathic pain, this is a misconception. PNS has been offering practitioners an excellent modality in the treatment of neuropathic pain for more than 40 years.[53,54]

Studies mentioning the use of PNS on various specific neural targets are available in the literature. In one of these studies, treatment was performed by targeting the Ulnar nerve with percutaneous implantation of a permanent stimulation electrode for chronic upper limb pain in 5 patients. After treatment, patients’ pain control increased and their quality of life improved in patients who were followed for 6 years.[55] In another study, a case report on the management of persistent pain with uncertain pathology by percutaneous implantation of a permanent stimulation electrode via a stimulating needle into the Brachial Plexus following a traction injury of the shoulder and Brachial Plexus was presented. After treatment, excellent pain control and unexpected beneficial sensory and motor changes were observed in the patient’s arms.[56] In the study, the preferability of percutaneous implantation was emphasized because it is a simpler method than surgical implantation. In another case series using PNS for Brachial Plexus injuries, PNS implantation was applied to patients with posttraumatic Brachial Plexus trauma. The 4-pole electrode tips are placed directly on the sensory peripheral branch of the main nerve concerned, proximal to the lesion site. Assessments were made after 1, 6 and 12 weeks. Although all patients initially complained of severe pain in the

median and radial regions, all patients experienced pain relief within a few minutes after treatment. Patients in this study showed promising results by showing 76.2% and 71.5% pain reduction at 6- and 12-month long-term follow-ups, respectively.[57] Another study presented reports of two patients with Ulnar nerve neuropathy and found that both patients had at least 75% relief in pain scores 6 months after Ulnar nerve PNS implantation. In addition, it has been reported that patients also experienced significant improvement in functional outcomes, achieved various achievements such as return to employment, the ability to perform daily life activities without any impairment, and improved quality of life.[58] In a case report in which PNS was applied to a patient diagnosed with Meralgia Paresthetica, which refers to compression of the Lateral Femoral Cutaneous nerve, the patient's pain decreased to 2 out of 10 with the use of gabapentin; after PNS implantation was applied as an alternative method, his pain decreased to 0 out of 10. The patient also reported improved quality of life with better sleep and less drowsiness. The application was made for 60 days and then the device was removed. It has also been reported that complete improvement in pain continues 12 months after the device implantation date.[59] Similar studies are available for neuropathic pain caused by Sciatic nerve, Median nerve, and Lumbar Plexus damage.[51]

Although PNS has shown tremendous clinical potential, as seen in the examples provided, there are also safety concerns and potential side effects. Stevanato et al. reported complications related to tendons, nerves, and vascular structures that caused distraction and translation of electrodes from the target nerves.[57] It is also reported in the literature that side effects have increased hospitalization and the need for surgical intervention. Decongestant hematomas, seromas, skin erosions, pain and numbness, allergic reactions to surgical equipment, headache, and muscle cramps, as well as biological side effects, are also among the complications of PNS.[51] More study is needed to identify the best candidates for PNS, select the best procedure and the best equipment for each patient, and define adequate expectations for patients and pain specialists.[54]

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS, which uses a small current to activate sensory axons without triggering muscle contraction, is being applied in physiotherapy and rehabilitation programs to improve sensory feedback and adjust neural network pathways. Sensory feedback also plays an important role in the motor activity. When muscle is damaged, TENS can be used to temporarily innervate the muscle to prevent muscle atrophy until it heals. However, it can also be used to prevent the loss of strength in the innervated muscles as much as possible during immobilization caused by any reason. Non-invasive ES, such as TENS, has gained popularity in the treatment of neuropathic pain over the past 10 years. TENS has high and low frequency modes. Low-Frequency TENS is defined as the transmission of pulsed currents in a burst mode of 10 Hz or lower. High-Frequency TENS, on the other hand, are typically used to define frequencies of 150-200 Hz. TENS can be used to relieve pain at a frequency as low as 2-10 Hz or at an ultra-high frequency. The frequency commonly used in clinical practice is 1-150 Hz. Low-Frequency TENS usually targets sensory nerves and does not produce a visible muscle contraction. If it is preferred for the treatment of neuropathic pain, it is usually applied at high intensities and close to the pain zone.[1,7]

Some studies conducted in the rat model have shown that the TENS effect occurs through local, spinal, and supraspinal pathways. According to the results of these studies, Low-Frequency TENS (<10 Hz) appears to work through μ-opioid, GABA, serotonin, and muscarinic M1 and M3 receptors. Repeated stimulation with TENS results in tolerance. Due to this condition, it is reported that TENS may be using opioids, serotonin, and cholinergic neurotransmitters to affect the descending inhibitory pathways. Studies in the literature have reported that High-Frequency TENS shows the effect of delta-opioid receptors in the bloodstream and cerebrospinal fluid through increased levels of beta-endorphin and methionine-enkephalin.[51]

In one study, TENS was found to be able to cure 72 non-cancer pain patients, including peripheral nerve pain that severely affects life lasting longer than 3 months. At the same time, many clinical studies have shown that TENS applied to the affected sensory nerve branches (mainly Brachial Plexus, Median nerve and Radial nerve) under the armpit with an implanted electrode shows a significant improvement in pain after PNI, and implantable TENS has shown to be an effective method for peripheral nerve pain caused by upper limb trauma.[1] Another study in which rats were subjected to ES for 4 hours, mandatory treadmill training for 5 days, or a treatment program in which both treatments were combined after Sciatic nerve repair, found that treadmill training and ES reduced neighboring neuropathic pain differently but positively before and after sciatic reinnervation. The combination of the two treatments has been indicated to cause enhanced motor and sensory re-innervation and strong agonistic effects in pain relief. The different effects of these treatments have been found to be associated with changes in the levels of neurotrophic factor mRNA in sensory and motor neurons.[40] Another study in the literature, a physiotherapy and rehabilitation method including TENS was applied in a 9-year-old pediatric patient with second Thoracic Longus palsy as a case report. In this study, 0.5-1 Hz Microcurrent around the sensitive area for hyperalgesia, cranial electrotherapy, acupuncture, a non-interventional pulsed radio frequency at 133.000 Hz superimposed on a low frequency square Direct current wave with 2 Hz pulse pitch, low level laser, TENS with a frequency of 200 Hz and an amplitude of 80 ms for pain, direct current for edema and inflammation, Faradic current to stimulate Deltoid, Trapezius and Serratus Anterior muscles, approaches such as breathing exercises and mirror therapy were applied over 13 sessions. As a result, it was reported that this patient's pain and paralysis completely recovered within 2 months, and that ES relieved pain, increased neural conduction, and improved mobility. It was also emphasized that the combination of treatments applied effected accelerating healing in the nerve.[60] High-Frequency TENS has been shown to be able to modulate Sciatic nerve activity and induce analgesia through increased serotonin release, in addition to blocking the cardiovascular and respiratory adverse effects of pain.[51] The difference between Low-Frequency TENS (110 Hz; 200 ms) and High-Frequency TENS (unmodulated 5-kiloHz; 200 ms) in terms of mechanical pain threshold, heat pain threshold, tactile threshold, and peripheral nerve conduction has not been found in the literature. However, patients may feel more comfortable with unmodulated 5-kiloHz currents. Some studies have shown that a Medium-Frequency Alternating Current [10 kiloHz, 0.3 seconds (s)] can be used to block unwanted sensory and motor activities and speed up nerve repair. When the TENS and NMES effects were compared, the results showed that ES can increase muscle hemodynamics. TENS can increase blood flow more than NMES.[1] There are few studies evaluating the effectiveness of TENS, and existing studies lack the power to show this technique as a clear way to treat chronic pain.[7]

Interferential Current

Interferential Current (IC) is an example of burst modulated Alternating current with sinusoidal modulation, also known as kilohertz frequency alternating current.[61] In clinical practice, IC is used for main purposes such as reducing pain, increasing blood flow, increasing tissue healing, and reducing edema.[62] IC uses a Medium Frequency current that penetrates deep into the muscles or joints.[63] Two pairs of electrodes placed directly on the patient's body are used for IC. During treatment, two separate electrical signals pass through the patient's body between each pair of electrodes. These two electrical signals create an interference zone in the body.[64] The frequency used is between 3500 and 5000 Hz.[65] By using two Medium Frequency Alternating currents, an amplitude modulated resultant current in the range of 2-250 Hz is produced.[66] Using the high-frequency current will reduce the impedance and thus reduce the disturbance caused by low-frequency currents. At the same time, IC produces low-frequency effects in the deeper tissues of the body, leading to the therapeutic effect

of low-frequency current therapy.[65] IC can also be used for muscle stimulation in clinical practice. This reportedly more relaxed current reaches deeper tissues and induces more muscle torque than low-frequency pulsed currents. However, caution is important with regard to muscle power generation because IC has been shown to generate a high degree of maximal voluntary isometric strength of the knee extensors in a study in healthy subjects. The literature on IC treatment states differrent parameters may have different physiological effects. For example, 130 Hz is more sedative, 0-100 Hz is more stimulating, 10-150 Hz increases blood flow, and 50-100 Hz produces sedative and spasmolytic effects. However, these claims seem to be based on the personal and clinical experiences of the authors rather than scientific evidence.[61] In the literature, EA has been tested in many patient groups, especially compared with TENS, with the aim of reducing pain.[66] However, when the literature on patients with PNI was searched, no studies were found.

Rehabilitation with an Electrical Stimulation of Neuromuscular Activation

NMES and FES are used to increase the strength, endurance, and functional use of skeletal muscle for various therapeutic purposes. More recent evidence suggests that NMES directly increases the volume or total number of motor units and activation time of these motor units.[19] However, IC and High-Voltage Pulsed Galvanic Electrical Stimulation (HVPGS) can also provide neuromuscular activation for amplification.

Neuromuscular Electrical Stimulation (NMES)

NMES is a general term describing a group of stimuli that use a pulsating alternating current to stimulate the innervated musculature.[67] Forms of NMES practiced by physiotherapists include applying ES to muscles and nerves to produce muscle contraction through depolarization of motor nerves. NMES is generally used for neuromuscular rehabilitation after nerve injury, prevent muscle contracture or disuse during prolonged bed rest or immobilization, maintaining or improving range of motion, reduce muscle tone, facilitating muscle contraction, alleviating the need for orthotic assistance, and retraining muscle function are the main goals of the practice.[67,68] NMES is often applied to superficial skeletal muscles by physiotherapists with the main purpose of triggering muscle contractions due to activation of motor neuron axons or intramuscular axonal branches.[1] With NMES, the intact peripheral nerve, which has a lower threshold for depolarization in the innervated muscle, depolarizes. Then the contraction of the skeletal muscle begins. The current gets its name from this period.[19] NMES typically uses an Alternating current. The modifiable properties of the current waveform are frequency and intermittency or burst time. The strength of an NMES-induced muscle contraction is partially determined by the frequency.[69] NMES generally produces muscle contraction at a frequency of 20-50 Hz and this frequency has been largely adopted in physiotherapy and rehabilitation practice to restore skeletal muscle mass and function in PNI patients. As the frequency increases, so does the force of muscle contraction until a smooth, tetanic contraction is achieved.[70] Intermittent stimulation is a common practice to maintain strength development and simultaneously increase comfort for patients. The duty cycle in therapy defines the actual on and off time of an NMES program and is usually expressed as a ratio of 1:2 (10 s on, 20 s off) or in percentages such as 70%. Common clinical practices use a 1:3 duty cycle as the standard, but this ratio can be modified to meet the needs of the patient as well as the goals of treatment.[71] The three main limitations of NMES are; significant discomfort, limited spatial uptake (which results in the formation of low excited tension and premature fatigue) and poor control of dosage. In particular, fatigue is a major limitation in NMES application. One of the causes of fatigue with NMES application is that NMES changes the normal engine unit firing order. Contrary to normal human movements, motor unit firing in electrically induced contractions occurs primarily randomly rather than in fatigue-resistant units. Another cause of fatigue is that the superficial electrodes divert current exactly below the

