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Narrative Review

The Application of Neuromuscular Electrical Stimulation Training in Various Non-neurologic Patient Populations: A Narrative Review

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Abstract

In the last 2 decades, neuromuscular electrical stimulation has been used increasingly in deconditioned patients with the aim of increasing muscle force. Much basic research has been conducted in the area of increasing a muscle's fatigue resistance by neuromuscular electrical stimulation but similarly thorough research with regard to increasing maximal force is missing. Insufficient clinical and basic knowledge exists on the selection of stimulation parameters that will optimize muscle hypertrophy and gains in muscle force. For volitional training, established stimuli for muscle hypertrophy (which more or less parallels maximal muscle force) are muscle tension, metabolic stress, and muscle damage. The present review summarizes findings from clinical and basic research in terms of muscle mechanical as well as acute and chronic physiologic effects of different stimulation protocols, explains the role of the various stimulation parameters in determining the effect of NMES training protocols, and gives clinical recommendations for the choice of stimulation parameters for different patient populations with different training goals, such as increasing muscle force, mass, endurance, or energy consumption. We limit this review to non-neurologic patients, because training goals of neurologic patients are specific to their functional deficits.

Introduction

Since approximately the 1990s, neuromuscular electrical stimulation (NMES) has been used increasingly for the purpose of muscle strengthening in deconditioned patients, for example, in patients before and/or after orthopedic surgery [1-3]. More recently, NMES has been implemented successfully in patients in the intensive care unit to curb the extensive muscle wasting [4]. Few studies have followed a similar aim and have assessed the efficacy of NMES in attenuating muscle wasting in the population of frail, elderly people [5]. Although much basic research has been carried out on how to achieve a more fatigue-resistant muscle by NMES comparing different stimulation protocols in carefully controlled animal experiments [6,7], similar studies following the aim of muscle hypertrophy and muscle strengthening are very rare [8,9]. In fact, a rational for why a chosen stimulation protocol should favor muscle hypertrophy is absent in most studies. There is clearly insufficient clinical and basic knowledge on the selection of stimulation parameters that will optimize muscle hypertrophy and gains in muscle force. In the absence of knowledge on hypertrophic stimuli from NMES, we consider it appropriate to assume that stimuli may be congruent to those from volitional training, notwithstanding that because of a mostly small stimulated muscle mass the effects of NMES generally are smaller compared with volitional training. For volitional training, the current consensus is that the main stimuli for muscle hypertrophy are muscle tension, muscle damage, and metabolic stress [10-13].

The aim of the present review is to explain the specific characteristics of NMES training protocols, to summarize findings from clinical and basic research in terms of muscle mechanical as well as acute and chronic physiologic effects of different stimulation protocols, explain the role of the various stimulation parameters in determining the effect of NMES training protocols, and to give clinical recommendations for the choice of stimulation parameters for different patient populations with different training goals, such as increasing muscle force, mass, endurance, or energy consumption. We limit this review to non-neurologic patients, because the training goals of neurologic patients are specific to their functional deficits.

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Literature Search Strategy

Literature research was performed, including all relevant studies up to October 2014 by searching the Medline/PubMed database and Web of Science using the following search terms: electrical stimulation, electrostimulation, electromyostimulation, muscle stimulation, neuromuscular stimulation, muscle hypertrophy, muscle fiber type, muscle fatigue, muscle force, muscle torque, muscle damage, stimulation frequency, pulse duration, electrical current, and electrode.

Acute Effects of NMES

This section summarizes evidence indicating that the stimuli for muscle hypertrophy with volitional training may also be achieved with NMES.

Force Production

There is much evidence for volitional muscle training that high-force contractions are needed to maximize gains in maximal muscle force [14,15]. Muscle force achieved by NMES usually is measured for the knee extensors by force transducer and reported as a percentage of the maximal voluntary contraction (MVC) force. Evoked torque achieved with NMES has been reported between 20% and 90% and 5% and 112% MVC in 2 reviews on healthy subjects and athletes, respectively [16,17], and is highly dependent on motivation of the subjects [17]. In patient populations, % MVC generally are around or below 30% MVC [18-20]. The force achieved by NMES increases in a sigmoidal manner with increasing stimulation frequency up to approximately 70-80 Hz [21,22], depending on the fiber type composition of the stimulated muscle [23]. With NMES, to achieve optimal force development greater stimulation frequencies are needed than the physiological firing frequency of the nerves because of the synchronous motor unit firing pattern [24]. In contrast to volitional contractions, motor unit recruitment pattern by NMES is nonselective, spatially fixed and temporally synchronous [25].

