INVITED REVIEW

ABSTRACT: This review provides a comprehensive overview of the clinical uses of neuromuscular electrical stimulation (NMES) for functional and therapeutic applications in subjects with spinal cord injury or stroke. Functional applications refer to the use of NMES to activate paralyzed muscles in precise sequence and magnitude to directly accomplish functional tasks. In therapeutic applications, NMES may lead to a specific effect that enhances function, but does not directly provide function. The specific neuroprosthetic or "functional" applications reviewed in this article include upper- and lower-limb motor movement for self-care tasks and mobility, respectively, bladder function, and respiratory control. Specific therapeutic applications include motor relearning, reduction of hemiplegic shoulder pain, muscle strengthening, prevention of muscle atrophy, prophylaxis of deep venous thrombosis, improvement of tissue oxygenation and peripheral hemodynamic functioning, and cardiopulmonary conditioning. Perspectives on future developments and clinical applications of NMES are presented.

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NEUROMUSCULAR ELECTRICAL STIMULATION IN NEUROREHABILITATION

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This article provides a comprehensive review of the clinical uses of neuromuscular electrical stimulation (NMES) in neurological rehabilitation. NMES refers to the electrical stimulation of an intact lower motor neuron (LMN) to activate paralyzed or paretic muscles. Clinical applications of NMES provide either a functional or therapeutic benefit. Moe and Post[207] introduced the term functional electrical stimulation (FES) to describe the use of NMES to activate paralyzed muscles in precise sequence and magnitude so as to directly accomplish functional tasks. In present-day applications, functional tasks may include standing or ambulatory activities, upper-limb performance of activities of daily living, and control of respiration and bladder function. A neuroprosthesis is a device or system that provides FES. Accordingly, a neuroprosthetic effect is the enhancement of functional activity that results when a neuroprosthesis is utilized. NMES is also used for therapeutic purposes. NMES may lead to a specific effect that enhances function but does not directly provide function. One therapeutic effect is motor relearning, which is defined as "the recovery of previously learned motor skills that have been lost following localized damage to the central nervous system."[180] Evolving basic science and clinical studies on central motor neuroplasticity now support the role of active repetitive-movement training of a paralyzed limb. If active repetitive-movement training facilitates motor relearning, then NMES-mediated repetitive-movement training may also facilitate motor relearning. Other examples of therapeutic applications include treatment of hemiplegic shoulder pain, cardiovascular conditioning, treatment of spasticity, and prevention of muscle atrophy, disuse osteoporosis, and deep venous thrombosis (DVT).

This review focuses on the clinical uses of NMES for functional and therapeutic applications in patients with spinal cord injury or stroke. In order to provide a foundation for the various clinical applications, the neurophysiology of NMES and compo-

nents of NMES systems are briefly reviewed. The specific neuroprosthetic or "functional" applications include upper- and lower-limb motor movement for self-care tasks and mobility, respectively, bladder function, and respiratory control. Specific therapeutic applications include poststroke motor relearning as well as the examples mentioned earlier. Lastly, perspectives on future developments and clinical applications of NMES are presented.

NEUROPHYSIOLOGY OF NMES

NMES is initiated with the excitation of peripheral nervous tissue. The mathematical characterization of neuronal action potential generation is largely predicated on the seminal work of scientists and neurophysiologists including Galvani,[106] Lapicque[175] and Hodgkin and Huxley.[130] More recently, McNeal[200] mathematically defined the time course of events following stimulus application to the propagation of the action potential in a normal healthy myelinated nerve. The term "stimulus threshold" defines the lowest level of electrical charge that generates an action potential. The "all or none" phenomenon of the action potential produced by natural physiologic means is identical to the action potential induced by NMES.

Conduction of impulses in a nerve is influenced considerably by the nerve's cable properties. Hodgkin and Rushton in 1946[131] used extracellular electrodes to measure applied current along lobster axons to describe the spread of current along nerve fibers of uniform diameter composed of a central conductor and insulating sheath. Nerve fiber recruitment and resultant force characteristics of muscle contraction are modulated by both stimulus pulse width[277] and stimulus frequency.[3] Other variables include distance from the stimulating electrode and membrane capacitance. The threshold for eliciting a nerve fiber action potential is 100 to 1,000 times less than the threshold for muscle fiber stimulation.[209] Thus, clinical NMES systems stimulate either the nerve directly or the motor point of the nerve proximal to the neuromuscular junction.

The nerve fiber recruitment properties elicited by NMES differ from those elicited by normal physiologic means. An action potential produced by normal physiologic mechanisms initially recruits the smallest-diameter neurons prior to recruitment of larger-diameter fibers, such as alpha motor neurons.[127] Rushton[248] was one of the first researchers to examine the theoretical relationship between fiber diameter and conduction velocity. Hodgkin[132] proposed that the velocity of action potential propagation should vary directly with the square root of the fiber diameter. The Henneman size principle of voluntary motor unit recruitment described this progressive size-dependent recruitment of motor units.[128] Arbuthnott et al.[9] examined in detail this relationship between fiber diameter and conduction velocity in peripheral nerve. The nerve fiber recruitment pattern mediated by NMES follows the principle of "reverse recruitment order" wherein the nerve stimulus threshold is inversely proportional to the diameter of the neuron. Thus, large-diameter nerve fibers, which innervate larger motor units, are recruited preferentially. Recent work by Lertmanorat and Durand[183] proposes the clinical applicability of a reshaping of the extracellular voltage that may allow the reversal of the "reverse recruitment order" elicited by NMES.

NMES is dependent on an intact (alpha) LMN. Several studies document the therapeutic benefit of electrical stimulation on muscle-fiber regeneration in LMN denervation[50,149,280]; however, the clinical application of NMES is presently limited to neurologic injuries involving the upper motor neuron (UMN) such as spinal cord injury (SCI), stroke, brain injury, multiple sclerosis, and cerebral palsy. NMES is delivered as a waveform of electrical current characterized by stimulus frequency, amplitude, and pulse width. The amplitude and pulse width determine the number of muscle fibers that are activated.[209] Temporal summation is determined by the rate at which stimulus pulses are applied to muscle. The strength of the resultant muscle contraction is modulated by adjustment of the stimulus parameters. The minimum stimulus frequency that generates a fused muscle response is ~12.5 Hz. Higher stimulus frequencies generate higher forces but result in muscle fiber fatigue and rapid decrement in contractile force. An optimal NMES system utilizes the minimal stimulus frequency that produces a fused response.[26,173,200] Ideal stimulation frequencies range from 12–16 Hz for upper-limb applications and 18–25 Hz for lower-limb applications (frequency range for NMES systems is 10–50 Hz). Greater muscle force generation is accomplished by either increasing the pulse duration (typically 200 μs) or stimulus amplitude to activate neurons at a greater distance from the activating electrode. Parameters for safe stimulation for implanted NMES systems have been established experimentally.[209]

The clinical application of NMES systems is complicated by the fact that the contractile force of muscle is highly nonlinear and variable over time. Muscle force generation is also impacted by multiple factors distinct from the stimulation parameters of the NMES system. These factors include the inherent length–ten-

sion characteristics of the muscle, impact of the joint angle on changes in the tendon arm moment arm, and volume conduction of the current that may recruit muscles beyond the targeted muscle.[115,153]

Skeletal muscle contains "fast" and "slow" muscle fibers that are distinguished on the basis of contraction kinetics. These fiber types are generally categorized according to the specific myosin heavy chain (MHC) isoforms that they express.[104,144] Histochemical analysis led to the original designations of types I and II muscle fibers. Slow-twitch, oxidative type I fibers generate lower forces, but are fatigue resistant; fast-twitch glycolytic type II fibers generate higher forces but fatigue more rapidly. Muscle fibers are typed using histochemical staining for myosin ATPase, MHC isoform identification, and biochemical identification of metabolic enzymes. Myosin ATPase histochemistry energy metabolism distinguishes the muscle fibers that comprise a motor unit, all of which exhibit similar contractile and fatigue characteristics. Motor units are thus classified based on fiber type contractile characteristics as either slow-twitch (S) or fast-twitch (F). The F motor units are classified as either fast-twitch fatigue-resistant (FR), fast-twitch fatigue-intermediate (Fint), or fast-twitch fatigable (FF).[256]

An alteration in functional demands result in conversion of muscle fiber types via altered gene expression, changes in the expression of contractile proteins and metabolic enzymes,[35] and adaptations in the cellular electrophysiologic properties (expression or function of ion channels).[171,312] Disuse muscle atrophy common in an UMN injury is characterized by conversion of type I muscle fibers to type II fibers.[242] An ideal application of NMES allows preferential stimulation of fatigue-resistant type I fibers. However, NMES systems preferentially recruit type II fibers due to lower stimulation thresholds. Chronic electrical stimulation facilitates reversal of fiber type conversion secondary to motor unit plasticity.[224] This reversal of fiber type conversion may be related to the motor neuron firing patterns that control expression of contractile proteins and metabolic enzymes in muscle fibers during electrostimulation.[172]

SYSTEM COMPONENTS

Most clinically available NMES systems fall into two broad categories: transcutaneous (surface) and implanted (percutaneous, epimysial, epineural, intraneural, and cuff) systems. NMES systems are either voltage- or current-regulated. Despite the variable motor response, voltage-regulated stimulation is more common with transcutaneous NMES systems;

as impedance (resistance) increases due to electrode–skin interface changes, current is decreased. Current density as opposed to absolute voltage determines the potential for tissue injury. Due to less variability in resistance and the need for muscle contraction consistency and repeatability, constant-current applications are more common in implanted NMES systems.