surface area of the electrode, reducing power and limiting the depth of penetration as the current travels through various subcutaneous tissue viscosities that create resistance. Studies have noted that with superficial electrodes, superficial motor units of 10-12 mm can be reached, and only larger motor units are detected from deeper tissues. Therefore, the activation of deeper structures is often not possible with standard surface stimulation. However, it should be noted that increased pulse width or amplitude can improve the current penetration. Low frequencies produce a striking effect in which individual pulses can be distinguished, while higher frequencies are generally more comfortable as they soften the force response.[71] However, high-frequency currents cause early muscle fatigue.[1] Therefore, in general, low-frequency ES may cause less discomfort to the patient. To avoid fatigue or discomfort, continuous low-frequency stimulation is used, which typically produces smooth contraction at low force levels.[71] Since excessive ES also causes muscle fatigue and weakens the effect of nerve healing, it is seen that low-frequency ES is used to support nerve regeneration in most studies. Considering that high-frequency ES may both increase nerve damage and cause more fatigue, it has been reported that the ES method and frequency range should be standardized.[1,72] It is also thought that electrical nerve stimulation may be more comfortable and cause less muscle fatigue than electrical muscle stimulation.[73] As for the depth of stimulation, a higher frequency could theoretically reach deeper tissue. However, if the frequency is higher, ES will be delivered during the period when the nerve is not responding. Therefore, ES pulses should be adjusted according to the nervous tissue.[68] In a study comparing several different frequencies and stimulation patterns, frequencies below 16 Hz failed to elicit a contraction strong enough to allow the Quadriceps Femoris muscle to reach a target of 40º. However, it has been observed that tired muscle stimulated at low frequencies of 10-30 Hz can produce lower forces, a condition lasting 24 hours or longer; the same effect was not observed when the muscle was stimulated with higher frequencies.[71,74] Another study showed that high stimulation frequencies of 50-80 Hz applied to the hand muscles caused a rapid decrease in strength after about 20 s.[71,75] In the study of Mang et al., when the Tibialis Anterior muscle was stimulated at 100 Hz, the activation of motor neurons was found to be highest compared with stimulation at 10 and 50 Hz.[71,76] Adjusting the pulse width is just as important as the frequency. A study comparing pulse widths of 50, 200, 500, and 1000 μs when 20 Hz stimulation was delivered to the Soleus muscle found that wider pulse widths produced stronger plantar flexion contractions and additionally increased overall contractile properties.[71] The position of the stimulation electrodes critically affects the path of the radiated current and its relative density along the sensory and motor branches of the peripheral nerve. Therefore, stimulation through motor points mainly involves motor branch stimulation. Suboptimal electrode positioning, on the other hand, will require higher current levels to reach and stimulate the motor branch, and with it, more stimulation of pain-transmitting fibers will occur. Therefore, the appropriate placement of stimulation electrodes at motor points allows at least partial overcoming of the discomfort and limited spatial improvement from NMES limitations.[77] Electrode placement is divided into monopolar and bipolar. For monopolar electrodes (cathode and anode), the cathode should be placed at the motor point of the target muscle. Bipolar electrodes, on the other hand, should be placed on the most bulging part of the muscle (belly) or on the proximal and distal ends of the muscle.[68] Because depolarization of the peripheral nerve innervating the muscle results in contraction in healthy and innervated muscles, electrode placement should be consistent with the anatomical location of the peripheral nerve to the muscles being treated, i.e., the motor point of the muscle. Therefore, in NMES practice, bipolar electrode placement, in which the electrodes are placed directly on the muscle to be stimulated, is frequently used (**Figure 36.6**).[19] It is important to correctly determine the motor point during practice. This process consists of muscle surface mapping using a stimulation pen electrode. For a

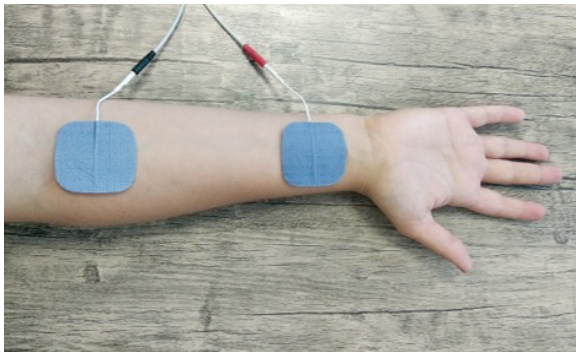

Figure 36.6 Bipolar electrode placement for forearm flexorsb

given electrical input, the region of skin above the muscle with the lowest motor threshold, that is, the skin region most responsive to ES, is identified (Figure 36.7). The motor point mapping procedure helps minimize the dose of current delivered and the level of discomfort due to the proper placement of stimulation electrodes. In this way it is ensured that the excited voltage of NMES is maximized. It is stated in the literature that it is advantageous to use such techniques in physiotherapy and rehabilitation practice because it is thought to increase both the stimulation efficiency and the patient's compliance with the treatment.[77]

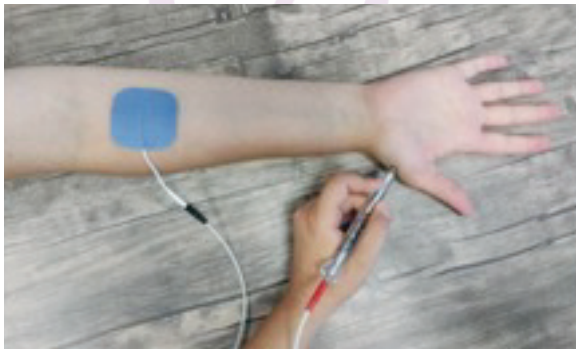

Figure 36.7 Monopolar electrode placement for the Abductor Pollicis muscle using a pencil electrode.

Although there are anecdotal reports of NMES being effective in studies questioning its efficacy after PNI, professional literature and data on NMES for the treatment of nerve injuries are still lacking. There is very little literature on the use of NMES, especially in children. There is a debate among physiotherapists as to whether NMES is appropriate for children with dysfunctional and numb upper extremities. Another controversial issue is the timing of the use of NMES, since definitive data on the age of initiation of this modality and its effect on nerve regeneration are not available.[67] It has been reported that ES [20 Hz, 3-4 Volts (V), 0.1 ms, 60 min] applied to the Proximal Femoral and Facial nerves in rats promotes Femoral nerve regeneration but does not improve Facial nerve repair.[78] Therefore, it could be said that ES has different effects on different peripheral nerves. In addition, it has been reported in the literature that immediate ES is more favorable for neuromuscular recovery than delayed ES after surgical intervention. In the literature, it has been reported that not only nerve cells but also Schwann cells are affected by ES. It has been observed in studies that once a short-term ES can transform M1 macrophages that cause inflammation into M2 macrophages that are beneficial for repair, rapidly remove myelin residues, and improve neurological function.[79,80] In cases where NMES is used for amplification, 50-75 burst or pulsed frequencies per second (Hz) are used according to existing studies in the literature.[81] Studies using NMES effectively suggest the maximum tolerable intensity that elicits a muscle contraction that is at least 50% of the maximum voluntary isometric contraction of the stimulated muscle. If the maximum isometric contraction of the involved muscle is contraindicated, 30% of the maximum isometric contraction of the unaffected muscle was more appropriate. It is also recommended to increase the intensity for 2-3 s with rest between contractions to maximize comfort and limit fatigue. Current research has used on:off cycles of 1:5 (usually 10-15 s on and 50-120 s rest) for a total of 10-15 contractions.[81] In a study conducted to demonstrate the effect of ES after Brachial Plexus injury (BPI), 11 children with BPI were prescribed regular physiotherapy and home exercise program after possible compression of the Musculocutaneous nerve and decompression. All patients were referred to a physiotherapy and rehabilitation program that included passive joint movements, weightlifting activities, appropriate games to encourage the use of the extremities, and NMES for the Biceps Brachii and Brachialis muscles in the

first postoperative week. The current was applied in 1 ms duration, 20 ms intervals and 25 interruptions per minute for 10 min. The current density is increased until a visible contraction occurs that can be tolerated without any signs of pain. A significant difference was found between the measurements of Biceps Brachii and Deltoid muscles in the Faradic Threshold Test results of all children at the 3rd and 12th months after the program was applied 3 times a week for 8 weeks and 12 months of follow-up. Based on this study, we can say that NMES application should be included in the physiotherapy and rehabilitation program after Musculocutaneous nerve decompression.[82] In another study aiming to evaluate the effects of NMES combined with weight-bearing exercises on shoulder function and bone mineral density in children with BPI, alternative symmetrical biphasic flow was applied to the treatment group in addition to exercise therapy. The application was started with a current of 10 Hz, which gives the feeling of touch, and after the sensation was tolerated, it was increased to 30 Hz to reveal muscle contraction. While the current was set to 300 μs, the intensity was increased slowly and gradually depending on the tolerance of each child. The current loop is set to be on for 10 s and closed for 20 s with a 1:2 period. When this cycle started to feel comfortable and no signs of fatigue were shown, a 1:1 cycle was started with 15 s on and 15 s off. The treatment took 15 min. Although there was no significant difference between the groups at the end of the treatment, significant differences were observed when the pre- and post-treatment scores of each group were compared. Even when post-treatment scores were compared, significant differences were noted in favor of the study group.[83]

Functional Electrical Stimulation (FES)

FES is preferred for facilitating or increasing functional movements, such as assisting in the dorsiflexion of the ankle or in the paretic Tibialis Anterior muscles or wrist extensors.[19] There are three types of stimulation methods for FES, called fully implanted, percutaneous, and surface stimulations. Superficial stimulation is preferred due to its non-invasive nature. Conventional surface electrodes are suitable for innervating large muscles close to the skin and use biocompatible gels that provide stability over the skin and uniform current distribution over the electrode surface. When using FES during walking, 30 min of stimulation can increase the stimulated motor potential of the Tibial nerve, and the effect is known to last for at least 30 min. The results of studies in the literature show that the combination of FES and exercise can lead to an increase in corticospinal excitability without cortical inhibition and further promote the afferent of the central nervous system. The practice of ES along with exercise can more strongly promote peripheral axon regeneration and relieve pain after PNI. In addition to the coordination of various parameters to achieve the purpose of stimulating muscle and nerve recovery, excessive muscle fatigue caused by FES will likely reduce the effect.[1]

It has been shown that the application of FES on the Ulnar and Median nerves is effective in the motor function of the upper extremities. After the FES practice on the proximal Ulnar and Median nerves, individual finger and joint grip movements were observed using 24 finger movements to measure hand grip patterns. The results showed that FES can stimulate individual and coordinated movements. In this study, it was reported that FES can be used in the treatment of weak grip in advanced stages of nerve injuries.[84]

Promising results of FES on preventing muscle atrophy have been reported in studies conducted in animal models. If FES preserves muscle mass and prevents atrophy, it seems logical to promote neural reconnection by preserving muscle viability and enabling it to accept reinnervation. In addition to studies reporting that ES applied to the denervated muscle helps reinnervation and functional recovery, there are also studies suggesting that ES has no effect on reinnervation. In an animal experiment, FES was applied to 2 dogs for 6 weeks after resection and anastomosis of the Recurrent Laryngeal nerve. Two additional animals were included as the control group. The results showed that FES caused general suppression of reinnervation. The indication that FES suppresses reinnervation may have harmful effects on restoring normal muscle

function. If the interaction occurs non-specifically, FES should not be used therapeutically or administered during muscle reinnervation. Alternatively, if reattachment suppression is specific to foreign nerve fibers then FES may provide a means to promote selective reinnervation of denervated muscle. Because of the small sample size of this preliminary study, the effects of FES on reinnervation need to be investigated more extensively before its clinical implications are fully understood.[85]

High Voltage Pulsed Galvanic Stimulation (HVPGS)