In summary, extrinsically measured muscle forces achieved with NMES generally are rather low, however, because often only a small portion of the muscle fiber pool is activated, intrinsic forces generated by these fibers may be substantial.

Metabolic Stress

In healthy subjects, oxygen consumption elicited by NMES, measured by spirometric methods, ranged between 7.3 and 14.9 mL*min^{-1}*kg^{-1}, corresponding to a 2- to 4-fold increase from rest [26,27].

On the level of the contracting muscle, NMES-induced contractions may, however, lead to an exaggerated oxygen consumption (VO_2) even at a relatively low mechanical load [28,29]. When VO_2 consumption during contractions of the knee extensors either by volitional or force-matched NMES-induced contractions was compared, VO_2 consumption was greater with NMES (11 versus 8 mL*min^{-1}*kg^{-1} at 46% MVC) [30]. Similarly, in a study using positron emission tomography, Vanderthommen et al measured a greater local oxygen consumption in NMES compared with volitional contractions (3.0 $\pm$ 2.3 versus 0.7 $\pm$ 0.3 mL O_2*min^{-1}*100 g^{-1}) [29]. The reason for a greater VO_2 demand may be a reduced mechanical efficiency because of the synchronous motor unit activation imposed by NMES, which requires greater frequencies to reach comparable forces [31]. However, compared with volitional whole-body exercise, metabolic demand is relatively low [26], because of the fact that usually only a small muscle mass is stimulated. Therefore, despite the rather low systemic VO_2 demand, some large acute local changes in metabolic parameters are seen during NMES. For example, serum lactate concentrations were higher with NMES of the knee extensors than with volitional cycling at VO_2-matched intensity [27] or compared with force-matched volitional knee extensions [32].

These results suggest that muscle contractions elicited by NMES are characterized by an increased contribution of the anaerobic metabolism. A review by Gregory and Bickel [33] highlights different possible reasons for the increased metabolic demand, which are mainly based on the unique motor unit recruitment pattern associated with NMES: continuous, synchronous, and exhausting contractile activity in a spatially fixed pool of motor units. We summarize that, despite an only moderate increase in systemic oxygen consumption during NMES, large local metabolic demands can be achieved.

Muscle Damage

Muscle damage may be experienced after NMES exercise sessions, particularly at the beginning of the training program. The extent of muscle damage was greater with NMES compared with force-matched volitional concentric and isometric muscle contractions [32,34] and can be similar to damage resulting from eccentric exercise. A potential reason for this may be the synchronous, spatially fixed, and therefore highly fatiguing recruitment pattern of NMES. Increased creatine kinase levels and delayed-onset muscle soreness (DOMS) were experienced even at very low contraction levels, such as 5.4% MVC [35]. NMES has been found to induce muscle damage that is characterized by histologic alteration of muscle fibers and connective tissue [36]. Indeed, Z-line disruption showed a positive correlation with the electrically induced force [35].

As a repair mechanism, NMES can result in remodeling of the skeletal muscle extracellular matrix [37]. Repeated bout effect also is observed with NMES. In fact, muscle creatine kinase concentration and soreness were much lower after the second NMES exercise bout, despite the same acute fatigue (reduction in MVC after training) [38,39]. In conclusion, muscle damage by NMES can be substantial and has to be taken into consideration when setting up NMES training prescriptions.

Evidence of Acute Cellular Responses to Hypertrophy Stimuli

In volitional exercise training, muscle hypertrophy is the result of increased postexercise protein synthesis, which is triggered by molecular and cellular events in response to mechanical load [11]. The same would logically apply to NMES training; however, the magnitude of these responses is likely to differ. For example, at the same force output, serum growth hormone concentrations were greater after a NMES training session compared with volitional exercise [32].

Muscle protein synthesis as an acute response to 60 min of NMES (60 Hz, 3 seconds on/3 seconds off) was clearly demonstrated in elderly diabetic men [40]. This protein synthesis rate was approximately 30% lower than the one achieved after 30 minutes of volitional resistance exercise in elderly men (employing a graded protocol at 40%-75% of 1 repetition maximum) [41].