Electrode type impacts on potential for tissue injury and efficacy of intervention. The simplest electrode is the transcutaneous electrode that is applied to the skin and stimulates directly over the peripheral nerve or motor point. The motor point is the muscle location that exhibits the most robust contraction at the lowest level of stimulation. All transcutaneous electrodes use external leads that connect to a stimulator. Two electrodes placed in either a monopolar or bipolar configuration are required to produce an electrical current flow. The active electrode is placed directly over the peripheral nerve or motor point; the indifferent electrode is placed either on fascia or a tendinous insertion (monopolar) or near the active electrode (bipolar). Bipolar stimulation creates a more localized electrical field, which may result in greater selectivity of muscles.[115] Transcutaneous electrodes pose a risk of tissue injury, particularly in patients with concomitant sensory or cognitive deficits. Activation of cutaneous pain receptors, difficulties in positioning, poor selectivity, insecure fixation on moving limbs, skin irritation, and cosmetic factors are common limitations of transcutaneous electrodes. Although a constant-voltage transcutaneous NMES system minimizes the risk of high current densities associated with tissue–electrode interface fluctuations, variability in muscle stimulation and inconsistent functional response can result. Transcutaneous electrodes are more commonly used for therapeutic applications.[22]

The minimally invasive percutaneous intramuscular electrode[201] reduces the risk of tissue injury yet poses other safety issues, including the risk of displacement or breakage associated with anchoring of the external lead and electrode-related infection and granuloma formation secondary to retained electrode fragments. The cumulative failure rate of percutaneous electrode varies between 56% and 80%,[160,202,261] which limits the use of a percutaneous electrode to less than 3 months. Other researchers have demonstrated lower failure rates with the use of ultrafine percutaneous electrodes.[124,255] All percutaneous electrodes connect to lead wires that exit the skin and connect to the stimulator. The advantages of the percutaneous electrode are the elimination of skin resistance and cutaneous pain issues, greater

muscle selectivity, and lower stimulation currents. Percutaneous electrodes are particularly usefully in activating small, deep muscles such as the intrinsic muscles of the hand. For intramuscular electrode applications, safe stimulation parameters include charge balanced, biphasic pulses with amplitudes of 20 mA, and frequencies ranging from 10–50 Hz.[209]

Surgically implanted electrodes designed for long-term use include epimysial, epineural, intraneural, and helix (cuff) electrodes. These electrodes all require open surgical procedures. They connect to implanted lead wires and require the implantation of a stimulator that receives power and command instructions through a radiofrequency (RF) telemetry link to an external control unit (ECU). Epimysial electrodes are sutured directly to the epimysium or fascia of the target muscle.[115,300] They are particularly useful for activation of broad, superficial, or thin muscles.[152,287] Nerve-based electrodes are indicated depending on location and recruitment requirements of the target muscle.[223] Epineural electrodes are sutured to connective tissue directly surrounding the nerve; intraneural electrodes that penetrate to the intrafascicular bundles[33,133,210] are presently limited to research applications. Direct nerve stimulation is most commonly achieved via a nerve cuff electrode which, by encompassing the nerve trunk, requires approximately one-tenth of the current necessary for intramuscular stimulation.[145,211,273,276] Nerve cuff electrodes are safe and effective.[111,154,301] Complications of nerve cuff electrodes include mechanical irritation at the cuff–nerve interface and tissue growth with resultant nerve compression or blockage.[211]

There are a number of safety and biocompatibility issues related to implanted electrodes utilized in various NMES systems.[4,176] Development of the ideal electrode requires minimizing issues of lead and electrode breakage, variability in electrode placement, nerve–electrode interface complications, surgical invasiveness, and optimization of stimulus parameters to generate sufficient sustained, predictable motor force. Although NMES systems are characterized by the peripheral nerve–electrode interface, research is increasingly focusing on new technologies such as harnessing cortical control signals that may provide an enhanced means of interfacing with a neuroprosthesis to facilitate functional movement.[178]

For neuroprostheses, there is the added requirement of volitional control to carry out specific functional tasks. FES control system design presents a significant challenge to correlate user intent to functional performance. An open-loop muscle activation control pattern is characterized by a preset pattern of neuromuscular stimulation. Most clinical FES systems employ open-loop control with sensory feedback limited to residual visual and proprioceptive input. A closed-loop control system allows for continuous real-time modification of the stimulation pattern based on sensory feedback. Given the nonlinear and temporal variability of contractile muscle force, a closed-loop system modulated by sensor-derived feedback signals offers clear advantages. There are a number of potentially reliable sources of control signals including biomechanical sensors,[49,64,236] tilt sensors,[74] accelerometers,[195,257,285] gyroscopes,[257,285] myoelectric control,[296] artificial neural networks (ANNs),[98] pattern generator/pattern shaper (PG/PS) controllers,[240] biopotentials[259] via neural cuff recordings,[232,275] a proportional integral derivative (PID) controller,[237] and brain cortical activity.[134] An optimal FES control system allows for consistent and predictable response to external perturbations including changing muscle loads and internal time variations such as fatigue. Specific control systems employed in available neuroprostheses systems are presented later in this review.

A special case of an electrode/stimulator system that does not fit well into the traditional classification scheme is the injectable microstimulator,[10,302,303] which is presently undergoing clinical trials for various applications. The device is no more than 2 cm long and functions as stimulator, electrode, and receiver. The individually addressable microstimulator is injected into or near the target tissue via a minimally invasive procedure. The target tissue is within the muscle or soft tissue contiguous to a specific nerve or motor point. The first-generation device was glass-encased with an external tantalum capacitor electrode. A second-generation device is designed to be more durable and less susceptible to mechanical and electrostatic trauma.[10] The device receives power and digital command data via a single external RF coil and generates stimulation pulses of 0.2–30 mA at 4–512 μs pulse duration. A battery-powered microstimulator is presently under development.

NEUROPROSTHESES

Upper-Limb Applications. *Spinal Cord Injury.* Neuroprostheses can provide grasp and release function for individuals with a complete SCI at the cervical level to facilitate activities of daily living. The majority of upper-limb neuroprostheses are targeted for individuals with C5 and C6 motor levels. Neuroprostheses can be applied to a limited extent to the C4 motor level, but there are no clinically deployable

FIGURE 1. A hybrid brace-transcutaneous neuroprosthesis system that is worn on the hand and forearm. The exoskeleton positions the wrist in a functional position and the five transcutaneous electrodes built into the exoskeleton stimulates specific muscles to provide coordinated hand opening and closing. (NESS H200, courtesy of Bioness Inc., Santa Clarita, CA.)

systems for this population to date. For individuals with C7 or C8 motor levels there are other treatment options (such as tendon transfers) that can provide considerable enhancement of function.

All existing upper-limb neuroprostheses consist of a stimulator that activates the muscles in the upper limb, an input transducer, and a control unit. The control signal for grasp is derived from retained voluntary function. For example, a person with C5 complete tetraplegia usually has the ability to retract and protract the shoulder. A shoulder position transducer can detect this movement to generate a command signal for hand opening and closing. The user typically has control over electrically stimulated gross hand grasp opening and closing, but does not have direct control over the activation of each muscle, thus simplifying the control task required by the user.

A hand neuroprosthesis system developed in Ra'anana, Israel, incorporates transcutaneous electrodes into a brace for hand grasp and release (Fig. 1). The brace fixes the wrist in neutral, making it

applicable primarily to persons with C5 complete tetraplegia who do not have a tenodesis grasp. In a clinical study, Snoek et al.[264] evaluated 10 individuals with C5/C6 tetraplegia for fitting of the neuroprosthesis, and four participated in the functional training portion of the study. These four subjects performed at least two tasks independently using the device that they could not perform otherwise. Three of the subjects demonstrated improvement in pouring from a can and opening a bottle. Other improved tasks include shaving, putting on socks, and handling a hammer. The system has Food and Drug Administration (FDA) approval in the United States and the CE marking ("Conformite Europeene," health, safety, and environmental protection designation) in Europe.

Handa and Hoshimiya,[123] of Sendai, Japan, developed a percutaneous neuroprosthesis system that uses up to 30 percutaneous electrodes to provide palmar, lateral, and parallel extension grasp patterns. Percutaneous systems address the problems of specificity and repeatability encountered with transcutaneous stimulation systems. The implantation is minimally invasive, requiring needle insertion only with no surgical exposure. Grasp opening and closing are controlled by a switch operated by the opposite arm or by respiration using a sip/puff type of control. The system is available primarily in Japan. However, there are no studies that formally assess outcomes with respect to disability and user satisfaction.

In 1986, Peckham et al.[221] in Cleveland, Ohio, implemented the first implanted hand neuroprosthesis (Fig. 2). The system consists of 8 implanted electrodes and an implanted receiver-stimulator unit, providing lateral and palmar grasp for persons with C5 and C6 complete tetraplegia.[260] An RF inductive link provides the communication and power to the implant receiver-stimulator. The proportional control of grasp opening and closing is achieved using shoulder motion, which is measured using an externally worn joystick on the chest and shoulder.[142] The implantable system has FDA approval in the United States and the CE mark in Europe.

Of the three commercialized devices, the implanted system underwent the most extensive assessment of functional outcomes. A multicenter clinical trial evaluating 50 individuals with C5 or C6 SCI implanted with the upper-limb neuroprosthesis showed significant reduction in impairments and activity limitations.[222] More than 90% of participants are satisfied with the neuroprosthesis, and most use it regularly. Follow-up surveys indicated that usage patterns are maintained for at least 4 years postimplant.[308] Adverse events due to the implanted com-
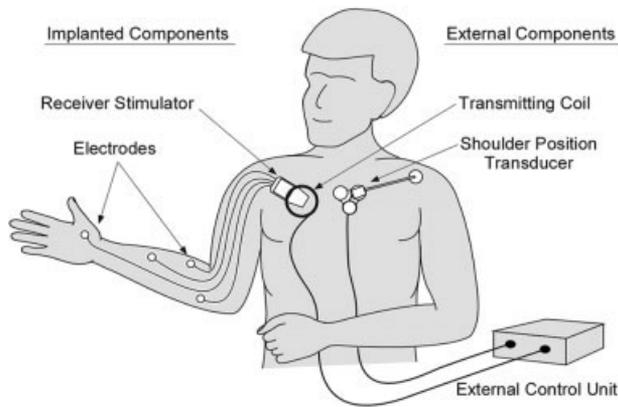
FIGURE 2. Schematic of the implantable hand neuroprosthesis system for tetraplegia. The system provides lateral and palmar grasp in response to activation of a shoulder-position transducer. The RF link provides the communication between the external control unit and the implanted stimulator. (Reproduced with permission. Chae et al. In: DeLisa J, editor. Physical medicine and rehabilitation: principles and practice. Philadelphia: Lippincott Williams & Wilkins, 2005. p 1405–1426. © 2005 Lippincott Williams & Wilkins.)

ponents and surgical installation are few. The infection rate is less than 2%. There are no cases of neuroprosthesis failure and less than 1% lead failures. Although the device is safe and clinically effective, the system is no longer commercially available. Reasons for this are complex and beyond the scope of this review. Cost, limited market, function limited to the hand, and insufficient "buy-in" by the rehabilitation community are all possible contributory factors.

New research in upper-limb neuroprostheses focuses on stimulation of additional muscles, implementation of new control methods, and incorporation of advanced technologies in order to broaden clinical indications and facilitate clinical implementation. Stimulation of triceps,[43] pronator quadratus,[182] and finger intrinsics[177] increases work space and enhances overall upper-limb and hand function. The incorporation of alternative command source strategies including wrist position,[125] activation of voluntary antagonists to control elbow angle and forearm supination/pronation,[182] myoelectric signal from either forearm or neck muscles,[159] and cortical control[306] are under investigation. The incorporation of advanced technologies such as implanted control transducers,[143] new electrode technology,[118] and use of devices that minimize surgical invasiveness[190] may further facilitate clinical implementation and enhance effectiveness. Finally, studies demon-

strate the feasibility of neuroprostheses for high tetraplegia (C2–4).[23,122]

Stroke. In view of the success of the hand neuroprosthesis in tetraplegia,[222] it is reasonable to apply the technology to persons with hemiplegia. However, review of the literature reveals only five full-length publications in English-language peer-reviewed journals that evaluate the effectiveness of a hand neuroprosthesis for enhancing the upper-limb function of stroke survivors. Two reports utilized customized transcutaneous electrical stimulation systems,[203,238] two utilized the previously described transcutaneous electrical stimulation-brace hybrid system,[5,6] and one utilized a percutaneous intramuscular electrical stimulation system (Fig. 3).[58] All studies used limited sample sizes and open-label designs with performance evaluated with and without the neuroprosthesis.