High voltage currents gained popularity in the 1970s with the interest in using high amplitude currents.[19] HVPGS is a monophasic pulsed electric current with a frequency of 1-120 Hz, consisting of double peak impulses (5–200 μs) at very high peak current amplitude (2-2.5 A) and high voltage (up to 500 V).[86] HVPGS, like most monophasic pulsed currents, have such short pulse durations and long interpulse intervals that any charge deposited at the electrode-skin interface dissipates before causing permanent reverse polar effects. In HVPGS, an electrode is placed over the treatment area, this is the active or therapy electrode. The other electrode is placed away from the treatment area, this is the reference or dispersive electrode. Most devices on the market allow to select the polarity of the active or therapy electrode, positive or negative. Since the specific waveform properties of HVPGS make it possible to stimulate both sensory and motor nerves, current can be used for various clinical purposes such as pain modulation, skeletal muscle activation, and tissue healing.[19] A study was conducted on 20 rats to evaluate the effect of HVPGS on regeneration after PNI. The study included a control group with no injury, a denervation group with only Sciatic nerve injury, an intervention group in which HVPGS was applied to Sciatic nerve injury, and a placebo group that received HVPGS without injury. HVPGS and placebo groups were stimulated with a current of 30 min a day, 5 days a week, 100 Hz, a minimum of 100 V, 20 μs, and 100 μs interpulse interval. The density of neural components, connective tissue, blood vessels, and macrophage areas were analyzed before injury and on days 7, 14, and 21 postoperatively. It has been reported that axon diameter, myelin sheath, and fibril thickness were higher in the HVPGS group than in the denervation group. According to the results of this study, HVPGS accelerates functional recovery, strengthens the maturation of nerve fibers, and accelerates neural repair by reducing macrophages and connective tissue area density.[87] Another study conducted with healthy male subjects designed to determine the effects of HVPGS on muscle strength gained after 6 weeks of ES, the right Quadriceps Femoris muscles of subjects in 3 different groups were electrically stimulated with a pre-set stimulator at pulse frequencies of 20 Hz, 45 Hz, and 80 Hz, respectively. Left limbs served as controls. ES was administered three times a week for 6 weeks. For all groups, the duty cycle of the stimulator was set to 1:5 (10 s on, 50 s off), and the maximum tolerable voltage was monitored for each subject. A maximum of 10 contractions were allowed in each training session. At the end of the 6th week of training, it was found that the right and left knee extension isometric strength increased by 24% and 10%, respectively. The increase in muscle strength continued 3 weeks after training. Findings revealed that the stimulator used in this study could increase the strength of normally innervated muscles, but none of the three selected beat frequencies provided any clinical advantage.[88] Since HVPGS can stimulate skeletal muscle, it can also be used for muscle retraining. HVPGS is perceived as painful by the patient because it requires a very short pulse duration and, accordingly, a high-intensity stimulus. To date, there is insufficient evidence to support the use of HVPGS to strengthen muscles despite its ability to stimulate skeletal muscle.[19] There are also no studies on muscle strengthening or pain reduction in patients with PNI. Other waveforms, which are more suitable for muscle activation and strengthening, are preferred in the current literature. New studies are needed on the use of HVPGS in PNI.

Conclusion

ES is a non-destructive, clinically applicable method to increase nerve regeneration and senso-

rimotor functional recovery.[89] ES applications in re-innervated muscles are often aimed at pain and strengthening the weak muscle and increasing its function. Although the most preferred current by physiotherapists for pain is TENS, if it is preferred for the treatment of neuropathic pain, it is usually applied close to the pain area and at high intensities (150-200 Hz). The most frequently preferred current by physiotherapists for muscle strengthening after PNI is NMES with a frequency of 20-50 Hz. Although several studies have reported positive results for ES application in the reinnervated muscle in the early and later stages, the application parameters and timing of ES for PNI are still controversial. At the same time, there is a need to better distinguish the safety limits for the stimulation of peripheral nerves.[29] Although ES is useful in the treatment of PNI, it also has side effects. For example, it can lead to bending of the axon and its cell architecture, and edema.[90] In addition, studies have shown that long-term ES causes decreased skeletal muscle excitability and abnormalities in the neuromuscular junction.[8] Furthermore, stimulation of innervated skeletal muscles may have adverse effects on surviving asynchronous nerves. If the stimulated nerves are connected asynchronously to the muscle, ES may compromise functional reinnervation.[91,92] It may also be argued that targeted rehabilitation or concurrent therapies, such as Restrictive Compulsive Movement Therapy, are needed to strengthen and activate new ES-stimulated circuits.[31] Therefore, there is a need for new studies on the use of ES in PNI.

References

1. Ni L, Yao Z, Zhao Y, Zhang T, Wang J, Li S, Chen Z. Electrical stimulation therapy for peripheral nerve injury. Front Neurol. 2023;14;1081458. doi:10.3389/fneur.2023.1081458.
2. Sunderland S. A classification of peripheral nerve injuries producing loss of function. Brain. 1951;74:491-516. doi:10.1093/brain/74.4.491.
3. Davis GA. Reflections on the history of nerve repair-Sir Sydney Sunderland's final presentation to the neurosurgical society of Australasia. Neurosurg. 2020;87:E373-82. doi:10.1093/neuros/nyaa059.
4. Power DM. The future of nerve repair and regeneration. J. Musculosklelet Surg Res. 2019; 3:2-3. doi:10.4103/jmsr.jmsr_103_18.
5. ElAbd R, Alabdulkarim A, AlSabah S, Hazan J, Alhalabi B, Thibaudeau S. Role of electrical stimulation in peripheral nerve regeneration: A systematic review. plastic and reconstructive surgery. Global Open. 2022;10(3):e4115. doi:10.1097/GOX.0000000000004115.
6. Lien SC, Cederna PS, Kuzon WM. Optimizing skeletal muscle reinnervation with nerve transfer. Hand Clinics. 2008;24(4):445-54. doi:10.1016/j.hcl.2008.08.001.
7. Soyuer F. Rehabilitation of traumatic peripheral neuropathies. Van Med J. 2002;9(4):119-25.
8. Chu XL, Song XZ, Li Q, Li YR, He F, Gu XS, et al. Basic mechanisms of peripheral nerve injury and treatment via electrical stimulation. Neural Regen Res. 2022;17(10):2185-93. doi:10.4103/1673-5374.335823.
9. Willand MP. Electrical stimulation enhances reinnervation after nerve injury. Eur J Transl Myol. 2015;25(4):243-8. doi:10.4081/ejtm.2015.5243.
10. Bjorgen H, Koppang EO, Gunnes G, Hordvik I, Moldal T, Kaldhusdal M et al. Ectopic epithelial cell clusters in salmonid intestine are associated with inflammation. J Fish Dis. 2018;41:1031-40. doi:10.1111/jfd.12780.
11. Conforti L, Gilley J, Coleman MP. Wallerian degeneration: An emerging axon death pathway linking injury and disease. Nat Rev Neurosci. 2014;15:394–409. doi:10.1038/nrn3680.
12. Ransom SC, Shahrestani S, Lien BV, Tafreshi AR, Brown NJ, Hanst B et al. Translational approaches to electrical stimulation for peripheral nerve regeneration. Neurorehabil Neural Repair. 2020;34(11):979-85. doi:10.1177/1545968320962508.
13. Al-Majed AA, Neumann CM, Brushart TM, Gordon T. Brief electrical stimulation promotes the speed and accuracy of motor axonal regeneration. J Neurosci. 2000;20(7): 2602-8. doi:10.1523/JNEUROSCI.20-07-02602.2000.
14. Brushart TM. Preferential reinnervation of motor nerves by regenerating motor axons. J. Neurosci. 1988;8(3):1026-31. doi:10.1523/JNEUROSCI.08-03-01026.1988.
15. Klimaschewski L, Hausott B, Angelov DN. The pros and cons of growth factors and cytokines in peripheral axon regeneration. Int Rev Neurobiol. 2013;108:137-71. doi:10.1016/B978-0-12-410499-0.00006-X.
16. Lundborg G, Rosén B. Hand function after nerve repair. Acta Physiol. 2007;189(2):207-17. doi:10.1111/j.1748-1716.2006.01653.x.
17. De Ruiter GCW, Spinner RJ, Verhaagen J, Malessy MJA. Misdirection and guidance of regenerating axons after experimental nerve injury and repair. J Neurosurg. 2014;120(2): 493-501. doi:10.3171/2013.8.JNS122300.
18. Witt A, Kristensen RS, Fuglsang-Frederiksen A, Pedersen TH, Finnerup NB, Kasch H et al. Muscle velocity recovery cycles in neurogenic muscles. Clin Neurophysiol. 2019;130:1520-7. doi:10.1016/j.clinph.2019.05.030.
19. Bellew JW, Michlowitz SL, Nolan TP. (2016), Michlovitz's modalities for therapeutic intervention, 6th Edition. Philadelphia: F. A. Davis Company. ISBN:0803657633, 9780803657632.
20. Aló KM, Abramova MV, Richter EO. Percutaneous peripheral nerve stimulation. Prog Neurol Surg. 2011;24:41-57. doi:10.1159/000323023.
21. Michlovitz SL. Is there a role for ultrasound and electrical stimulation following injury to tendon and nerve? J Hand Ther. 2005;18(2):292-6. doi:10.1197/j.jht.2005.02.013.
22. Truong AD, Kho ME, Brower RG, Feldman DR, Colantuoni E, Needham DM. Effects of neuromuscular electrical stimulation on cytokines in peripheral blood for healthy participants: A prospective, single-blinded study. Clin Physiol Funct Imaging. 2017;37:255-262. doi:10.1111/cpf.12290.
23. Geremia NM, Gordon T, Brushart TM, Al-Majed AA, Verge VM. Electrical stimulation promotes sensory neuron regeneration and growth-associated gene expression. Exp Neurol. 2007;205(2):347-59. doi:10.1016/j.expneurol.2007.01.040.

24. Dow DE, Cederna PS, Hassett CA, Kostrominova TY, Faulkner JA, Dennis RG. Number of contractions to maintain mass and force of denervated rat EDL muscles. Muscle Nerve. 2004;30:77-86. doi:10.1002/mus.20054.
25. Acaröz Candan S, Akoglu AS, Büğüşan S, Yüksel F. Effects of neuromuscular electrical stimulation of quadriceps on the quadriceps strength and functional performance in nursing home residents: A comparison of short and long stimulation periods. Geriatr Gerontol Int. 2019;19:409-13. doi:10.1111/ggi.13633.
26. Mani D, Almuklass AM, Amiridis IG, Enoka RM. Neuromuscular electrical stimulation can improve mobility in older adults but the time course varies across tasks: Double-blind, randomized trial. Exp Gerontol. 2018;108:269-75. doi:10.1016/j.exger.2018.04.018.
27. Hyer CF, Berlet G, Philbin T, Bull P, Brandão R, Prissel M, et al. Does functional neuromuscular electrical stimulation (NMES) influence calf atrophy following achilles tendon surgery? Prospective double-blind randomized controlled trial on the use of immediate postoperative electrical muscle stimulation to preserve muscle function and volume. J Foot Ankle Surg. 2021;60:683-8. doi:10.1053/j.jfas.2020.12.005.
28. Piccinini G, Cuccagna C, Caliandro P, Coraci D, Germanotta M, Pecchioli C, et al. Efficacy of electrical stimulation of denervated muscle: A multicenter, double-blind, randomized clinical trial. Muscle Nerve. 2020;61:773-8. doi:10.1002/mus.26880.
29. Günter C, Delbeke J, Ortiz-Catalan M. Safety of long-term electrical peripheral nerve stimulation: Review of the state of the art. J NeuroEngineering Rehabil. 2019;16:1-16. doi:10.1186/s12984-018-0474-8.
30. Lee SK, Wolfe SW. Peripheral nerve injury and repair. J Am Acad Orthop Surg. 2000;8(4):243-52. doi:10.5435/00124635-200007000-00005.
31. Qian Y, Cheng Y, Cai J, Zhao X, Ouyang Y, Yuan WE, Fan C. Advances in electrical and magnetic stimulation on nerve regeneration. Regen Med. 2019;14(10):969-79. doi:10.2217/rme-2018-0079.
32. Zuo KJ, Gordon T. Chan KM, Borschel GH. Electrical stimulation to enhance peripheral nerve regeneration: Update in molecular investigations and clinical translation. Exp Neurol. 2020;332:113397. doi:10.1016/j.expneurol.2020.113397.
33. Javeed S, Faraji AH, Dy C, Ray WZ, MacEwan MR. Application of electrical stimulation for peripheral nerve regeneration: Stimulation parameters and future horizons. Interdisciplinary Neurosurgery. 2021;24:101117. doi:10.1016/j.inat.2021.101117.
34. Juckett L, Saffari TM, Ormseth B, Senger JL, Moore AM. The effect of electrical stimulation on nerve regeneration following peripheral nerve injury. Biomolecules. 2022;12(12):1856. doi:10.3390/biom12121856.
35. Huang J, Zhang Y, Lu L, Hu X, Luo Z. Electrical stimulation accelerates nerve regeneration and functional recovery in delayed peripheral nerve injury in rats. Eur J Neurosci. 2013;38:3691-701. doi:10.1111/ejn.12370.
36. Ray WZ. Mackinnon SE. Management of nerve gaps: Autografts, allografts, nerve transfers, and end-to-side neurorrhaphy. Exp Neurol. 2010;223:77-85. doi:10.1016/j.expneurol.2009.03.031.
37. Hoben GM, EeX, Schellhardt L, Yan Y, Hunter DA, Moore AM, Snyder-Warwick AK, et al. Increasing nerve autograft length increases senescence and reduces regeneration. Plast Reconstr Surg. 2018;142:952-961. doi:10.1097/PRS.0000000000004759.
38. Gordon T. Peripheral nerve regeneration and muscle reinnervation. Int J Mol Sci. 2020;21(22):8652. doi:10.3390/ijms21228652.
39. Thomas CK, Stein RB, Gordon T, Lee RG, Elleker MG. Patterns of reinnervation and motor unit recruitment in human hand muscles after complete ulnar and median nerve section and resuture. J Neurol Neurosurg Psychiatry. 1987;50:259-68. doi:10.1136/jnnp.50.3.259.
40. Cobianchi S, Casals-Diaz L, Jaramillo J, Navarro X. Differential effects of activity dependent treatments on axonal regeneration and neuropathic pain after peripheral nerve injury. Exp Neurol. 2013;240:157-67. doi:10.1016/j.expneurol.2012.11.023.
41. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg. 1967;46(4):489-91. PMID:4952225.
42. Long DM. Electrical stimulation for relief of pain from chronic nerve injury. J Neurosurg. 1973;39(6):718-22. doi:10.3171/jns.1973.39.6.0718.
43. Shealy CN. Dorsal column stimulation: optimization of application. Surg Neurol. 1975;4:142-5. PMID:1080897.
44. Burton C. Pain suppression through peripheral nerve stimulation. Annual Houston Neurological Symposium, Houston, 1973.
45. Akgün MY, İşler C. Ağrı cerrahisinde güncel gelişmeler ve gelecek. Türk Nöroşir Derg. 2019;29(2):127-33.
46. Eser P, Bekar A. Spinal Kord Stimülasyonu: Endikasyonlar ve Sonuçlar. Türk Nöroşir Derg 2021;31(3):355-9.
47. Özdemir İ, Akbaş M, Yeğin A, Dağıstan G, Erkan DÖ. Spinal kord stimülasyonu uygulanan 62 hastanın retrospektif değerlendirilmesi. Agri 2017;29(1):25-32 doi:10.5505/agri.2016.08870.
48. Cavlak U, Altuğ F, Ünal A, Kara G. (2019), Nörolojik rehabilitasyonda kanıta dayalı nöromodülasyon uygulamaları. Yazıcıoğlu Şener FG (ed.) Fizyoterapi ve Rehabilitasyonda Kanıta Dayalı Yaklaşımlar. 1. Baskı. Ankara: Türkiye Klinikleri; p.6-14.
49. Linderoth B, Foreman RD. Physiology of spinal cord stimulation: Review and update. Neuromodulation. 1999;2(3):150-64. doi:10.1046/j.1525-1403.1999.00150.x.
50. Abd-Elsayed A, Schiavoni N, Sachdeva H. Efficacy of spinal cord stimulators in treating peripheral neuropathy: A case series. J Clin Anesth. 2016;28:74–7. doi:10.1016/j.jclinane.2015.08.011.
51. Chakravarthy K, Nava A, Christo PJ. et al. Review of recent advances in peripheral nerve stimulation (PNS). Curr Pain Headache Rep. 2016;20:60. doi:10.1007/s11916-016-0590-8.
52. Abejón D, Pérez-Cajaraville J. Peripheral nerve stimulation: Definition. Prog Neurol Surg. 2011;203-9. doi:10.1159/000323052.
53. Petersen EA, Slavin KV. Peripheral nerve/field stimulation for chronic pain. Neurosurg Clin N Am. 2014;25(4):789-97. doi:10.1016/j.nec.2014.07.003.
54. Slavin KV. Peripheral nerve stimulation for neuropathic pain. Neurotherapeutics. 2008;5(1):100-6. doi:10.1016/j.nurt.2007.11.005.
55. Kothari S, Goroszeniuk T. Percutaneous permanent electrode implantation to ulnar nerves for upper extremity chronic pain: 6 years follow up: 201. ASRA Pain Medicine. 2006;31:16. doi:10.1016/rapm-00115550-200609002-00029.
56. Goroszeniuk T, Kothari SC, Hamann WC. Percutaneous implantation of a brachial plexus electrode for management of pain syndrome caused by a traction injury. Neuromodulation 2007;10(2):148-55. doi:10.1111/j.1525-1403.2007.00103.x.
57. Stevanato G, Devigili G, Eleopra R, Fontana P, Lettieri C, Baracco C, et al. Chronic post-traumatic neuropathic pain of brachial plexus and upper limb: a new technique of peripheral nerve stimulation. Neurosurg Rev. 2014;37(3):473-80. doi:10.1007/s10143-014-0523-0.
58. Langford B, D'Souza RS, Pingree M, Mauck WD. Treatment of ulnar neuropathic pain with peripheral nerve stimulation: Two case reports. Pain Medicine. 2023;24(5):566–9. doi:10.1093/pm/pnac157.

59. Langford B, Mauck WD. Peripheral nerve stimulation: A new treatment for meralgia paresthetica. Pain Medicine. 2021;22(1):213-6. doi:10.1093/pm/pnaa326.
60. Berger P. Electrical current and acupuncture treatment for a paediatric patient with recurring long thoracic nerve paralysis. Acupuncture and Related Therapies. 2014;2(1):14-8. doi:10.1016/j.arthe.2013.11.002.
61. Rampazo ÉP & Liebano RE. Analgesic effects of interferential current therapy: A narrative review. Medicina. 2022;58(1):141. doi:10.3390/medicina58010141.
62. Goats GC. Interferantial Current Therapy. Br H Sports Med. 1990;24:87-92. doi:10.1136/bjsm.24.2.87.
63. Mohammed Y, Eslami P, Shaik M, Akula R, Abdel-Motaleb IM. Integrated ultrasonic/interferential current system for injured bones, muscles, and nerve therapy. IEEE International Conference on Electro/Information Technology. 2010. doi:10.1109/eit.2010.5612189.
64. Hall DO. (1989), U.S. Patent No. 4,848,347. Washington, DC: U.S. Patent and Trademark Office.
65. Crouch, T. (1995), Carpal tunnel syndrome and repetitive strain injuries: The comprehensive guide to prevention, treatment, and recovery. Frog Books.
66. Hussein HM, Alshammari RS, Al-Barak SS, Alshammari ND, Alajlan SN, Althomali OW. A systematic review and meta-analysis investigating the pain-relieving effect of interferential current on musculoskeletal pain. Am Phys Med Rehabil. 2022;101(7):624-33. doi:10.1097/PHM.0000000000001870.
67. Ramos LE, Zell JP. Rehabilitation program for children with brachial plexus and peripheral nerve injury. Semin Pediatr Neurol. 2000;7(1):52-7. doi:10.1016/s1071-9091(00)80010-8.
68. Chen PY, Cheen JR, Jheng YC, Wu HK, Huang SE, Kao CL. Clinical applications and consideration of interventions of electrotherapy for orthopedic and neurological rehabilitation. J Chin Med Assoc. 2022;85(1):24-9. doi:10.1097/JCMA.0000000000000634.
69. Bertoti DB. Electrical stimulation: a reflection on current clinical practices. Assist Technol. 2000;12:21-32. doi:10.1080/10400435.2000.10132007.
70. Manal TJ. (2005), Electrical stimulation to augment muscle strengthening: Guidelines for surgical procedures, diagnosis, and co-morbidities. Paper presented at: American Physical Therapy Association Combined Sections Meeting; New Orleans, LA.
71. Doucet BM, Lam A, Griffin L. Neuromuscular electrical stimulation for skeletal muscle function. Yale J Biol Med. 2012;85(2):201-15. PMID:22737049
72. Haastert-Talini K, Schmitte R, Korte N, Klode D, Ratzka A, Grothe C. Electrical stimulation accelerates axonal and functional peripheral nerve regeneration across long gaps. J Neurotrauma. 2011;28:661-74. doi:10.1089/neu.2010.1637.
73. Inns TB, McCormick D, Greig CA, Atherton PJ, Phillips BE, Piasecki M. Factors associated with electrical stimulation-induced performance fatigability are dependent upon stimulation location. Exp Physiol. 2021;106:828-36. doi:10.1113/EP089204.
74. Kebaetse MB, Turner AE, Binder-Macleod SA. Effects of stimulation frequencies and patterns on performance of repetitive, nonisometric tasks. J Appl Physiol. 2002;92(1):109-16. doi:10.1152/jappl.2002.92.1.109.
75. Fuglevand AJ, Keen DA. Re-evaluation of muscle wisdom in the human adductor pollicis using physiological rates of stimulation. J Physiol. 2003;549(Pt3):865-75. doi:10.1113/jphysiol.2003.038836.
76. Mang CS, Lagerquist O, Collins DF. Changes in corticospinal excitability evoked by common peroneal nerve stimulation depend on stimulation frequency. Exp Brain Res. 2010;203(1):11-20. doi:10.1007/s00221-010-2202-x.
77. Gobbo M, Maffiuletti NA, Orizio C, Minetto MA. Muscle motor point identification is essential for optimizing neuromuscular electrical stimulation use. J NeuroEngineering Rehabil. 2014;11:17. doi:10.1186/1743-0003-11-17.
78. Raslan A, Salem MAM, Al-Hussaini A, Guntinas-Lichius O, Irintchev A. Brief electrical stimulation improves functional recovery after femoral but not after facial nerve injury in rats. Anat Rec (Hoboken). 2019;302:1304–1313. doi:10.1002/ar.24127.
79. Keane GC, Pan D, Roh J, Larson EL, Schellhardt L, Hunter DA, et al. The effects of intraoperative electrical stimulation on regeneration and recovery after nerve isograft repair in a rat model. Hand (N Y). 2022;17:540-8. doi:10.1177/1558944720939200.
80. McLean NA, Verge VM. Dynamic impact of brief electrical nerve stimulation on the neural immune axis polarization of macrophages toward a pro-repair phenotype in demyelinated peripheral nerve. Glia. 2016;64:1546-61. doi:10.1002/glia.23021.
81. Dolan MG, Windley TC. The Efficacy of neuromuscular electrical stimulation for muscle strength augmentation. Athl Ther Today. 2007;12(1):39–42. doi:10.1123/att.12.1.39
82. Fırat T, Delioğlu K, Tunç Y, Üzümcügil A, Yörübulut M, Leblebicioğlu G. The results of decompression of the musculocutaneous nerve entrapment in children with obstetric brachial plexus palsy. Childs Nerv Syst. 2020;36:2815-23. doi:10.1007/s00381-020-04828-8.
83. Elnaggar RK. Shoulder function and bone mineralization in children with obstetric brachial plexus injury after neuromuscular electrical stimulation during weight-bearing exercises. Am Phys Med Rehabil. 2016;95(4):239-47. doi:10.1097/phm.0000000000000449.
84. Shin H, Watkins Z, Hu X. Exploration of hand grasp patterns elicitable through non-invasive proximal nerve stimulation. Sci Rep. 2017;7:16595. doi:10.1038/s41598-017-16824-1.
85. Zealear DL, Billante CL, Chongkolwatana C, Herzon GD. The effects of chronic electrical stimulation on laryngeal muscle reinnervation. ORL. 2000;62(2):87-95. doi:10.1159/000027723.
86. Polak A, Franek A, Taradaj J. High-voltage pulsed current electrical stimulation in wound treatment. Adv Wound Care. 2014;3(2):104-17. doi:10.1089/wound.2013.0445.
87. Teodori RM, Silva AM, Silva MT, Oliveira LS, Polacow ML, Guirro EC. High-voltage electrical stimulation improves nerve regeneration after sciatic crush injury. Rev Bras Fisioter. 2011;15(4):325-31. doi:10.1590/s1413-35552011005000008.
88. Balogun JA, Onilari OO, Akeju OA, Marzouk DK. High voltage electrical stimulation in the augmentation of muscle strength: Effects of pulse frequency. Arch Phys Med Rehabil. 1993;74(9):910-6. PMID:8379835.
89. Senger JL, Chan KM, Macandili H, Chan AW, Verge VM, Jones KE, et al. Conditioning electrical stimulation promotes functional nerve regeneration. Exp Neurol. 2019;315:60-71. doi:10.1016/j.expneurol.2019.02.001.
90. Martellucci J, Bergamini C, Palla G, Simoncini T, Naldini G, Valeri A. (2015), Functional anatomy of the pelvic floor. In: Martellucci J. (eds) Electrical stimulation for pelvic floor disorders. Springer, Cham. doi:10.1007/978-3-319-06947-0_2.
91. Hussain G, Zhang L, Rasul A, Anwar H, Sohail MU, Razzaq A, et al. Role of plant-derived flavonoids and their mechanism in attenuation of Alzheimer's and Parkinson's diseases: An update of recent data. Molecules. 2018;23:814. doi:10.3390/molecules23040814.
92. Hussain G, Wang J, Rasul A, Anwar H, Qasim M, Zafar S et al. Current status of therapeutic approaches against peripheral nerve injuries: A detailed story from injury to recovery. Int J Biol Sci. 2020;16:116-34. doi:10.7150/ijbs.35653.