These reports share several common themes. The ability of the neuroprostheses to provide clinically relevant improvement is limited to a small number of selected functional tasks. When the limb is in a resting position, the various systems open and close the hand without difficulty. However, when patients are asked to perform a specific functional task a great deal of mental and physical effort is required, which is often associated with an increase in generalized hypertonia. In the face of increased hypertonia, neuroprostheses do not open the hand effectively or reliably.

At the present time a clinically viable hand neuroprosthesis system is not available for persons with hemiparesis and additional research is required. A
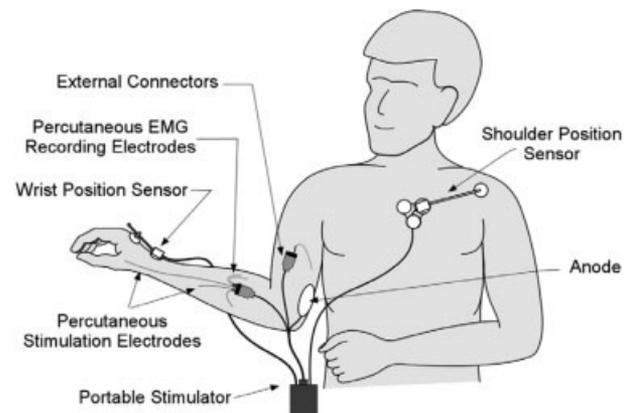
FIGURE 3. Schematic of a percutaneous hand neuroprosthesis system for hemiplegia. The RF link with the stimulator shown in Figure 2 is now replaced by direct percutaneous connection. Three control options of shoulder transducer, wrist joint angle transducer, and EMG controller are illustrated. However, only one control method is used at any one time. (Reproduced with permission. Chae J, Hart R. Neurorehabil Neural Repair 2003; 17:109–117. © 2003 SAGE.)
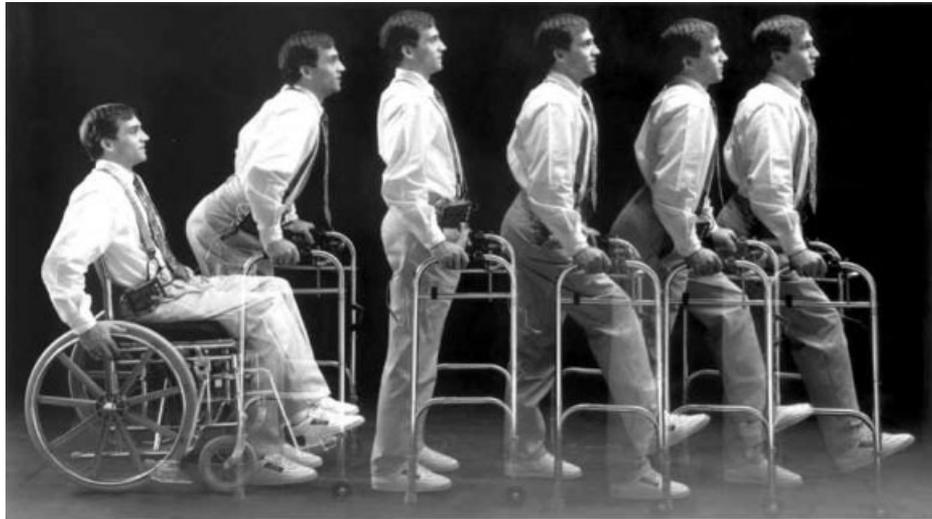
FIGURE 4. A transcutaneous multichannel neuroprosthesis system allows persons with paraplegia unbraced ambulation for home and short community distances. (Parastep I System User, courtesy of Sigmedic Inc., Fairborn, OH.)

clinically deployable system must demonstrate the ability to: (1) facilitate bilateral tasks, (2) provide proximal and distal control, (3) have sufficient miniaturization to not interfere with ambulation, (4) utilize control paradigms that produce effortless movement of the impaired upper limb without compromising the function of the intact limb, and (5) "turn off" overactive muscles as well as stimulate weak muscles.[58]

Lower-Limb Applications. *Spinal Cord Injury.* Multichannel transcutaneous electrical stimulation systems are successful in producing standing and stepping for persons with complete SCI. These systems are relatively simple, consisting of 2–6 channels of continuous stimulation.[116,140,168,310] Systems employing percutaneous intramuscular electrodes allow for more complex movements[196] and can provide simple mobility and one-handed reaching tasks.[162,286] A cochlear implant modified to stimulate motor neurons[78] and a 12-channel system for activation of the L2-S2 motor roots[86] have been used for exercise and standing in a limited number of volunteers. For long-term clinical application, implanted systems such as these provide major advantages over transcutaneous and percutaneous systems including convenience, cosmetic benefit, reliability, and repeatability.

The pioneering work in the application of neuroprostheses for restoration of standing and walking for individuals with complete and incomplete SCI conducted in the 1970s and 1980s continues to be employed in many laboratories and clinics around the world.[14,168] Standing is achieved by simultaneously activating both sets of quadriceps in response to a command input. A stride is produced by maintaining activation to the quadriceps of the stance leg while initiating a flexion withdrawal in the contralateral limb.[155,295] To complete the stride, activation of the knee extensors on the swinging limb is initiated while the reflex is still active and flexing the hip. These implementation procedures for standing and stepping with transcutaneous stimulation are incorporated in a system that has FDA approval (Fig. 4).[105,116] However, complicating issues include poor standing posture due to hip flexion generated by the rectus femoris when the quadriceps are stimulated, lack of or habituation of a strong flexion withdrawal reflex, and difficulty in controlling the swing limb motion due to the mass flexion response of the reflex.

With the assistance of the neuroprosthesis, many persons with neurologically incomplete spinal cord lesions can become functional ambulators because some degree of motor, sensory, and proprioception function is preserved. NMES augment muscle contraction increases stride length and reduces physiologic cost index during walking. In some patients exaggerated extensor tone provides safe standing, but does not facilitate step initiation. In these patients peroneal nerve stimulators may inhibit extensor tone and help to initiate a step.[13,169] When necessary, hip abductors, hamstrings, and trunk extensors are included in the stimulation patterns.[114] Nevertheless, the high neurologic variability of the incomplete SCI population requires caution in the application of neuroprostheses.

These approaches have implications for implanted lower-limb systems. However, implanted systems activate individual muscles rather than relying on the flexion withdrawal reflex or extensive bracing. Complex lower-limb motions are synthesized by activating up to 48 separate muscles with chronically indwelling percutaneous intramuscular electrodes. Some well-trained subjects are able to walk 300 m repeatedly at 0.5 m/s with this system.[163] However, implanting and maintaining a system consisting of a large number of percutaneous electrodes is not practical. Therefore, implantable receive-stimulators are used as a platform for clinical trials of walking system for persons with complete and incomplete thoracic SCI. A multicenter clinical trial of a lower-limb neuroprosthesis system that utilizes a single implanted 8-channel device for standing and transfers is presently under way.[77] A 16-channel lower limb implanted system is also presently under investigation (Fig. 5).[165]

Hybrid systems employing various brace and stimulation components are reliable and relatively simple to implement in clinical environments with orthotic and prosthetic fabricating capacity. These systems are fitted to patients with complete or incomplete paraplegia.[146,197,265,266] One design combines a Louisiana State University Reciprocating Gait Orthosis (LSU-RGO) with a 4-channel transcutaneous stimulator and a flexible copolymer electrode cuff. Follow-up studies on RGO-based hybrid orthoses show that up to 41% of system recipients use it for gait[101] and 66% use it for exercise.[267] Standing with the knee joints of the brace locked allows stimulation to be discontinued, thus postponing the onset of fatigue. The orthotic components of these systems may also protect the insensate joints and osteoporotic bones of users with long-standing SCI from possible damage resulting from the loads applied during weight-bearing and ambulation. Other more recent developments include hybrid FES with a medial-linkage knee–ankle–foot orthosis,[254] energy storage orthosis,[90] more energy-efficient and cosmetically accepted hip–knee–ankle orthosis,[206,251] and implantable multichannel FES with trunk–hip–knee–ankle foot orthosis.[164]

In summary, the inherent value of lower-limb neuroprosthesis systems for persons with SCI in their current forms is in the ability to provide short-duration mobility-related tasks, such as overcoming physical obstacles or architectural barriers and exercise. The literature suggests that ambulation with lower-limb neuroprosthesis is an option for short distances but is unlikely to be an alternative to a wheelchair. The metabolic energy currently required to walk
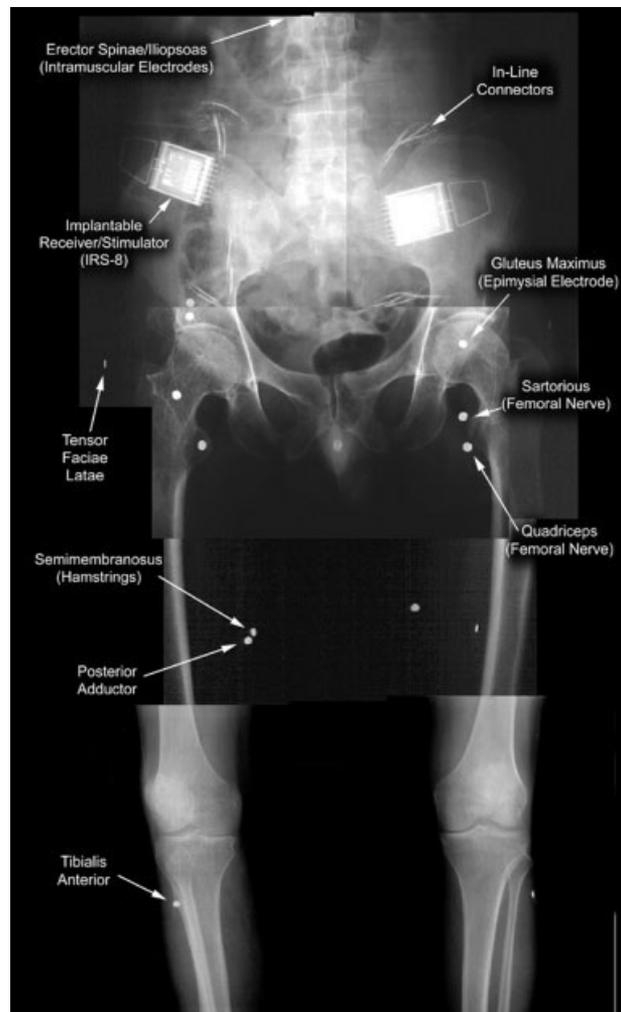
FIGURE 5. A radiograph of a 16-channel implanted lower-limb mobility neuroprosthesis system for paraplegia. (Reproduced with permission. Kobetic et al. IEEE Trans Rehabil Eng 1999;7: 390–398. © 1999 IEEE.)

with a neuroprosthesis is too high to make it a practical alternative to the wheelchair for long-distance transportation over level surfaces, although this remains a worthwhile and achievable long-term goal.

Stroke. The initial application of neuroprostheses in hemiplegia focused on transcutaneous peroneal nerve stimulation to treat ankle dorsiflexion weakness. In a 1961 publication, Lieberson et al.[187] described a stimulator that dorsiflexes the ankle during the swing phase of gait. In the only randomized study of transcutaneous peroneal stimulation, Burridge et al.[46] reported that stroke survivors treated with the device exhibit significantly greater increase in walking speed with the device relative to baseline without the device, whereas the control group does not. However, despite demonstrated effectiveness, transcutaneous peroneal
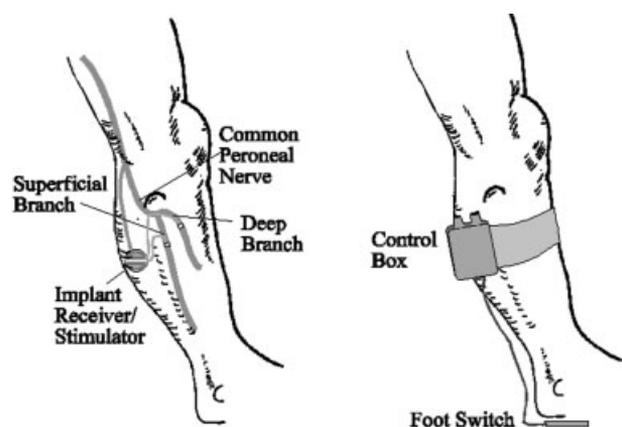
FIGURE 6. Three FDA-approved transcutaneous peroneal nerve stimulators. The Odstock Dropped Foot Stimulator (top left, courtesy of Department of Medical Physics and Biomedical Engineering, Salisbury District Hospital, Salisbury, UK.) and the wireless NESS L300 (right, courtesy of Bioness Inc., Santa Clarita, CA) both use a heel switch to trigger ankle dorsiflexion. The WalkAide (Bottom left, courtesy of Hanger Orthopedic Group/Innovative Neurotronics, Bethesda, MD) uses a tilt sensor to trigger ankle dorsiflexion.

nerve stimulation is not routinely prescribed in the United States for footdrop in hemiplegia. Likely reasons are difficulty with electrode placement, insufficient medial–lateral control during stance phase, lack of technical support, and the availability of custom-molded ankle–foot orthoses. Nevertheless, recent FDA approval of three surface peroneal nerve stimulators (Fig. 6) and demonstrated comparability of the peroneal nerve stimulator to an ankle–foot orthosis in improving hemiplegic gait[252] may facilitate broader clinical prescription and usage of these devices.

Implantable systems may address the difficulties associated with transcutaneous systems. An early study by Waters et al.[299] reported a significant increase in walking speed, stride length, and cadence with a single-channel implantable device relative to preimplantation performance. However, technical limitations include difficulty in balancing inversion and eversion, lack of an in-line connector, which necessitates removal of the entire implant in the event of component failure, and poor reliability of the heel switch and foot-floor contact transmitter. Kljajic et al.[158] also reported significant benefit of a single-channel implantable stimulator. However, nearly half of all subjects require reimplantation due to electrode displacement or failure. At present, two multichannel implantable peroneal nerve stimula-

tors are undergoing clinical investigations in Europe. A dual channel device developed at the University of Twente and Roessingh Research and Development (The Netherlands) stimulates the deep and superficial peroneal nerves for better control of eversion and inversion (Fig. 7).[148] A four-

FIGURE 7. A two-channel implantable peroneal nerve stimulator (STIMuSTEP) allows individual stimulation of the deep and superficial branches of the common peroneal nerve for eversion-inversion balance. (Courtesy of Department of Medical Physics and Biomedical Engineering, Salisbury District Hospital, Salisbury, UK.)

channel device, developed at Aalborg University (Denmark) utilizes a nerve cuff with four tripolar electrodes, oriented to activate different nerve fibers within the common peroneal nerve.[44] Both devices have the CE mark in Europe. Finally, an injectable microstimulator, which is percutaneously placed via a minimally invasive procedure, is also under investigation for the correction of foot drop.[303]

In order to address gait deviations due to deficits proximal to the ankle, several studies have evaluated multichannel transcutaneous systems.[29,30,271] However, although these systems were clinically implemented as neuroprostheses, neuroprosthetic outcomes were not assessed. Instead, these studies focused on therapeutic or motor relearning effects and therefore are discussed in the section on motor relearning.

In summary, although the development of lower-limb neuroprostheses for hemiplegia is further along than upper-limb systems, several issues presently limit their clinical implementation. First, transcutaneous systems are limited by discomfort and difficulty with electrode placement for reliable muscle contraction. Percutaneous and implanted systems may address these issues, but potential benefits must be tempered with the risks and costs associated with an invasive procedure. Second, the indications for the level of complexity required for a specific individual remain undefined. Some individuals will require complex multichannel systems, whereas simple dorsiflexion assist devices will suffice for others. Third, it remains unclear as to when the motor relearning period ends and the indication for FES for neuroprosthetic purposes begins. Nearly all studies in this review report some evidence of motor relearning, even among chronic stroke survivors. Finally, clinical relevance must be established by evaluating the effects of the intervention on mobility and quality of life, and by comparing the neuroprosthetic system to a comparable standard of care such as the ankle–foot orthosis. Despite these issues, there are sufficient data to justify pursuit of large, multicenter, randomized clinical trials to demonstrate the clinical efficacy of simple transcutaneous peroneal nerve stimulators for ankle dorsiflexion assist. The development of more sophisticated implanted systems that activate multiple muscles is presently under investigation and should be pursued further.

Bladder Neuroprosthesis. Patients with suprasacral spinal cord lesions can have electrical stimulation applied to the intact sacral nerves or nerve roots to produce effective micturition and improve bowel function,[141] significantly reducing complications

and costs of bladder and bowel care.[71] An implantable device for this purpose used by over 2,000 patients in at least 20 countries is presently FDA-approved in the United States and has the CE mark in Europe (Fig. 8).[41,289] Micturition by electrical stimulation requires intact parasympathetic neurons to the detrusor muscle. The function of these neurons is demonstrated by reflex detrusor contractions on a cystometrogram. Patients are implanted at any time after reaching neurologic stability. They should also have an appropriate degree of emotional and social stability. Frequent urinary tract infections and problems tolerating catheters or anticholinergic medication are further indications. Electrodes are placed either intradurally on the sacral anterior nerve roots in the cauda equina via a lower lumbar laminectomy, or extradurally on the mixed sacral nerves in the sacral canal via a laminectomy of S1–3.[72] Intraoperative electrical stimulation and recording of bladder pressure is used to confirm the identity of the nerves supplying the bladder. Leads from the electrodes are tunneled subcutaneously to a radio-receiver/stimulator placed under the skin of the abdomen or chest and powered and controlled by a battery-powered remote control operated by the patient. Posterior rhizotomy is performed to abolish detrusor hyperreflexia and eliminate reflex incontinence. Postoperatively, urodynamic studies are used to guide the setting of stimulus parameters to give an acceptable voiding pressure and rate and pattern of flow. The stimulus program is checked between 1 and 3 months after surgery since the response of the bladder may change with repeated use; thereafter, review is recommended at least annually, monitoring lower and upper urinary tract function.[59]

The majority of patients with an implanted bladder neuroprosthesis use the device routinely for micturition 4–6 times per day. Urodynamic studies show substantial increases in bladder capacity and compliance following posterior rhizotomy.[191,291] Residual volumes in the bladder following implant-driven micturition are usually less than 60 ml and often less than 30 ml.[288,289] The use of the implant is associated with significant reduction in the incidence of symptomatic urinary tract infections.[42,68,193,289] Continence is achieved in over 85% of patients,[92,290] although 10%–15% report some stress incontinence of urine following the procedure.[191] Several centers in Europe have long-term follow-up experience with the device, particularly with regard to the upper tracts.[243,288,289,291] Trabeculation, ureteric reflux, and hydronephrosis tend to decrease in patients who undergo implantation and posterior rhizotomy. There is also a reduction in the incidence of auto-
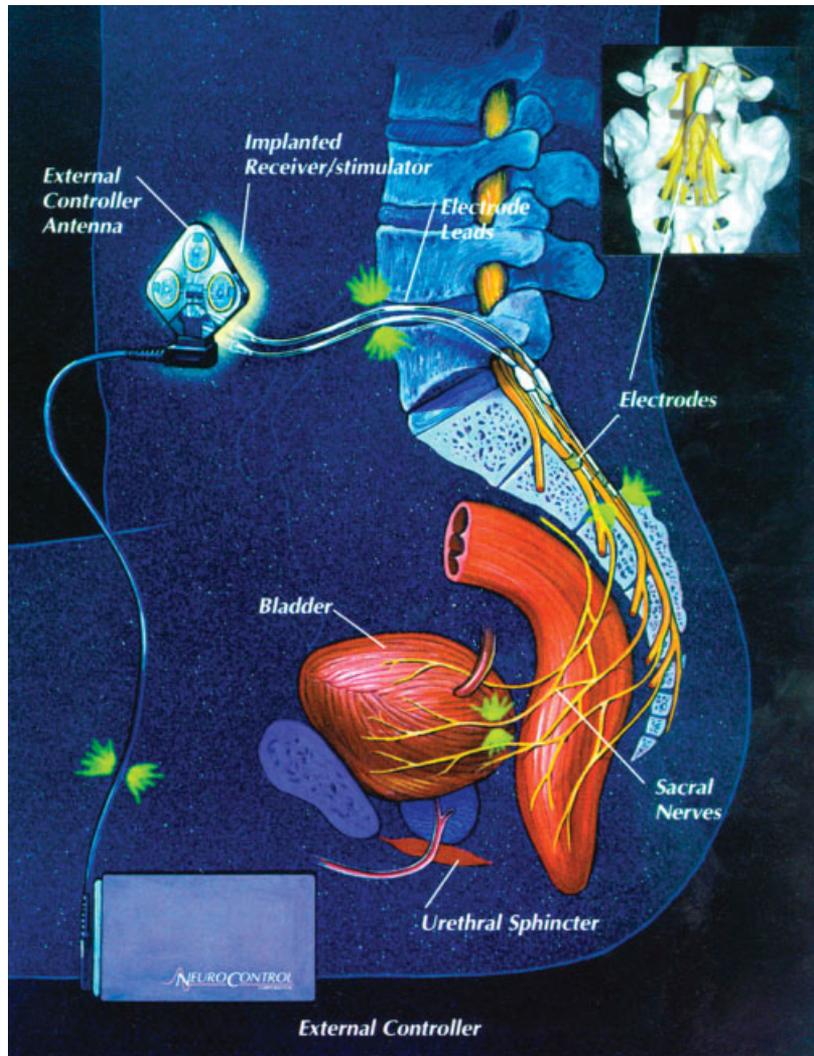
FIGURE 8. The implanted bladder neuroprosthesis system (Vocare, courtesy of NeuroControl, North Ridgeville, OH).

nomic dysreflexia due to the interruption of afferent fibers from the bladder. Reduction of urinary tract infection results in substantial reduction in antibiotic usage. Regular stimulation of the sacral parasympathetic nerves contributes to transport of stool through the distal colon into the rectum, and most users report a reduction in constipation and the need for laxatives and stool softeners.[192] Finally, studies in Europe and the USA indicate that the use of the implanted stimulator together with posterior sacral rhizotomy results in substantial savings in the cost of bladder and bowel care, particularly from reduction in supplies needed for bladder care, medications, and visits to physicians for management of complications.[71,73,304]

Infection of these implants is rare, occurring in 1% of the first 500 implants. Infection is usually introduced at surgery or through a subsequent break in the skin. However, a technique of coating the implants with antibiotics reduces the infection rate.[247] Technical faults in the implanted equipment are uncommon, occurring on average once every 19.6 implant-years.[41] The most common sites for faults are in cables, which are repaired under local anesthesia.