Co-funded by the Erasmus+ Programme of the European Union

Electrophysiological Tests

FURKAN BILEK • NILUFER CETISLI-KORKMAZ

Introduction

The diagnosis of neurological diseases or nerve damage is made by anamnesis, clinical symptoms and electrophysiological tests.[1,2] The definitive diagnosis of peripheral neuropathies is made by electrophysiological tests. These tests are frequently used to detect the integrity of the peripheral nerve-muscle complex and to determine nerve conduction velocity.[2,3] The purpose of using electrophysiological tests is to determine the amount of motor and sensory nerve fibers and the motor fiber conduction velocity of the nerve, thus determining the current function of the nerve.[1,2] Electrophysiological test methods are examined in two groups as invasive and non-invasive test methods. Needle electromyography (n-EMG) is given as an example of invasive electrophysiological tests. The transmission rate, amplitude and latency of the stimulus are recorded with the n-EMG method.[3,4]

There are non-invasive electrophysiological test methods frequently used by physiotherapists in the evaluation of peripheral neuropathies and determination of nerve excitability characteristics.[1,5,6] Non-invasive electrophysiological test methods include methods such as Strength–Duration Curve (SDC), Faradic Test, Accommodation Ratio, Rheobase, and Chronaxie. Since these methods are non-invasive, they can be tolerated more easily by patients.[6,7] In addition, other advantages are that it is more common in clinics, its cost is low, and it allows the motor excitability thresholds of the peripheral nerve to be obtained.[8] Studies have shown that non-invasive methods provide information about the excitability of the nerve and provide the opportunity to reliably monitor the nerve healing process.[1,3,6,8] In addition, it seems to be advantageous over n-EMG, as it can be used to determine the severity of peripheral nerve involvement and to objectively evaluate nerve healing after a surgery or injury.[8,9] Researchers reported that the combined measurement of non-invasive methods showed 100% sensitivity for n-EMG results for acute phase and complete denervation, and 86% sensitivity for subacute phase and partial denervation.[8] There are a limited number of studies in the literature investigating the relationship between invasive electrophysiological tests and non-invasive electrophysiological tests.[1,8,9]

The widespread availability of non-invasive electrophysiological test methods in physiotherapy and rehabilitation clinics, the easy detection of individuals with peripheral nerve injury, the opportunity to objectively evaluate the extent of degeneration and regeneration in the nerve, and denervation or reinnervation occurring in the muscle are among its very important advantages. Therefore, it also allows the planning of the treatment specific to the existing recovery phase of the patients or the evaluation of the effectiveness of the treatment applied. In this section, electrophysiological evaluation approaches will be explained.

Denervation Process

Neurapraxia is the mildest form of peripheral nerve injury. They are usually compression-type injuries in which the axon is not damaged, caus-

ing temporary conduction block with mild demyelination.[10,11] Transient conduction blocks are caused by segmental demyelination. This level of injury has a good prognosis, usually without surgical treatment.[12] However, if chronic compression causes progressive dysfunction in myelin-producing Schwann cells, the impact has the potential to progress to involve the axon and connective tissues.[13]

Axonotmesis is a second level injury and shows the clinical picture in which the axon is affected but the connective tissue layers surrounding the nerve are preserved to varying degrees. Wallerian Degeneration occurs at this level. It refers to the deterioration of the axon and myelin structures located distal to the region where the axonal continuity is interrupted over time. Functional recovery can occur within months without the need for surgery.[14] Regeneration takes place along the endoneurium by axonal regrowth. Sprouting in the endoneural tubes continues at 1-2 mm per day. It takes as long as 14 days to degenerate. The distal portion of the nerve remains excitable and can transmit impulses before degeneration occurs. Therefore, complete evaluation of the lesion may not be possible for up to 3 weeks after nerve injury is suspected.[15]

The degree of involvement in third-level axonometric injuries is higher than in second-degree injuries. The perineurium is not affected, but the endoneurium and Schwann cells are affected. Protection of the perineurium allows nerve shoots to progress within a fascicle. Recovery at this level of injury depends on the ability of the axons to extend beyond the lesion site and find the endoneural tubes. Functional recovery in this type of nerve injury can vary from very mild to complete loss.

The fourth-degree injury includes Schwann cells, endoneurium and perineurium. At this level, the integrity of the axon is impaired, except for the epineurium. Scar formation within the nerve prevents the nerve fibers from re-connections. The prognosis is poor.

The most severe injury is neurotmesis type injury. An injury at this level results with the loss of integrity of the axon and all layers of connective tissue. Healing through regeneration cannot occur without surgical intervention in neurotmesis type injuries. Seddon and Sunderland classifications are shown in detail in Table 37.1.[10,11,16]

The time required for complete healing will depend on the location of the lesion and the length of the nerve that needs to regrow. The regrowth rate is somewhat variable, at first up to 5 mm per day faster, but is generally considered to average 1-2 mm per day. When nerve fiber degeneration occurs, the normal response is reduced or lost, and the changes become evident 3 or 4 days after injury. Changes in the reaction obtained with stimulus over the muscle can be observed before the end of the 1st week.

Table 37.1 Seddon and Sunderland classifications in peripheral nerve lesions.[10,11,16]

Seddon Classification	Sunderland Classification	Histological Features of a Peripheral Nerve Lesion	Anatomical Lesion
Neuropraxia	*Level 1*	There is myelin damage and anatomical deterioration, but the nerve is physiologically preserved	Myelin damage. No axon damage
Axonotmesis	*Level 2*	There is damage to the axon, but the endoneurium and perineurium are preserved.	Axon
	Level 3	There is damage to the axon, but the perineurium is preserved and the epineurium is damaged.	Myelin, axon and endoneurium
	Level 4	There is damage to the axon, but the epineurium is preserved and the perineurium is damaged.	Axon, myelin, endoneurium, and perineurium
Neurotmesis	*Level 5*	With the axon damage, all the connective tissue layers surrounding the nerve are damaged.	Axon, myelin, endoneurium, perineurium, and epineurium
	Level 6	MacKinnon classification. All structures have varying levels of influence. It is difficult to treat.	

The important criteria for the prognosis of the degeneration reaction are as follows:

- Recovery is expected in 6 weeks in the Partial Degeneration Reaction.
- Recovery is expected in 6 weeks in the Complete Degeneration Reaction.
- In Definite Degeneration Reaction, recovery is not expected before 1-2 years or there is never a return.[17,18]

Faradic Current

Faradic type current is a short-term interrupted direct current with a pulse duration of 0.1-1 ms and a frequency range of 50-100 Hz, used to stimulate the innervated muscles. The term Faradism was formerly used to denote the type of current produced by the first Faradic coil, and is the current that varies chaotically with each cycle consisting of two unequal phases:

1. Low-intensity long-term current.
2. High intensity short-time current.

Faradic spirals have now been replaced by electronic stimuli, which have almost the same physiological effect but different waveforms. The properties required to produce these physiological effects are impulses with a frequency of 50-100 Hz and a duration of 0.1-1 millisecond (ms).[19]

Faradic type current provides impulses with a duration of 0.1-1 ms and a frequency of 50-100 Hertz (Hz). These cause tetanic contraction of the innervated muscles, but due to the short duration of the stimuli with a Faradic helix, it is difficult or impossible to obtain a response from the denervated muscle. However, with modern stimuli, a response from denervated muscles can usually be obtained with impulses of this duration, as more output and a more tolerable form of current are produced from the old device.[19-21]

Intermittent direct current is used for pulses of about 100 ms duration, which are generally repeated 20 times per minute. These parameters generally cause rapid contraction of innervated muscle fibers while slow contraction of denervated fibers. If the temperature is below the innervated muscles respond slowly, while the contraction of the denervated muscle becomes faster as the temperature rises.[21-23]

Interrupted Galvanic Current

It is called long duration current, starting from at least 1 ms up to a maximum of 300 or 600 ms. Interruption is the most usual variation of direct current, the flow of current starts and stops at regular intervals. The rise and fall of density can be abrupt and can be of rectangular, sawtooth, triangular and trapezoidal type.[19,21]

The impulse in which the current gradually rises is often called "selective" because contraction of the denervated muscle can often be produced with a current density that is insufficient to stimulate the motor nerve. It often happens that the longer the denervation takes, the slower the increase in current density required.[21,24]

Usually, an impulse of 100 ms duration is used, which requires a frequency of 30 Hz. However, as the duration increases, the frequency should be reduced. To eliminate the danger of chemical burns, reverse current wave, i.e. depolarizing pulses that also reduce skin irritation, should be used.[21,23,25]

Degeneration Reaction

Both Galvanic and Faradic currents are used to determine the extent of the Degeneration Reaction.