In summary, electrical stimulation of the sacral parasympathetic nerves restores effective micturition for persons with suprasacral spinal cord damage, reducing urinary tract infections and the use of catheters. It is often combined with posterior sacral rhizotomy to increase bladder capacity and abolish reflex incontinence and sphincter contraction. The rhizotomy also reduces the risk of renal damage and autonomic dysreflexia, and the use of anticholinergic medication and urine collection devices; however, it also abolishes reflex erection and reflex ejac-

ulation, which may need to be provided by alternative techniques. Overall, these interventions dramatically improve bladder and bowel function, reduce complications and costs, and increase quality of life after spinal cord injury.

Although the implanted neuroprosthesis is clearly effective in providing urine storage and micturition, the need for a rhizotomy dampens the level of enthusiasm among both clinicians and patients. In order to address this issue, various groups are investigating alternative means of reducing detrusor hyperactivity. Sensory neuromodulation via stimulation of the dorsal penile/clitoral nerve increases bladder capacity among patients with SCI[8] and multiple sclerosis.[249] However, the approach does not abolish reflex sphincter contractions. Thus, other investigators focus on direct blockage of nerve impulses via high-frequency electrical stimulation. Although this approach is still at the level of animal experimentation, its clinical implications reach far beyond the bladder application[24] and may include management of the broader problems of spasticity and pain.[25,151] Other forms of neuromodulation to treat uninhibited bladder contractions are reported in the literature.[241] However, these are generally applied to able-bodied populations and thus are not included in this review.

Respiratory Neuroprostheses. Phrenic nerve pacing has been applied to more than 1,200 patients worldwide and is now a clinically accepted technique to provide artificial ventilatory support in patients with trauma, with respiratory failure secondary to cervical SCI.[108,109,112,136,137,284] There are several commercially available phrenic nerve pacing systems, but each system has a similar configuration. The stimulating electrodes are implanted directly on each phrenic nerve. Small wires tunneled subcutaneously connect the electrodes to an RF receiver, which is implanted in an easily accessible area over the anterior portion of the thorax. External antennas connect to the transmitter. The transmitter generates an RF signal, which is inductively coupled to the implanted receiver. The signal is demodulated by the receivers, which converts it to electrical signals, and then delivered to the stimulating electrodes. Bilateral phrenic nerve stimulation results in descent of each diaphragm and decrease in intrathoracic pressure resulting in inspiration. Cessation of stimulation results in diaphragm relaxation, an increase in intrathoracic pressure, and exhalation.

All potential candidates must demonstrate intact phrenic nerves on nerve conduction studies. They must be free of significant lung disease or primary muscle disease. Patients' psychosocial conditions are also important considerations. Before any technical assessment a critical evaluation of the motivation of both the patient and family members is mandatory. The patient should also have a clear understanding of the potential benefits to be achieved.

Electrodes are positioned around the phrenic nerve in either the cervical region or within the thorax.[108,110,112] Although the thoracic approach requires a thoracotomy, this is the preferred approach, as the cervical approach has the risk of not being able to stimulate the entire nerve.[100,293] An RF receiver is positioned in a subcutaneous pocket on the anterior chest wall. Wires from the electrode are passed through the 3rd or 4th intercostal space and connected to the receiver. Postimplantation, the diaphragm must be gradually reconditioned to improve strength and endurance.[111] During the conditioning phase the patient must be monitored for signs of fatigue, which is usually manifested by the patient's complaint of shortness of breath or reduction in inspired volume.

Although a number of complications have been reported since phrenic nerve pacing was first introduced, technical developments and patient experience have markedly reduced their incidence.[85,107] Nevertheless, all patients require a back-up mechanical ventilator in the event of pacemaker failure. Reported modes of failure include (1) low battery charge, (2) antenna wire breakage, (3) iatrogenic injury to the phrenic nerve, (4) postimplantation adverse tissue reaction and scar tissue formation, (5) device infections, (6) collapse of the upper airway or obstructive apnea due to diaphragm contraction without coincident contraction of the upper airway muscles, and (7) in children, reduction in inspired volume due to paradoxical movement of the rib cage.

Phrenic nerve pacing is clearly an effective means of providing ventilatory support with significant advantages over mechanical ventilation.[108,109,112] Unfortunately, there are few recent analyses of modern-day success rates and incidence of side effects and complications. A long-term follow-up study of 14 tetraplegic patients who use bilateral low-frequency stimulation reported successful use of the device for as long as 15 years, with a mean use of 7.6 years.[107] A more recent study of 64 patients (45 tetraplegic patients) who underwent phrenic nerve pacing for a mean of 2 years showed the incidence of electrode and receiver failure as 3.1% and 5.9%, respectively, which is significantly lower than earlier reports. At this time there are no controlled studies relative to mechanical ventilators. However, it is possible that phrenic nerve pacing improves life expectancy in

patients with tetraplegia. Carter et al.[51] reported only 63% survival at 9 years for patients on positive pressure ventilation. In contrast, all 12 tetraplegic patients who completed the Yale phrenic nerve pacing protocol were alive after 9 years.[93]

Phrenic pacing provides important health and lifestyle benefits relative to mechanical ventilation. However, many patients with ventilator-dependent tetraplegia cannot be offered phrenic nerve pacing due to partial or complete injury of one of the phrenic nerves. Combined intercostal and unilateral diaphragm pacing may be a useful therapeutic modality in selected patients with only unilateral phrenic nerve function.[84] Conventional placement of phrenic nerve electrodes carries the risk of phrenic nerve injury and generally requires a thoracotomy, which is a major surgical procedure with associated risk, in-patient hospital stay, and high cost. Preliminary results suggest that intramuscular diaphragm pacing provide similar benefits as conventional phrenic nerve pacing without the need for an invasive surgical procedure and less risk of phrenic nerve injury.[83] The laparoscopy guided procedure is performed on an outpatient basis and is therefore less costly. The development of fully implantable intramuscular diaphragm system will eliminate the need for the application of devices on the body surface and the risk of decoupling between the transmitter and receiver.

NMES FOR MOTOR RELEARNING

Evolving basic and clinical studies on central motor neuroplasticity support the role of goal-oriented, active repetitive movement training of a paretic limb to enhance motor relearning. Asanuma and Keller[12] demonstrated that electrical stimulation of the somatosensory cortex alone or in conjunction with thalamic stimulation in an animal model induces long-term potentiation (LTP) in the motor cortex. They hypothesized that proprioceptive and cutaneous afferent impulses associated with repetitive movements induce LTP in the motor cortex, which then modify the excitability of specific motor neurons and facilitate motor relearning.[11] Consistent with this hypothesis, nonhuman primate research has demonstrated that after local damage to the motor cortex, goal-oriented, active repetitive movement training of the paretic limb shapes subsequent functional reorganization in the adjacent intact cortex, and that the undamaged motor cortex plays an important role in motor relearning.[214] Specific types of behavioral experiences that induce long-term plasticity in motor maps are repetitive movements that entail the development of new motor skills. That is, the motor tasks are new and therefore "require" significant cognitive effort to complete.[213] When animals are trained to perform new tasks such as retrieving food pellets from a small well[212,215,230] or a rotating well,[157] there is evidence of task-specific cortical reorganization. However, repetitive movement tasks that do not require new skill acquisition (i.e., motor tasks that are already mastered and therefore are easy to carry out and require minimal or no cognitive effort) are not associated with any significant changes in the motor cortex.[157,230]

If goal-oriented, repetitive movement therapy facilitates motor relearning, it is possible that electrical stimulation–mediated goal-oriented repetitive movement therapy also facilitates motor relearning. Acute administration of electrical stimulation to a peripheral nerve activates both sensory and motor structures in the brain[82,270] and reduces intracortical inhibition.[229,239] Functional magnetic resonance imaging (fMRI) studies show activation of the contralateral somatosensory cortex and bilateral supplementary motor areas in response to NMES-mediated wrist extension activity,[120] as well as a dose–response relationship between fMRI and NMES of the lower-limb muscles.[262] These data suggest that repetitive movement therapy mediated by NMES has the potential to facilitate motor relearning via cortical mechanisms.

It is also possible that electrical stimulation facilitates motor relearning via spinal mechanisms. Rushton[246] theorized that the corticospinal–anterior horn cell synapse is a Hebb-type, modifiable synapse and that the synapse can be modified by NMES. "Hebb's rule" proposed in 1949 by Donald Hebb[126] states: "When an axon of cell A. . .excite[s] cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency as one of the cells firing B is increased." The synapse is thought to be strengthened by the coincidence of presynaptic and postsynaptic activities. Under normal circumstances neural activity in the pyramidal tract easily discharges the anterior horn cells and the strength of the presumed Hebb-type pyramidal tract/anterior horn cell synapse is maintained by this traffic. However, following brain injury, neural activity in the pyramidal tract is significantly reduced. Failure to restore this traffic leads to "decorrelation" of presynaptic and postsynaptic activities, which weakens the synapse. Rushton suggested that NMES-mediated antidromic impulses provide an artificial means to synchronize presynaptic and postsynaptic activity in the affected population of anterior horn cells. Accord-

ingly, he predicted that combining NMES with simultaneous voluntary effort is an effective means of facilitating motor relearning.

This article limits the review of NMES effectiveness in enhancing motor relearning to the stroke population. Although there is evidence of the role of NMES in facilitating motor relearning in SCI, the breadth and depth of this literature is limited.[199] NMES can be used by patients with hemiparesis who do not have enough residual movement to take part in volitional, active repetitive movement therapy. Regardless of cortical or spinal mechanisms, the experimental and theoretical considerations suggest that the necessary prerequisites for NMES-mediated motor relearning include repetition, novelty of activity, concurrent volitional effort, and high functional content.

Three types of electrical stimulation are available for motor relearning: cyclic NMES, electromyography (EMG)/biofeedback-mediated NMES, and neuroprostheses. Cyclic NMES activates paretic muscles at a set duty cycle for a preset time period. The patient is a passive participant and does not require a cognitive investment, in the form of either initiation of muscle contraction, interpretation of afferent signals, or functionality of motor task. The second type of NMES includes EMG or biofeedback-mediated electrical stimulation, which couples afferent feedback to NMES-induced repetitive movement therapy. These techniques may be applied to patients who can partially activate a paretic muscle but are unable to generate sufficient muscle contraction for adequate exercise or functional purposes. Whereas the patient is a passive participant when using cyclic NMES, EMG or biofeedback-mediated NMES requires greater cognitive investment, which may result in greater therapeutic benefit. The third type of NMES includes neuroprosthetic applications that provide FES. In this strategy repetitive movement training is performed in the context of meaningful, functional behavioral tasks and has a theoretical advantage over both cyclic and EMG/biofeedback mediated NMES.

Upper-Limb Applications. There are four randomized clinical trials investigating the efficacy of cyclic NMES in enhancing upper-limb motor relearning.[56,234,268,269,307] Note that the two studies by Sonde et al.[268] refer to the same study with the 1998 publication reporting end of treatment results and the 2000 publication[269] reporting 3-year follow-up results. All four studies reported improved outcomes in motor impairment at the end of treatment, with mild to moderately impaired subjects benefiting most. Among the three studies that provided follow-up data, the two acute stroke studies reported enduring effects,[56,234] whereas the one chronic study did not.[269] All four studies evaluated activity limitation. However, only two of these reported improvements at the end of treatment,[234,307] and the one study with follow-up data demonstrated no enduring effect on activity limitation.[234]

In the most methodologically sound of the four studies, Powell et al.[234] reported that isometric wrist extension torques were significantly higher for the treatment group at the end of treatment and at 32 weeks. The grasp and grip subscores of the Action Research Arm Test were significantly higher for the treatment group at the end of treatment, but not at 32 weeks. A post-hoc subset analysis indicated that the intervention was most effective for those with residual wrist extension torque at study entry.

The strengths of these studies rest on their randomized designs. However, numerous methodological limitations render the results difficult to interpret. Two of four studies were not blinded.[268,269,307] Of the two blinded studies, only one was double-blinded.[56] Three of four studies reported unequal treatment intensity where the treatment group received NMES and "therapy," while the control group received only "therapy."[234,268,269,307] Of the two studies with follow-up data, the one study with a significant drop-out rate did not use intent-to-treat analysis.[56] Although methodological limitations prevent formulation of definitive conclusions, these four randomized trials do suggest that cyclic NMES enhances the upper-limb motor relearning of stroke survivors. The effect appears to be more significant and enduring for acute stroke survivors and for those with milder baseline impairments. The effect of cyclic NMES on activity limitations, however, remains uncertain.

There are six controlled trials using EMG biofeedback, position, or EMG-triggered NMES for upper-limb motor relearning.[34,54,55,102,156,166] All six studies demonstrated improved outcomes in motor impairment at the end of treatment. In the one study with follow-up data, the effect was enduring after 9 months of follow-up.[166] In the two studies that evaluated activity limitation, improved outcomes were noted.[102,156] Finally, three studies reported evidence of central mechanisms using neurophysiologic assays such as reaction time and fMRI.[54,55,156]

In the most recent of the six studies, Kimberly et al.[156] evaluated 16 chronic stroke survivors in a double-blinded, randomized clinical trial. The treatment group received 60 hours of NMES therapy over a 3-week period applied to the extensor muscles of the hemiplegic forearm to facilitate hand opening. Half

of the 60 hours were devoted to EMG-triggered NMES and the other half to cyclic NMES. The control group received sham treatment, but participants were asked to extend the finger in a repetitive manner. The EMG-triggered NMES group demonstrated significant improvements in measures of grasp and release of objects (box and block test and Jebsen Taylor hand function), isometric finger extension strength, and self-rated activity limitation (motor activity log). In addition, using fMRI and a finger-tracking task, an index of cortical intensity in the ipsilateral somatosensory cortex (relative to hemiparetic limb) increased significantly from pretest to posttest following treatment. The participants receiving sham treatments did not improve on any of the outcome measures except isometric finger extension strength.

Unfortunately, as with the cyclic NMES studies, numerous methodological deficiencies limit the interpretation of results. Only two of six studies[102,156] used blinded assessments. Five of the six studies did not include follow-up evaluations.[34,54,55,102,156] The one study with long-term follow-up did not use a randomized design.[166] Only one study was double-blinded.[156] In all studies, demographic or baseline differences between groups were present or differences could not be assessed. One of the two studies that reported improvements in activity limitation used a modified version of the self-care component of the Functional Independence Measure with unknown psychometric properties.[102] Finally, all studies used small sample sizes. As with cyclic NMES, methodological limitations prevent formulation of definitive conclusions regarding the effectiveness of EMG or biofeedback-mediated NMES. Nevertheless, data suggest that such NMES reduced upper-limb motor impairment and these changes, to at least some degree, translated into improvements in activity limitations.

Finally, hand neuroprostheses may facilitate motor relearning. Studies evaluating hand neuroprostheses for persons with hemiplegia were reviewed earlier.[5,6,58,203,238] Although the primary objective of these earlier studies was to demonstrate a neuroprosthetic effect, nearly all reported some evidence of improved motor ability when the device was turned off. More recent studies used neuroprostheses to specifically demonstrate a motor relearning effect. Alon et al.[7] reported on 77 chronic stroke survivors treated with a home-based training program using the previously described hybrid brace-NMES neuroprosthesis. After 5 weeks of training, significant improvements in motor impairment and activity limitations were noted relative to baseline. In the only

controlled trial of an upper-limb neuroprostheses as a motor relearning tool, Popovic et al.[231] reported that performing intensive exercises with the assistance of a neuroprosthesis resulted in significant improvement in upper-limb motor function in acute hemiplegia.

Lower-Limb Applications. A limited number of studies have explored the potential motor relearning effect of NMES in the lower limb. As noted earlier, Lieberson et al.[187] described the first single-channel transcutaneous peroneal nerve stimulator to provide ankle dorsiflexion during the swing phase of gait. However, they also commented that, "On several occasions we observed, after training with the electrophysiologic brace [peroneal nerve stimulator] . . .patients acquire the ability of dorsiflexing the foot by themselves." Since then, numerous case series using either implanted or transcutaneous systems have described similar observations of improved ambulation function, more normal EMG muscle activation patterns, emergence of EMG signals in previously silent muscles, increased strength of EMG activity, and decreased co-contraction of antagonist muscles.[48,158,272,278,279,283,299] The role that voluntary drive plays on motor relearning in repetitive electrical stimulation has been explored.[150] However, to date there are no blinded randomized clinical trials evaluating the motor relearning effects of a peroneal nerve stimulator during ambulation training.

Merletti et al.[204] demonstrated increased dorsiflexion moments in hemiparetic subjects treated with cyclic peroneal nerve stimulation. Studies of stroke patients treated with lower-limb NMES have demonstrated enhanced walking ability, increased maximal isometric contraction of the ankle dorsiflexors and plantarflexors, increased dorsiflexion torque, increased agonist EMG activity, and decreased EMG co-contraction ratios.[184,309] EMG-triggered NMES of the lower limb is associated with increases in voluntary EMG activity and mobility.[99] FES combined with biofeedback is associated with improvements in knee and ankle joint angles, ambulation velocity, symmetry in stance phase, and cycle time.[69] Finally, Burridge et al.[45] reported that after an extended period of use of a transcutaneous peroneal nerve stimulator, a subset of subjects no longer needed the device due to improved ankle control, thought to be secondary to motor relearning.

Since gait deviation in hemiplegia is not limited to ankle dysfunction, several studies have investigated multichannel transcutaneous stimulation systems. Stanic et al.[271] reported significant improve-

ments in qualitative and quantitative measures of gait after training with a 6-channel transcutaneous neuroprosthesis system, which provided ankle dorsiflexion, eversion, and plantarflexion, knee flexion and extension, and hip extension and abduction. Bogataj et al.[30] reported similar findings with a 6-channel NMES system, which provided ankle dorsiflexion and plantarflexion, knee extension and flexion, and hip extension. There was sufficient motor relearning effect to allow all subjects to continue with gait training without the neuroprosthesis. Bogataj et al.[29] also reported a controlled trial of a multichannel transcutaneous neuroprosthesis system for hemiplegic gait. They reported significantly greater improvements in gait performance and motor function among participants treated with the neuroprosthesis for 3 weeks compared with those treated with conventional therapy.

As the number of electrodes increases, transcutaneous systems become more difficult to implement clinically. Reduced muscle selectivity, poor reliability of stimulation, and pain of sensory stimulation further limit the practicality of multichannel transcutaneous lower-limb systems. Accordingly, Daly et al.[76] are investigating a multichannel percutaneous system to facilitate lower-limb motor relearning and mobility. In a single-blinded randomized clinical trial, chronic stroke survivors receiving percutaneous NMES treatments demonstrated significant improvements in gait components and knee flexion coordination relative to controls who did not receive NMES.[75]

Summary and Future Directions. Despite the numerous methodological limitations of controlled trials to date, the weight of the scientific evidence still suggests that NMES-mediated repetitive movement therapy reduces motor impairment in hemiplegia. There is some evidence that the effect is enduring and translates into clinically relevant improvements in hemiparetic arm-specific activity limitation. Although there are theoretical bases for expecting that EMG-triggered NMES is more effective than cyclic NMES, there are no direct comparison studies demonstrating the superiority of one over the other. Similarly, there is limited experimental evidence that neuroprostheses facilitate motor relearning. However, due to the high functional content, neuroprostheses may have enhanced efficacy compared to cyclic or EMG-mediated NMES in facilitating motor relearning.

Future investigations should address issues on two fronts. First, the effect of NMES on motor relearning and impact on clinical outcomes should be confirmed by addressing the methodological limitations of prior studies. Future studies should be large, multicenter, randomized clinical trials, which should be at least single-blinded. Investigators should carefully define the subject population including their stroke characteristics, identify potential confounds, and evaluate immediate and long-term outcomes using valid and reliable outcome measures of motor impairment, energy consumption (such as physiologic cost index and oxygen consumption), activity limitations, and quality of life. These trials should directly compare EMG-triggered NMES, cyclic NMES, and neuroprostheses to identify the most effective paradigm and the populations that will most likely benefit from each approach. The second front for future investigations is refinement of stimulation technique to maximize patient compliance and clinical outcomes. Studies should be carried out in order to determine the optimal dose and prescriptive parameters. In order to increase cognitive investment, systems that require initiation, maintenance, and termination of NMES, such as an EMG-controlled NMES system,[57] should be considered. Future studies should also investigate more sophisticated proxies for cognitive intent such as cortical control.[177] Neuroprostheses that provide clear functional benefit to a broad range of stroke survivors should be developed in order to provide goal-oriented, repetitive movement therapy in the context of functional and meaningful tasks. Finally, basic studies should further investigate mechanisms in order to optimize the treatment paradigm.