- Partial Degeneration Reaction: The response to Faradic current decreases in the nerve, more current is required. Response to Galvanic current is normal in muscle and nerve.
- Complete Degeneration Reaction: Response to Faradic current cannot be obtained in the nerve. Response to Galvanic current is normal in muscle and nerve (7-21 days).
- Definite Degeneration Reaction: Response to Faradic and Galvanic current cannot be taken in the nerve. Response to Galvanic current is protracted in the muscle.[18,25,26]

Faradic Excitability Test

Faradic Excitability Test (FET) is performed using a Faradic current, which is an asymmetrical biphasic

pulse varying at a frequency of 50 Hz. The duration of a Faradic pulse is typically 1 ms, which causes contraction of all innervated skeletal muscles. Tetanization does not occur because it is applied intermittently 25 times in 60 seconds (s). Thus, contraction with Faradic current is accepted as a sign of re-innervation after denervation. Lower threshold values are interpreted as better innervation of a muscle. FET should be done firstly for the healthy side than the injured side. According to the comparison, decisions were given for the type of excitability.[27,28]

- Hyperexcitability (degeneration)
- Hypoexcitability (regeneration)
- Inexcitability (complete degeneration)

Rheobase and Chronaxie

Quantitative stimulation became possible with the device that Hoorweg invented in 1892 and called the Galvanometer, in which current and voltage values can be measured precisely.[29] As a result of his experiments in the same period, Georges Weiss was able to estimate the current and load by calculating the resistance of the circuit and measuring the voltages.[30] Louis Lapicque investigated the excitability of nerves and muscles of vertebrates and invertebrates at the same time. Unlike other researchers, his aim was to create a theoretical model. Lapicque introduced two terms that made the physiological mechanism of the hyperbolic Strength–Duration relationship intelligible, which had already been published by Weiss in 1907.[31] It is the concept that he called the "basic threshold value" in his work until that day, and that he called "rheobase (the basis of the current)" after that day. The rheobase shows the intensity of the sudden onset and long-lasting current excitation threshold.[32] In the same study, Lapicque defined the time required to obtain minimal contraction at twice the rheobase intensity as "chronaxie".[32]

In order to create an action potential in the motor or sensory fibers of the peripheral nerve, the applied current must reach the minimum threshold current value. Otherwise, the action potential does not occur. The rheobase is equal to the smallest 1000 ms rectangular wave pulse intensity (expressed in milliamperes [mA]) that causes the excitable tissue to respond with minimal apparent contraction.[33] The duration of the application also affects the threshold level. As the application time of the current gets shorter, the required threshold stimulus current density increases.[34] Rheobase is defined as the minimum current intensity required for a very long-lasting stimulus to generate the stimulus. Rheobase, in other words, is the stimulation intensity required to stimulate a nerve fiber with the longest stimulation time and to reach the threshold level of the stimulus.[7,35] The normal value of the rheobase is between 2 and 8 mA. There are differences between normal rheobase values of various muscle groups.[22,34] For example, it is 5mA for Deltoid muscle, 4mA for Frontalis muscle, and 8mA for Abductor Digiti Minimi muscle. In denervation, the rheobase may be less than that of the innervated muscle and is often elevated when reinnervation begins. Rheobase varies considerably in various muscles, skin resistance and temperature. The elevation of rheobase may be due to fibrosis of the muscle.[36]

Chronaxie is the duration of the shortest impulse to produce a response with twice the current of the rheobase. If a constant voltage stimulator is used, the chronaxie of the innervated muscle is significantly less than that of the innervated muscle, with the former less and the latter more than 1 ms. Rheobase and chronaxie refer to measures of excitability of nerve axons, and fibers with low chronaxies have high excitability.[37,38] Rheobase and chronaxie values reach higher values than the normal range in case of injury to the peripheral nerve that is large enough to cause denervation.[37,39] The mean chronaxie value of a completely healthy muscle with inversion is 0.4 ms.[22] When denervation occurs in the muscle, the chronaxie value rises above 1 ms.[22,37]

Axonal excitability values are affected by physiological conditions. Age, temperature, subdermal adipose tissue, skin conductivity, edema, fatigue, reinnervation, partial denervation, and full denervation status can be given as examples of factors affecting rheobase and chronaxie values.[37,40,41] It is stated that stimuli with short pulse durations

during application can be tolerated more easily compared to long pulse durations.[42] Electrodiagnostic tests are usually performed with a square wave intermittent Galvanic current. Because the shortest pulse duration and the lowest current intensity can be achieved with a rectangular waveform. For this reason, the rectangular waveform is accepted as the optimal form in order to reach the threshold level in the shortest and most comfortable way.[37,43]

Accommodation Rate

The accommodation factor is applied to determine the muscle's ability to adapt to the slowly increasing intensity of the triangular stimulus. To define the accommodation coefficient, it is necessary to establish the triangular pulse intensity lasting 1000 ms, as well as the accommodation threshold value, which means the lowest value of the rheobase (Figure 37.1).[44] Normal neuromuscular excitability is determined in the range of 3-6, a value below 3 indicates a decrease until the ability to adapt is completely lost, a value above 6 indicates increased adaptability.[37,45,46]

The accommodation rate allows to determine the muscle's ability to adapt to a slowly increasing triangular pulse intensity relative to a rectangular pulse over their duration of 500 ms with minimal apparent contraction. Values in the range of 1.6-2.5 indicate that the adaptability of the muscle is normal, the capacity of accommodation increases in the range of 3-4, and decreases from 1.5 to a value of 1 when the adaptability is completely lost.[45,46]

Strength–Duration Curve

The Strength–Duration Curve (SDC) shows the relationship between the magnitude of the stimulus change and the duration of the stimulus. Plotting an SDC requires stimulating a muscle with a constant pulse duration current ranging from 0.01 to 300 ms at the motor point and recording the current power in mA required to elicit threshold twitch contraction (Figure 37.2a).[44] Obtained mA values and used pulse duration (ms) are plotted on the SDC graph on the X and Y axis, respectively.[47] SDC was historically applied to evaluate nerve injuries from the 1930s to the 1960s before the widespread use of EMG and nerve conduction testing.[47] SDC is one of the methods of assessing the severity and subsequent healing of a nerve injury. Provides a graphical representation of the integrity of the muscle-nerve complex. Although electrophysiological assessment techniques have become more complex over the past three decades, SDC remains useful, still a reliable index of muscle/nerve functional integrity.[47,48] The curve provides valuable information about the excitability state of the nerve lesion. It should be done 21 days after the nerve injury.

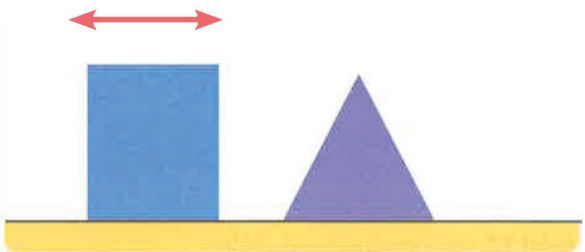

Figure 37.1 Triangular and rectangular wave currents.[44]

In case of partial denervation of the muscle, it is necessary to reach a high stimulation threshold for the deinnervated muscles. It is possible that partial denervation is concealed by intact axons with a lower threshold level with complete innervation.[37,49] Indeed, the amount of muscle fiber that is not specifically affected by stimulation cannot be demonstrated using SDC. The slope of the SDC gives information about the excitability of the axon and the integrity, quality and quantity of the axon. The curve shifts to the left when the axon is more excitable (Figure 37.2b).[44] This indicates that the same responses can be obtained at lower stimulus intensity. In cases where the curve shifts to the right, it is concluded that the axon can be stimulated more difficult (Figure 37.2c).[5,6,44,47] The time constant obtained from SDC is equal to the chronaxie and constitutes the time-dependent parameter of axonal excitability. Studies are based on different impulse times to evaluate rheobase and chronaxie.[5,6,47,50] This situation can be an obstacle to the determination of the optimal diagnostic method.

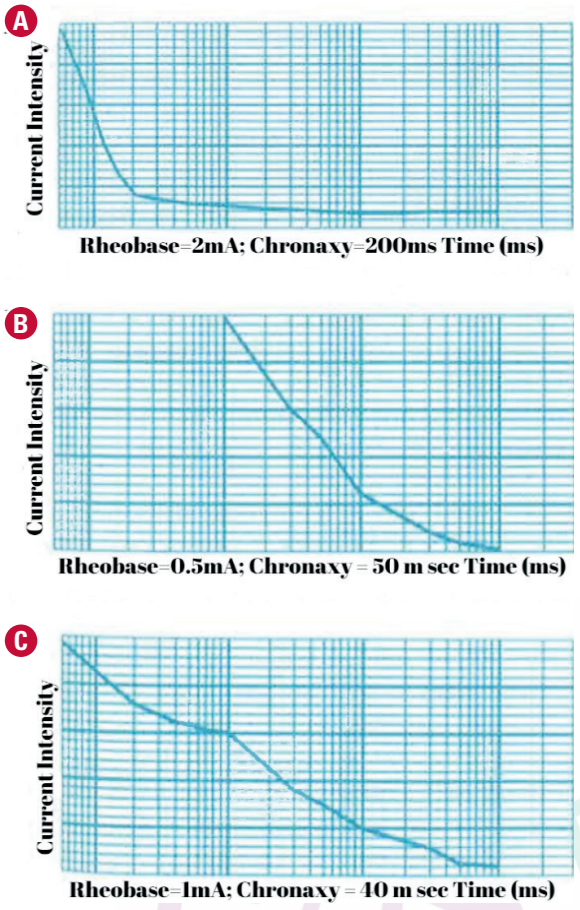

Figure 37.2 Strength-Duration Curve **A.** SDC in normal muscle, **B.** SDC in denervated muscle, **C.** SDC in re-innervated muscle.[44]

Normal Innervation

When all nerve fibers innervating the muscle are intact, the SDC normally has a shape characteristic of the innervated muscle. This is because all impulses of longer duration require the same stimulus strength to produce a response, while those of shorter duration require an increase in the strength of the stimulus with each shortening of the duration.[47-50]

Partial Denervation

The shorter the impulses, the more difficult the denervated fibers respond. Thus, stronger stimulation is required. The characteristic curve obtained when some of the nerve fibers supplying a muscle degenerates while others are intact clearly indicating partial denervation. The right side of the curve is similar to the denervated muscle, and the left side is similar to the innervated muscle, and a bend is seen at the junction of the two parts.[47-50]

Complete Denervation

When all the nerve fibers supplying a muscle degenerate, the duration of stimulation produced is characteristic of full denervation. For all impulses of 100 ms duration or less, the intensity of the stimulus must be increased each time the duration is decreased, and impulses of very short duration do not respond. Thus, the curve rises steeply and is more to the right than a normally innervated muscle.[47-50]

Galvanic Tetanus Ratio

In square wave Galvanic current, it is the ratio of the current intensity at which maximum contraction is achieved to the current intensity at which minimal contraction is achieved (rheobase) (Figure 37.3).[48] Due to accommodation in the nerve, the tetanus current intensity is several times greater than the Galvanic current intensity under normal conditions. Since there is little or no accommodation in denervated muscle, both values are close to each other.[37,51]

Galvanic tetanus ratio in normal muscle: 3.5-6:1

Galvanic tetanus ratio in denervated muscle: 1:1

Galvanic tetanus ratio in regenerated muscle: 2-20:1

Pfluger's Law

In 1858, Pfleuger first discovered that a healthy muscle could be stimulated with less current, with the cathode rather than the anode. In addition, while being stimulated with the cathode; when the circuit is closed (CCC), the axon becomes more excitable compared to the open circuit (ACC). If physical anode and cathode are applied on human nerves, physiological anode and cathode are formed under them. When the current is closed, excitation occurs at the physiological cathode. However, the intensity of the current is higher at the physiological cathode, which is the starting point

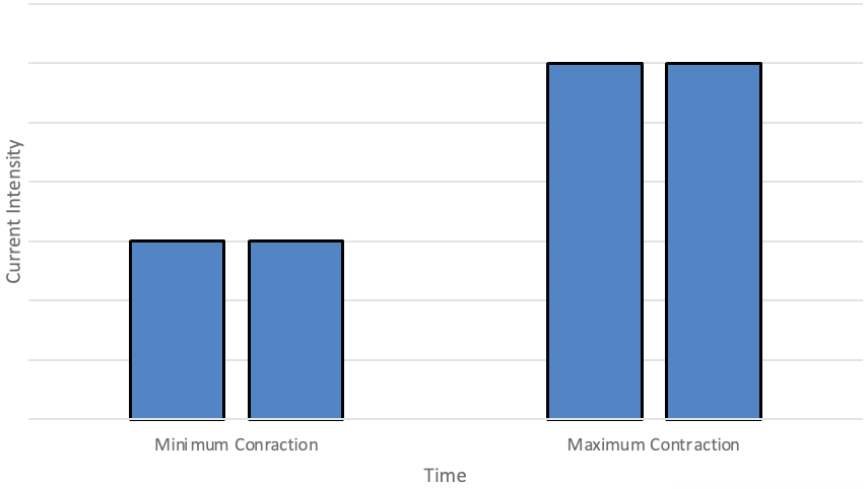

Figure 37.3 Rectangular wave Galvanic currents of different intensities used to determine the Galvanic Tetanic Ratio.

of the closing contraction. However, the closing contraction begins at this point. When the intensity of the current is increased, the same situation is observed at the physiological cathode. According to Pfluger's Law, strong currents are required at the physiological anode to generate excitation, and excitation also occurs at the physiological anode.[52]

Accordingly, by examining 4 variations, he came to the following conclusion;

CCC>ACC>AOC>COC

- Cathodal closing contraction (CCC): contraction of muscle at the cathode upon closure of the electric circuit.
- Anodal closing contraction (ACC): contraction of muscle at the anode upon closure of the electric circuit.
- Anodal opening contraction (AOC): contraction of muscle at the anode upon opening of the electric circuit.
- Cathodal opening contraction (COC): contraction of muscle at the cathode upon opening of the electric circuit.[44]

In the case of degeneration, the opposite situation occurs, which is expressed as the "Erb Phenomenon".[52]

Polar and Apolar Stimulation Law

The Polar Stimulation Law is valid for direct current and low frequency currents. Depolarization and action potential take place under the cathode. The Apolar Stimulation Law is valid for medium frequency currents. Depolarization and action potential occur under both poles.[44]

Du-Bois Reymond's Law

When a current is applied to the nerve suddenly, the nerve can be stimulated with approximately 1 V, while the stimulation threshold of the nerve can reach up to 5 Volts (V) when the current is gradually increased. Therefore, since the slow applied current increases the excitation threshold of the nerve, more amplitude current is required to exceed the threshold. The rise time of the current should be less than 60 ms in order to avoid accommodation while stimulating the nerve with direct current. The duration of the stimulus must be long enough so that the latent period, action potential and healing can occur.[53,54]

Abnormal Reactions

Longitudinal Reaction

When the muscle is stimulated, the contraction is not taken from the motor point, but slightly below the motor point.[55]

Remark Reaction

When the muscle is stimulated, the response is protracted rather than suddenly.[44]

Myotonic Reaction

It is generally seen in myotonia congenita disease. When the muscle is stimulated, although the flow is interrupted, the muscle remains contracted for a while.[56]

Myasthenic Reaction

It is mostly seen in Myasthenia Gravis disease. It manifests itself with fatigue very quickly. The first few responses when the muscle is stimulated are fine. However, after a while the answer decreases, becomes difficult and disappears.[57]

Electromyography

Electromyography (EMG) is used to read myoelectric signals through electrical measurements. These myoelectric signals are generated from motor neurons, which are part of the central nervous system. Because EMG signals are dependent on neuromuscular activity, they can be used to diagnose muscle injury, nerve damage, and muscle dysfunction due to neurological and muscular dysfunction. EMG, which is usually performed together with nerve conduction studies including sensory nerve conduction, motor nerve conduction, and late responses, can be quite painful, uncomfortable, and time consuming.[58]

Sensory Nerve Conduction Studies

Standard sensory conduction studies are performed by giving supramaximal stimulus to the nerve from one point and recording the compound nerve action potential from the other point. A supramaximal stimulus is a stimulus of sufficient intensity to initiate an action potential in all axons of the nerve that is stimulated. Since the compound nerve action potential is the simple sum of the action potentials of all axons in the nerve, the peripheral sensory action potential can provide information about various disease processes. By making use of the anatomical features of peripheral sensory neurons, we can divide clinical sensory impairment into two categories as preganglionic and postganglionic, depending on whether the pathological process of sensory dysfunction is distal or proximal to the sensory neuron cell body. In preganglionic disorders (eg, radiculopathies, cauda equina lesions, and posterior cord disease), the sensory cell in the dorsal root ganglion is not significantly damaged and its distal axon remains intact. In these diseases, even if the clinical sensory function is markedly impaired, the sense is normal in electrodiagnostic studies. Postganglionic diseases damage the sensory cell body, axon or associated Schwann cells; these diseases result in direct or indirect axon dysfunction. If the damage is severe in these diseases, electrical sensory studies may be abnormal.

In sensory nerve conduction studies, information such as sensory nerve action potential (SNAP) conduction velocities, SNAP amplitudes and shapes are obtained in various segments of the nerve. Analysis of SNAP amplitude, shape, distal latency, and conduction velocity provides specific information about the number, type, and myelination status of sensory axons functioning in various segments of the nerve.[59]

The SNAP measured in routine electrodiagnostic studies is a complex derivative of the sum of the longitudinal currents created by the action potential of each sensory axon in the nerve, and its value varies between 2 and 100 mV, depending on the features of the nerve.[60]

Motor Nerve Conduction Studies

Motor nerve conduction studies are performed by stimulating motor nerves and the resulting compound muscle action potential (CMAP) is recorded from the muscle. Any process that damages the anterior horn cell, its axon and associated Schwann cells, neuromuscular junction, or muscle cells affects motor neurotransmission studies results. Unlike in sensory neurons, where peripheral lesions can be preganglionic or postganglionic, in motor neurons all lesions occur distal to the cell body, in axons, and may affect axon function.

In motor nerve conduction studies, nerve conduction velocities in various segments, CMAP amplitude and shape are examined, as in sensory nerve conduction studies. Interpretation of motor

conduction velocity and CMAP form is the same as for sensory nerves, but there is a significant difference in interpretation of CMAP amplitude. Unlike SNAP, CMAP amplitude determines primarily the density of muscle fibers innervated by axons, not the number of axons. These two parameters are not always strongly correlated with each other.

With motor nerve conduction studies, we can obtain information about motor nerve action potential conduction velocity, CMAP amplitude and shape in various segments of motor axons. By analyzing the amplitude, shape, distal latency, and motor nerve conduction velocity of CMAP, specific information is obtained about the myelination status of motor axons functioning in various segments of the nerve, the number of innervated and processed muscle fibers, and the functional status of the neuromuscular junction. CMAP amplitudes for frequently studied muscles vary between 2 and 25 millivolt (mV), varying from muscle to muscle.[61,62]

Late Responses

Due to technical difficulties in selective stimulation of nerves and roots close to the spine, it is difficult to assess nerve conduction velocity in the most proximal parts of peripheral nerves, such as the proximal plexus and roots. When the need to examine these parts of the peripheral nerves arises, a group of nerve conduction studies called "late responses" are performed. These studies include the H-reflex and F-response, so named because their responses appear much later than the direct CMAP response. For now, we can define these nerve conduction studies as the nerve action potential initiated distally (in the sensory axon for the H-reflex, in the motor axon for the F-response) and spreading proximally, initiating a motor neuron action potential at the spinal cord level and recording it as a muscle response by transmitting it distally.

The H-reflex or H-response is the electrical analog of the muscle stretch reflex with the contribution of muscle spindles. This reflex is obtained by distally stimulating the afferent fibers from the muscle spindles, which go to the spinal cord and initiate the monosynaptic stretch reflex and stimulate a motor response in the relevant muscle.[63] Normally, the mean H-reflex latency in the population is 29.8 ± 2.74 ms and there is a difference between 1.0 and 2.0 ms between the two sides, depending on the sensitivity criteria used. If the main concern is S1 radiculopathy, a difference of more than 1.5-2 ms between the two sides is considered in favor of this diagnosis.[64,65]

The F-response or F-wave is the action potential initiated by a stimulus, reaching the proximal anterior horn cell body along the motor axon, triggering a new discharge in the same anterior horn cell.[64,66] The action potential generated by this discharge goes distally and stimulates a muscle action potential. Like the H-reflex, the F-response is useful as a long-distance nerve conduction study that examines the proximal segments of nerves, plexuses, and roots. Unlike the H-reflex, it can be obtained from almost all muscles, so it is superior in terms of applicability. The ease of obtaining F-responses depends on the excitability of the anterior horn cell and thus the effects of central nervous system on the anterior horn cell.[66] F-response latency is a highly variable phenomenon, when the examiner stimulates the nerve multiple times in the same study, the shortest and longest F-latency for a particular muscle may differ by 3-6 ms.[67] The right-left difference of the F-response latency in the normal individual is approximately 2 ms for the upper extremity and 4 ms for the lower extremities.[65]

References

1. Fernandes LF, Oliveira NM, Pelet DC, Cunha AF, Grecco MA, Souza LA. Stimulus electrodiagnosis and motor and functional evaluations during ulnar nerve recovery. Braz J Phys Ther. 2016;20(2):126-32. doi:10.1590/bjpt-rbf.2014.0138.
2. Choi JM, Di Maria G. Electrodiagnostic testing for disorders of peripheral nerves. Clin Geriatr Med. 2021;37(2):209-21. doi:10.1016/j.cger.2021.01.010.
3. Han JH, Lee JY, Yun DH, Moon CW, Cho KH. Prediction of lower extremity strength by nerve conduction study in Cauda Equina Syndrome. Medicine (Baltimore). 2022;101(34):e30124. doi:10.1097/MD.0000000000030124.
4. Santana L, Fachin-Martins E, Borges DL, Tenório Cavalcante JG, Babault N, Neto FR, et al. Neuromuscular disorders in women and men with spinal cord injury are associated with changes in muscle and tendon architecture. J Spinal Cord Med. 2022;1-11. doi:10.1080/10790268.2022.2035619.
5. Rodríguez-Fernández ÁL, Rebollo-Roldán J, Jiménez-Rejano JJ, Güeita-Rodríguez J. Strength-Duration Curves of the common fibular nerve show hypoexcitability in people with functional ankle instability. PMR. 2016;8(6):536-44. doi:10.1016/j.pmrj.2015.09.009.