HEMIPLEGIC SHOULDER PAIN

Shoulder pain is a common complication following stroke.[292] There are many possible causes of shoulder pain in hemiparesis, including adhesive capsulitis, impingement syndrome, complex regional pain syndrome, brachial plexopathy, spasticity, and subluxation.[21] Figure 9 shows a theoretical framework describing the genesis and maintenance of hemiplegic shoulder pain. The general features of this framework include initial spasticity and weakness leading to mechanical instability and immobility of the glenohumeral joint. These conditions may cause pain directly or they may place the capsule and extracapsular soft tissue at risk for micro- and macrotrauma, which then leads to inflammation, immobility, and pain. In view of the importance of repetitive and functional use of the limb for motor recovery, the immobility exacerbates the state of the already paretic muscles (Fig. 9). The cycle repeats with worsening of the condition. Numerous treatment ap-
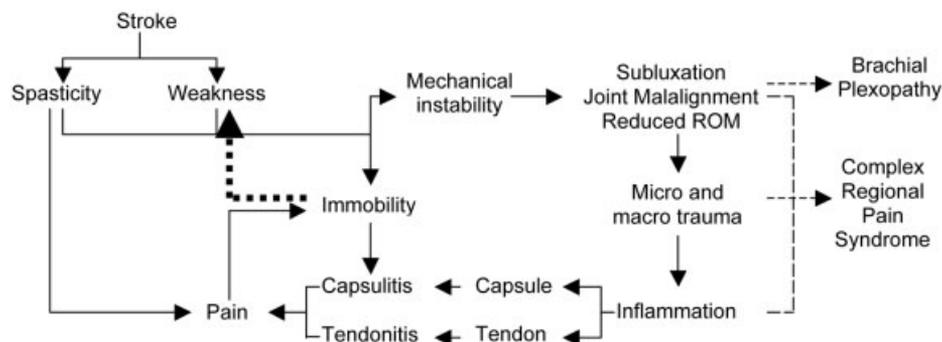
FIGURE 9. Theoretical framework describing the genesis and maintenance of hemiplegic shoulder pain.

proaches have been reported, but with limited success.[263] However, transcutaneous and intramuscular NMES of the supraspinatus, trapezius, and deltoid muscles to reduce subluxation and improve biomechanical integrity and thereby reduce pain are potential treatment options under investigation.

Transcutaneous Systems. There are nine controlled clinical trials of transcutaneous NMES for the treatment of hemiplegic shoulder pain in the literature.[15,61,62,95,161,179,188,297,298] The two publications by Wang et al.[297,298] include separate trials for acute and chronic stroke survivors and the two studies report different outcomes from the same study. Seven studies evaluated NMES as a treatment modality,[15,61,62,161,179,297,298] one evaluated prevention[188] and one evaluated a combination of treatment and prevention.[95] Five studies evaluated acute stroke survivors,[61,62,95,188,297,298] two studies evaluated a combination of acute and chronic stroke survivors,[15,179] and two studies evaluated chronic stroke survivors.[161,297,298]

Radiographic glenohumeral subluxation is the most consistently evaluated outcome measure. Eight of nine studies[15,61,62,95,161,188,297,298] evaluated radiographic inferior glenohumeral subluxation and seven of these[15,61,62,95,161,188,297,298] reported improvements. The six of seven trials that demonstrated a significant effect on subluxation included only acute stroke survivors[61,62,95,188,297] or a combination of acute and chronic stroke survivors.[15] Among these, only two reported sustained improvements beyond the end of treatment.[61,95] A more recent trial of chronic stroke survivors reported no significant effect on inferior subluxation.[297] The one trial of chronic stroke survivors reported significant effect by stressing or loading the hemiparetic upper limb.[161] Without this stressing, there was no significant difference in subluxation between treatment and control groups.

Other commonly evaluated measures include pain-free passive range of motion (ROM), motor impairment using a standardized measure, and resting shoulder pain. Several studies[61,95,179,188,298] evaluated pain-free passive ROM; significant and sustained improvement in pain-free ROM in the treatment group compared to controls was reported in only one study.[61] In two studies[95,179] improvements were noted only using within-group analyses, i.e., the authors reported significant changes in pain-free ROM in the treatment group compared to baseline, but this was not the case in the control group. Three studies reported no significant effect. Several studies evaluated motor impairment using a standardized measure.[61,62,95,188,298] Two acute studies reported improvements at end of treatment and at follow-up.[61,298] One acute study demonstrated improvement at the end of treatment, but not at follow-up.[95] Three studies (two acute and one chronic) reported no improvements in motor impairment.[62,188,298] Two treatment and one prevention studies evaluated shoulder pain at rest. The treatment studies reported improvements, whereas the prevention study did not.

As with NMES for motor relearning, numerous methodological limitations make these results difficult to interpret. Seven of the nine studies used small sample sizes.[62,95,161,179,188,297,298] Only three studies were blinded.[15,179,188] Of these, only one study was double-blinded,[179] but the sample size was too small to make any definitive statistically statement.

Two meta-analyses of the efficacy of NMES for the treatment of hemiplegic shoulder pain have been reported. The Cochrane review[235] assessed four studies[95,179,188,268] and concluded that NMES improved pain-free passive ROM and reduced subluxation, but did not improve shoulder pain or motor impairment. Ada and Foongchomcheay[2] included seven studies[15,95,161,188,297,298] to assess the

effects of NMES on shoulder subluxation and motor impairment as a function of stroke acuity. They concluded that NMES reduced or prevented subluxation and improved motor impairment in the acute phase, but not in the chronic phase. They also concluded that NMES did not improve passive lateral pain-free ROM in the acute phase, but that it may improve active pain-free ROM in the chronic phase. The differences in conclusions between the two meta-analyses are likely due to the differences in inclusion criteria used to accept specific studies in the respective studies.

Intramuscular Systems. Despite the evidence for therapeutic benefit, the clinical use of transcutaneous NMES for shoulder subluxation and pain in hemiplegia is limited for several reasons. First, stimulation of cutaneous pain receptors cannot be avoided, resulting in stimulation-induced pain that limits tolerance and compliance. Second, activation of deep muscles cannot be achieved without stimulation of more superficial muscles. Third, stimulated muscle contraction cannot be titrated precisely. Finally, clinical skill is required to place electrodes and adjust stimulation parameters to provide optimal and tolerable treatment. A potential solution is intramuscular NMES systems, which can be injected or percutaneously placed into the target muscle. These systems are less painful during stimulation, which enhances patient compliance. Motor points do not need to be located with each treatment session, which eases donning and doffing of the device. Since the electrodes are implanted, repeatability and reliability of stimulation are enhanced, which minimizes the need for skilled care. And finally, due to the focal nature and reliability of intramuscular stimulation, the best muscles to stimulate can be identified and current intensity on multiple channels can be titrated easily. Two intramuscular electrical stimulation systems are under investigation: an injectable system with an external antenna and a percutaneous system with an external stimulator.

The previously described injectable microstimulator is presently under investigation to treat hemiplegic shoulder dysfunction. Preliminary results from a randomized clinical trial demonstrated reduction in shoulder subluxation and an increase in the thickness of the stimulated muscles.[88] However, the effect on shoulder pain is still under investigation. The stimulators are permanently implanted and, if shoulder subluxation or pain recurs, additional treatments can be provided without an additional invasive procedure. However, the system also requires a large antenna that must be worn, which
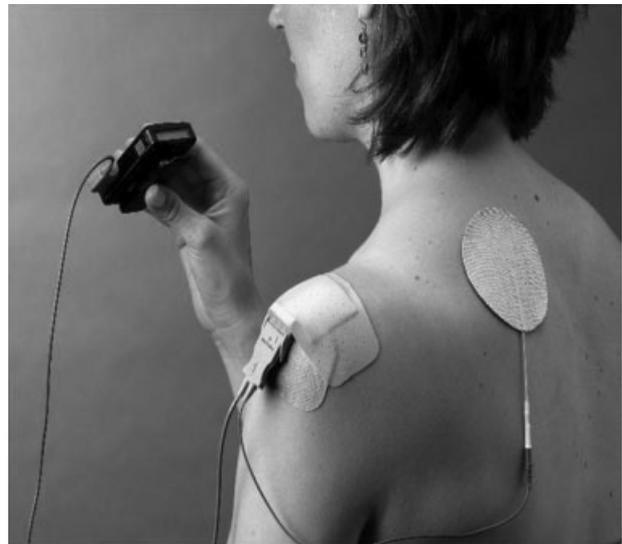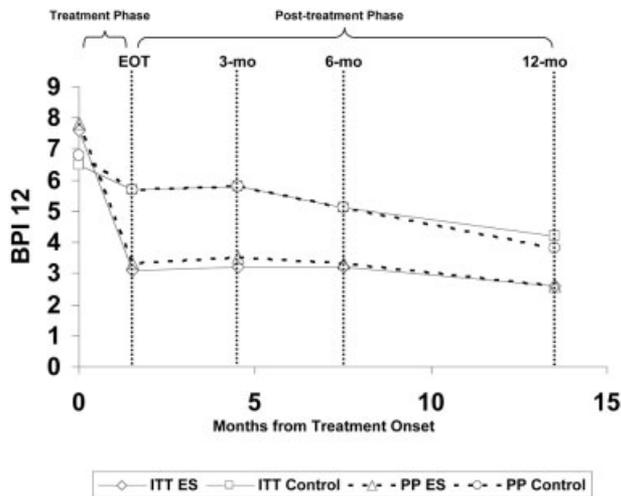

FIGURE 10. A percutaneous intramuscular electrical stimulation system for treatment of hemiplegic shoulder pain. The pager-size stimulator is connected to the implanted electrodes via a connector that can be disconnected when not in use. (RestoreStIM, courtesy of NeuroControl, North Ridgeville, OH.)

may interfere with daily activities and compromise clinical acceptance.

The percutaneous system includes helical intramuscular electrodes, which are percutaneous-placed, a "pager" size stimulator, which is worn on a belt, and a connector, which connects the electrodes to the stimulator (Fig. 10). Electrodes traverse the skin and remain across the skin for the duration of treatment. Therefore, the system is at risk for infection. The electrodes are removed by gentle traction after completion of treatment. A multicenter clinical trial demonstrated that the percutaneous system is effective in reducing hemiplegic shoulder pain and improving shoulder pain-related quality of life of chronic stroke survivors for up to 12 months after completion of treatment (Fig. 11).[60,311] There were no instances of electrode-related infections.