6. de la Cruz Torres B. Strength-Duration Curves of radial nerve in patients with lateral elbow pain. J Sport Rehabil. 2019;29(6):754-9. doi:10.1123/jsr.2018-0405.
7. Lee WD, Kim JH, Lee JU, Kim MY, Lee LK, Yang SM, et al. Differences in Rheobase and Chronaxie between the paretic and non-paretic sides of hemiplegic stroke patients: A pilot study. J Phys Ther Sci. 2013;25(6):717-9. doi:10.1589/jpts.25.717.
8. Paternostro-Sluga T, Schuhfried O, Vacariu G, Lang T, Fialka-Moser V. Chronaxie and Accommodation Index in the diagnosis of muscle denervation. Am J Phys Med Rehabil. 2002;81(4):253-60. doi:10.1097/00002060-200204000-00003.
9. Ervilha UF, Araujo RC. Estudo sobre a frequência de distribuição da cronaxia ea sua correlação com distintos graus de lesões nervosas periféricas. Rev Bras Fisioter. 1997;1(2):45-50.
10. Seddon HJ. Three types of nerve injury. Brain. 1943;66(4):237-88. doi:10.1093/brain/66.4.237.
11. Sunderland S. A classification of peripheral nerve injuries producing loss of function. Brain. 1951;74(4):491-516. doi:10.1093/brain/74.4.491.
12. Lee EY, Lim AYT. Nerve compression in the upper limb. Clin Plast Surg. 2019;46(3):285-93. doi:10.1016/j.cps.2019.03.001.
13. Netscher D, Murphy K, Fiore NA. (2012), Hand surgery: Ch. 70 nerve compression syndrome. 19th ed. Townsend: Sabiston Textbook of Surgery. Elsevier.
14. Robinson LR. Traumatic injury to peripheral nerves. Muscle Nerve. 2000;23(6):863-73. doi:10.1002/(sici)1097-4598(200006)23:6<863::aid-mus4>3.0.co;2-0.
15. Tapadia M, Mozaffar T, Gupta R. Compressive neuropathies of the upper extremity: Update on pathophysiology, classification, and electrodiagnostic findings. J Hand Surg Am. 2010;35(4):668-77. doi:10.1016/j.jhsa.2010.01.007.
16. Menorca RM, Fussell TS, Elfar JC. Nerve physiology: Mechanisms of injury and recovery. Hand Clin. 2013;29(3):317-30. doi:10.1016/j.hcl.2013.04.002.
17. Pollock LJ, Golseth JG. Electrodiagnosis of lesions of peripheral nerves in man. Arch Neurol Psychiatry. 1948;60(1):1-19. doi:10.1001/archneurpsyc.1948.02310010007001.
18. Groff RA. Diagnosis and management of peripheral nerve injuries. Postgrad Med. 1947;1(6):413-20. doi:10.1080/00325481.1947.11691705.
19. Nanivadekar P, Kar S. Microcontroller based rehabilitation stimulator. Int J Comput Applicat. 2013;975(8887):17-21.
20. Boonstra AM, van Weerden TW, Eisma WH, Pahlplatz VB, Oosterhuis HJ. The effect of low-frequency electrical stimulation on denervation atrophy in man. Scand J Rehabil Med. 1987;19(3):127-34. PMID:2831623
21. Jagmohan S. (2011), Manual of practical electrotherapy. Jaypee Brothers Publishers. ISBN:978-93-5025-059-4
22. Licht S. (1971), Electrodiagnosis and electromyography. Vol 1: E. Licht.
23. Fischer E. The effect of faradic and galvanic stimulation upon the course of atrophy in denervated skeletal muscles. AJP-Legacy Content. 1939;127(4):605-619. doi:10.1152/ajplegacy.1939.127.4.605.
24. Merletti R, Parker PJ. (2004), Electromyography: physiology, engineering, and non-invasive applications (Vol. 11). John Wiley & Sons. ISBN:0-471-67580-6
25. Batra SP, Sinha A, Singh NN, Abrol BM. Electro-diagnosis in peripheral facial nerve paralysis. Indian Journal of Otolaryngology. 1973;25:76-86.
26. Solomen S, Babu B, Muralidharan PC, Sreejith K, Gafoor A. Conservative management of brachial plexus injury through a structured rehabilitation protocol: A case report. RGUHS Journal of Physiotherapy. 2021;1(3):31-8. doi:10.26463/rjpt.1_3_1
27. Kirdi N, Yakut E, Firat T, Turan D, Leblebicioglu G. Physiotherapy approaches for iatrogenic injury of the spinal accessory nerve: A case report. Pain Clin. 2003;15(1):51-4. doi:10.1163/156856903321196492.
28. Shafshak TS. The treatment of facial palsy from the point of view of physical and rehabilitation medicine. Eura Medicophys. 2006;42(1):41-7. PMID:16565685
29. Hoorweg JL. Condensatorentladung und auseinandersetzung mit du Bois-Reymond. Pflugers Arch. 1892;52:87-108.
30. Weiss G. Sur la possibilite de rendre comparables entre eux les appareils servant a l'excitation electrique. Archives Italiennes de Biologie. 1901;35(1):413-45. doi:10.4449/aib.v35i1.1355.
31. Rabinovitch A, Braunstein D, Biton Y, Friedman M, Aviram I. The Weiss-Lapicque and the Lapicque-Blair Strength-Duration Curves revisited. Biomed Phys Eng Express. 2016;2(1):015019. doi:10.1088/2057-1976/2/1/015019.
32. Lapicque L. Recherches quantitatives sur l'excitation electrique des nerfs traitee comme une polarization. Journal de Physiologie et de Pathologie Générale. 1907:9;620-35.
33. Wróbel B, Dolibog P, Penkala A, Kierszniok K, Król P. The Determination of normative values for the median nerve using classic electrodiagnostic methods. Med Rehabil. 2021;25(4):9-14. doi:10.5604/01.3001.0015.7048.
34. Bostock H, Cikurel K, Burke D. Threshold tracking techniques in the study of human peripheral nerve. Muscle Nerve. 1998;21(2):137-58. doi:10.1002/(sici)1097-4598(199802)21:2<137::aid-mus1>3.0.co;2-c.
35. Tsui BC. The effects of general anaesthesia on nerve-motor response characteristics (Rheobase and Chronaxie) to peripheral nerve stimulation. Anaesthesia. 2014;69(4):374-9. doi:10.1111/anae.12540.
36. Salian SC, Yardi S, Kadam VP. A Comparative study to ascertain differences between rheobase, girth and isometric strength amongst dominant and non-dominant upper limb in normal subjects. Physiotherapy and Occupational Therapy. 2011;5(4):170-5.
37. Paternostro-Sluga T, Schuhfried O, Vacariu G, Lang T, Fialka-Moser V. Chronaxie and Accommodation Index in the diagnosis of muscle denervation. Am J Phys Med Rehabil. 2002;81(4):253-60. doi:10.1097/00002060-200204000-00003.
38. Kiernan MC, Burke D, Andersen KV, Bostock H. Multiple measures of axonal excitability: A new approach in clinical testing. Muscle Nerve. 2000;23(3):399-409. doi:10.1002/(sici)1097-4598(200003)23:3<399::aid-mus12>3.0.co;2-g.
39. Chandrasekaran S, Davis J, Bersch I, Goldberg G, Gorgey AS. Electrical stimulation and denervated muscles after spinal cord injury. Neural Regen Res. 2020;15(8):1397-407. doi:10.4103/1673-5374.274326.
40. Casanova I, Diaz A, Pinto S, de Carvalho M. Motor excitability measurements: The influence of gender, body mass index, age and temperature in healthy controls. Neurophysiol Clin. 2014;44(2):213-8. doi:10.1016/j.neucli.2014.03.002.
41. Kiernan MC, Bostock H, Park SB, et al. Measurement of axonal excitability: Consensus guidelines. Clin Neurophysiol. 2020;131(1):308-23. doi:10.1016/j.clinph.2019.07.023.
42. Sprague S, Goldberg ME. Modalities part 3: Electrotherapy and electromagnetic therapy. Physical rehabilitation for veterinary technicians and nurses. John Wiley & Sons, Inc. 2017;241-61. doi:10.1002/9781119389668.ch16.

43. Misra UV, Kalita J. (2019), Clinical neurophysiology: Nerve conduction, electromyography, evoked potentials. Elsevier Health Sciences. ISBN:9788131256053.
44. Kirdi N. (2015), Elektroterapide temel prensipler ve klinik uygulamalar. Hipokrat Kitabevi: Ankara. ISBN: 978-605-9160-03-2
45. Georgiew F, Kania A, Gancarz E. Porównanie progu pobudliwości czuciowej i ruchowej nerwu pośrodkowego przy pomocy krzywej i/t. Medical Review. 2012;(4):418-27.
46. Friedli WG, Meyer M. Strength-Duration Curve: A measure for assessing sensory deficit in peripheral neuropathy. J Neurol Neurosurg Psychiatry. 1984;47(2):184-9. doi:10.1136/jnnp.47.2.184.
47. Jablecki CK, Andary MT, Di Benedetto M, Horowitz SH, Marino RJ, Rosenbaum RB, et al. American Association of Electrodiagnostic Medicine guidelines for outcome studies in electrodiagnostic medicine. Muscle Nerve. 1996;19(12):1626-35. doi:10.1002/(SICI)10974598(199612)19:12<1626::AIDMUS18>3.0.CO;2-P.
48. Wood MD, Kemp SW, Weber C, Borschel GH, Gordon T. Outcome measures of peripheral nerve regeneration. Ann Anat. 2011;193(4):321-33. doi:10.1016/j.aanat.2011.04.008.
49. Schuhfried O, Kollmann C, Paternostro-Sluga T. Excitability of chronic hemiparetic muscles: Determination of Chronaxie values and Strength-Duration Curves and its implication in functional electrical stimulation. IEEE Trans Neural Syst Rehabil Eng. 2005;13(1):105-9. doi:10.1109/TNSRE.2005.843439.
50. Pollock LJ, Golseth JG, Arieff AJ. Use of galvanic tetanus and the galvanic tetanus ratios in electrodiagnosis of lesions of peripheral nerves. Arch Neurol Psychiatry. 1945;54:317. PMID:21006516
51. Wright EB, Ooyama H. Anode break excitation and Pfluger's Law. Am J Physiol. 1961;200:219-22. doi:10.1152/ajplegacy.1961.200.2.219.
52. Honorata NB, Marek T, Leszek K. Electrodiagnostics; Chronaxymetry. 1996:1-9. https://www.ump.edu.pl/media/uid/9e29c-_ad00018574a_2/5679d6.pdf. (accessed:19.04.2023)
53. Norrsell U, Finger S, Lajonchere C. Cutaneous sensory spots and the "law of specific nerve energies": History and development of ideas. Brain Res Bull. 1999;48(5):457-65. doi:10.1016/s0361-9230(98)00067-7.
54. Pearce JM. Emil Heinrich Du Bois-Reymond (1818-96). J Neurol Neurosurg Psychiatry. 2001;71(5):620. doi:10.1136/jnnp.71.5.620.
55. Subcommittee of the Medical Research Council's Nerve Injuries Committee. Electrodiagnostic stimulators. Br Med J. 1958;2(5098):714. PMID: 13572877.
56. Hehir MK, Logigian EL. Electrodiagnosis of myotonic disorders. Phys Med Rehabil Clin N Am. 2013;24(1):209-20. doi:10.1016/j.pmr.2012.08.015.
57. Huffmann G, Leven B. "Ermüdungsreaktion" bei myasthenischen syndromen ["fatiguability" in myasthenic syndromes]. Fortschr Neurol Psychiatr Grenzgeb. 1975;43(6):313-9. PMID:1041494.
58. Lazaro RP. Electromyography in musculoskeletal pain: A reappraisal and practical considerations. Surg Neurol Int. 2015;6:143. doi:10.4103/2152-7806.163816.
59. Rathi N, Taksand, B, Kumar S. Nerve conduction studies of peripheral motor and sensory nerves in the subjects with prediabetes. J Endocrinol Metab. 2019;9(5):147-50. doi:10.14740/jem602.
60. Mommaerts W, Junge D, Jackson MB. Excitation and nerve conduction. Comprehensive human physiology: from cellular mechanisms to integration. Berlin, Heidelberg: Springer, 1996;283-94. doi:10.1007/978-3-642-60946-6_14.
61. Robinson LR. Traumatic injury to peripheral nerves. Muscle Nerve. 2000;23(6):863-73. doi:10.1002/(sici)1097-4598(200006)23:6<863::aid-mus4>3.0.co;2-0.
62. Frontera WR, DeLisa JA, Gans BM, Robinson LR. (2019), DeLisa's physical medicine and rehabilitation: Principles and practice. Lippincott Williams & Wilkins; 61-91.
63. Thompson AK, Wolpaw JR. H-reflex conditioning during locomotion in people with spinal cord injury. J Physiol. 2021;599(9):2453-69. doi:10.1113/JP278173.
64. Jerath N, Kimura J. F wave, A wave, H reflex, and blink reflex. Handb Clin Neurol. 2019;160:225-39. doi:10.1016/B978-0-444-64032-1.00015-1.
65. Frontera WR, DeLisa JA, Gans BM, Walsh NE, Robinson LR, Basford J. (2010), Physical medicine and rehabilitation: Principles and practice. Lippincott Williams & Wilkins Health. ISBN:0-7817-4130-0
66. Fisher MA. F-waves--physiology and clinical uses. ScientificWorld Journal. 2007;7:144-60. 2007. doi:10.1100/tsw.2007.49.
67. Fisher MA, Hoffen B, Hultman C. Normative F wave values and the number of recorded F waves. Muscle Nerve. 1994;17(10):1185-9. doi:10.1002/mus.880171009.

CK4STEM