Summary. The use of transcutaneous NMES appears to reduce shoulder subluxation and pain-free ROM and facilitate motor recovery, especially among acute stroke survivors. However, additional studies that address the previously noted methodological limitations are needed to address more definitively the question of clinical efficacy. Intramuscular systems are still under investigation. The injectable system is undergoing clinical trials of initial effectiveness for hemiplegic shoulder pain and the percutaneous system is presently being compared to transcutaneous electrical nerve stimulation

FIGURE 11. Results of multicenter randomized clinical trial of percutaneous intramuscular electrical stimulation (ES) for the treatment of hemiplegic shoulder pain. Per-protocol (PP, dashed lines) and intent-to-treat (ITT, solid lines) approaches both showed that percutaneous intramuscular ES significantly reduces hemiplegic shoulder pain (Brief Pain Inventory Question 12) for up to 12 months after completion of treatment compared with controls who were treated with a cuffed hemisling. (Reproduced with permission, Chae et al. Am J Phys Med Rehabil 2005;84:832–842. © 2005 Lippincott Williams & Wilkins.)

(TENS) in a second clinical trial to satisfy FDA 510K regulatory requirements.

OTHER THERAPEUTIC APPLICATIONS

Muscle Strengthening and Atrophy. Muscle fiber alterations at the cellular level form the basis of the present understanding of NMES-associated muscle strength enhancement. NMES has the ability to reverse the transformation of type I fibers to type II fibers seen in UMN injury.[225,227] The specific effect of NMES-facilitated exercise on the motor unit has been reviewed.[91] Numerous skeletal-muscle biochemical and physiological adaptations are induced by chronic low-frequency electrical stimulation in an animal model.[189] Fast to slow twitch alterations of muscle fibers are associated with alterations of calcium dynamics and myofibrillar proteins; white to red fiber transformations are associated with changes in mitochondrial enzymes, myoglobin, and the induction of angiogenesis.[189] Metabolic and phenotypic characteristics of human skeletal muscle fibers are used as predictors of glycogen utilization during electrical stimulation.[117] Intracellular changes induced by NMES form the basis of muscle strength alterations and preservation in neurological rehabilitation.

In humans, there are physiologic differences between volitional muscle contraction and electrically activated muscle contractions.[81] Human[198] and animal[89] studies characterize how the specific pattern of electrical stimulation impacts muscle strength alterations. A study evaluating healthy men showed that shorter duty cycles produced more fatigue, possibly due to greater intracellular acidosis and reduced availability of high-energy phosphate.[198] Mathematical muscle modeling is proposed to predict the force necessary to achieve therapeutic loading conditions in SCI in order to better define the use of electrical stimulation for isometric training and functional activities.[103] A recent study evaluated the therapeutic effect of combining volitional muscle contraction and electrical stimulation in a training program with healthy adults and did not demonstrate significant benefit from superimposed therapies.[220] Theoretically, a greater number of motor units is recruited with volitional muscle contraction and electrical stimulation as compared to volitional contraction alone due to the phenomenon of reverse recruitment order. However, there is also the theoretical possibility of collision blocking, reducing the net efferent output of the alpha motoneuron.

The literature supports the therapeutic application of NMES to enhance muscle strength, retard muscle atrophy, and reduce spasticity.[16,87] Enhanced quadriceps muscle performance as reflected in load resistance, repetitions, and knee ROM can occur with a NMES knee-extension system used in SCI.[244] Arm crank ergometry with NMES enhances upper-limb manual muscle scores in cervical spinal cord injury.[47] FES cycle ergometry (FES-CE) may provide greater benefit than unloaded isometric FES contractions (FES-IC). A study involving 26 acute SCI subjects demonstrated that an FES-CE training program, but not an FES-IC training program, prevented muscle atrophy at 3 months and caused significant hypertrophy at 6 months.[17] Researchers utilize various methods to quantify morphologic and therapeutic response to NMES including MRI,[216] PET scan,[294] and 99mTC-sestamibi muscle scintigraphy.[226] Although this review confines itself to the role of NMES for persons with SCI and stroke, the ability of NMES to enhance muscle strength and mass for the broader neurologic and orthopedic applications are also reported in the literature.[119,121,174,185,274]

Deep Venous Thrombosis Prevention. NMES may be effective in reducing the risk of venous stasis and thromboembolism. Several studies evaluated NMES for the prevention of neurosurgical postoperative

thromboembolism[32] and post-arthroplasty venous complications including DVT.[208] Cardiovascular effects, consistent with decreased lower-limb venous stasis, including increased stroke volume and cardiac output have been documented when lower-limb electrical stimulation is used during surgery.[96] A study of immobilized subjects showed that electrical stimulation of the foot and calf decreases venous stasis and reduces the risk of DVT.[147] A review article of the etiology, incidence, and prevention of DVT in acute SCI supported the use of electrical stimulation in combination with low-dose heparin for the prevention of thromboembolic disease.[205]

Bone Mass/Density. Physiological alterations of bone associated with immobility in the neurologically impaired patient are well documented. Following SCI, weight-bearing trabecular-rich sites such as the distal femur and proximal tibia show the greatest demineralization. Pathological fractures following minor trauma are caused by reduced bone mass in association with modified bone matrix composition.[194] Animal studies demonstrate the prevention and reversal of osteoporosis with capacitively coupled electrical fields.[37–40,186] Various forms of electrical stimulation affect growth, repair, and remodeling of soft and hard tissues in animals.[28]

Several studies have described the effect of FES lower-limb cycling on bone density in SCI. A trend toward increased bone lumbar spine bone density is seen in chronic SCI with neurogenic osteoporosis.[19] In two studies, FES cycling exercises for 6 months enhanced the bone mineral density of the distal femur and proximal tibia,[20,63] although the effect was not sustained with discontinuance of FES.[63] However, other studies have failed to corroborate these findings.[94,181] A recent review article suggested that FES cycle ergometry helps prevent bone loss in women, specifically with acute spinal cord injuries.[219]

Tissue Oxygenation and Peripheral Hemodynamic Functioning. NMES may improve tissue oxygenation and peripheral hemodynamic function. Eight weeks of stimulation is associated with an increase in the unloaded tissue oxygen level and a reduction in the ischial region pressure, although total interface pressures does not change.[31] Animal studies demonstrate increased microvascular perfusion with transcutaneous NMES.[65–67] The ability of TENS to impact peripheral vascular resistance and cause a transient local increase in blood flow is dependent on stimulation intensity.[253]

The impact of NMES on peripheral hemodynamic functioning is the focus of several studies.[18,52,228,250,313] In one study there was a linear increase in femoral arterial blood flow with increasing stimulation rates of TENS.[313] However, a recent study evaluating peripheral vascular responses to NMES in chronic SCI showed improved muscle fiber size and fatigue without impact on femoral arterial diameter or blood flow.[250] After NMES-assisted treadmill training for 3 months in chronic SCI, there was an increase in systolic blood pressure at rest as well as during exercise.[52] In a study using arm crack ergometry and NMES-induced leg contractions, an increase in blood flow and decrease in venous pooling were associated with a reduced rate pressure product.[228]

Cardiorespiratory Conditioning. Enhancement of cardiorespiratory fitness is associated with the use of NMES in SCI. Exercise recommendations for SCI presently include the use of NMES to facilitate exercise either via NMES leg cycle ergometry or NMES-assisted treadmill gait training.[138] A study of peak and submaximal physiological responses in SCI showed a significant increase in peak rate of oxygen consumption.[135] NMES leg cycle ergometry increases functional capacity in SCI subjects,[70] although high peak NMES-assisted pedal forces contribute to low efficiency in paraplegic subjects.[258] The rate of fatigue during NMES-assisted exercise is greater than during volitional exercise.[27]

NMES-assisted ambulation training and arm ergometry in SCI is associated with central cardiovascular adaptations including increased time to fatigue, peak power output, and peak rate of oxygen consumption.[139] Studies evaluating energy expenditure with NMES-assisted treadmill gait training and partial body-weight support in SCI have shown improvements in the rate of oxygen and energy consumption, which is consistent with enhanced metabolic and cardiovascular responses.[53,79,80]

CONCLUSIONS

The principal goal of rehabilitation management of persons with UMN paralysis is to maximize quality of life. NMES systems bypass the injured central circuitry to activate neural tissue and contract muscles to provide function to what is otherwise a nonfunctioning limb or structure. Recent advances in clinical medicine and biomedical engineering make the clinical implementation of NMES systems to enhance the mobility and function of paralyzed person more feasible. Hand neuroprosthesis systems can

significantly enhance the upper-limb function of persons with tetraplegia. The application of this technology for persons with hemiplegia is in its infancy and must await further technical and scientific developments if it is to be applicable to the broader stroke population. Several lower-limb systems with and without bracing are being investigated for the purpose of functional transfers and standing, and to a lesser degree for ambulation for patients with paraplegia. While multichannel neuroprosthesis systems for hemiplegia are still under development, the footdrop stimulator is ready for large-scale multicenter clinical trials. The bladder neuroprosthesis can provide catheter-free micturition for persons with either paraplegia or tetraplegia. Phrenic and diaphragmatic pacing systems can provide artificial ventilatory support for patients with ventilator-dependent tetraplegia. NMES for motor relearning in hemiplegia is a promising application of goal-oriented repetitive movement therapy and is ready for large-scale multicenter clinical trials. NMES for treatment of shoulder subluxation and pain in hemiplegia has yielded encouraging results and is ready for confirmatory large-scale multicenter clinical trials. Finally, NMES may be effective in strengthening muscles, preventing muscle atrophy, preventing DVT, improving tissue oxygenation and peripheral hemodynamic functioning, and facilitating cardiopulmonary conditioning.

Although this review was limited to applications in the SCI and stroke populations, work with multiple sclerosis,[282] traumatic brain injury,[217] and cerebral palsy[129,218,233] is in its early stages and will undoubtedly expand. Clinical practice is rarely limited to a single intervention. Thus, with the development of pharmacological interventions,[113] neuronal regeneration,[36] and other innovations such as robotic therapy,[97,170] mental imagery,[1] virtual reality,[167,245] and constraint-induced therapy,[281,305] the future will likely embrace combination therapies to treat the motor dysfunction of persons with central nervous system paralysis.

After decades of development, the clinical utility of NMES systems is finally becoming realized. By necessity, scientists and clinicians must continue to explore new ideas and improve upon the present systems. Components will be smaller, more durable, and more reliable. The issues of cosmesis and ease of donning and doffing will require systems to be fully implantable. Control issues will remain central, and the implementation of cortical control will dictate the nature of future generations of neuroprosthesis systems. Future developments will be directed by consumers. In the present healthcare environment where cost is an overwhelming factor in the development and implementation of new technology, the consumer will become one of technology's greatest advocates. Finally, the usual drive toward greater complexity will be tempered by the practical issues of clinical implementation where patient and clinician acceptances are often a function of a tenuous balance between the "burden and cost" associated with using a system and the system's impact on the user's quality of life.

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