A NMES study in mice found positive correlations of the p38 and mTOR signaling with the force-time integral independently from markers of metabolic load. These findings suggest that maximizing the force-time integral during NMES training may be important for achieving muscle hypertrophy [8]. We therefore suggest that postexercise protein synthesis increases as a consequence of NMES and, similarly to volitional training, depends on training parameters.

Chronic Effects of NMES Training

In this section, chronic adaptations to NMES training programs in various (patient) populations are summarized.

Effects on Muscle Force and Muscle Mass

Two reviews of studies in healthy subjects have shown MVC force improvements of between 7% and 62% [24,42]. NMES training also was effective in improving muscle strength in patients with advanced disease, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF), in whom a Cochrane Review found significant improvements in quadriceps muscle strength [43]. The magnitude of strength improvements is likely to depend on individual characteristics, on the training load, on the stimulation parameters, as well as the methodologies for strength assessment. When muscle force improvements by NMES training have been compared with volitional training, results achieved by NMES were mostly inferior to volitional training [44,45].

The physiologic adaptations leading to strength gains with NMES are, similarly to volitional exercise, of neuronal and myocellular nature. Increases in strength already were found after 4 weeks of NMES training, whereas at that time only limited muscle hypertrophy was observed [46,47]. This has led some authors to suggest that NMES can induce adaptations within the neural system before structural changes are evident [46-48], similarly to the time course of neural adaptations in voluntary exercise [49]. The neural adaptations to NMES training were summarized in a review by Hortobagyi and Maffiuletti [50]. They suggested that acute bouts of NMES may activate sensory, sensorimotor, and motor areas and possibly interhemispheric paths in the brain. This is further supported by the cross-education effect on the contra-lateral leg in unilateral exercise that has been found to be higher with NMES compared to volitional contractions [51,52].

Muscle hypertrophy has been found as early as 6 [20] and 8 weeks [18,53] into NMES training programs in both healthy [53-55] and diseased [18,20,56] populations ranging from 6%-16%. In summary, NMES training consistently has been found to improve muscle strength. The gain in muscle force is based on both neural and structural adaptations.

Effects on Muscle Fiber Type Composition

The various and even conflicting effects of NMES training on distinct skeletal muscle fiber types have been summarized in a recent systematic review [57]. This inconsistency may be attributable to the use of different stimulation protocols, inclusion of different subject populations, or the methods used to characterize muscle fiber type. Several studies have found hypertrophy of both type I and type II muscle fibers with NMES between 45 and 75 Hz [48,58,59]. In contrast, some studies have found an increase only in type I fiber cross-sectional area but a decrease in type II fiber cross-sectional area [60,61]. Most studies having quantified changes in muscle fiber composition after NMES training have found a shift from the fast fatigable type IIx to the more oxidative type IIa fibers [48,58]. This is also reflected at the muscle fiber enzyme level, where an increase in citrate synthase activity and a decrease in glyceraldehyde activity, marker enzymes of the citric acid cycle, and glycolysis were found after NMES training [19,57,58].

The most consistently found adaptation of muscle fibers to NMES is an increase in their oxidative capacity; however, effects of NMES on individual muscle fibers of specific fiber types have not been fully understood.

Effects on Exercise Capacity

The improvements in aerobic capacity at the muscle fiber protein level as well as at the enzymatic level after NMES training is mostly, but not always [62], reflected in increases in maximal systemic oxygen uptake and exercise capacity. NMES training programs in very weak individuals, such as patients with congestive heart disease, have led to increases in VO_2 peak as high as 20% [19,63,64], whereas such increases were absent in patients with diabetes [65]. Increases in maximal oxygen uptake may depend on selection of stimulation parameters and training protocol; however, they also are strongly affected by the stimulated muscle mass (ie, number of stimulated muscle groups and number of recruited motor units per stimulated muscle group). We suggest that NMES training has, if appropriate stimulation parameters are chosen, the potential to improve exercise capacity, particularly in very deconditioned patients.

Clinical Recommendation for NMES Applications

This part of the review aims at providing practical recommendations with regard to the selection of NMES protocols in various patient populations. The choice of the stimulation protocol and stimulation parameters depends on the therapeutic training goals and the disease conditions.

Variable Parameters of NMES Protocols

Electrode Types

Although most studies have used commercially available self-adhesive electrodes, Lieber and Kelly [66] found that carbonized rubber electrodes produced the greatest evoked torque of knee extensors. Carbonized rubber electrodes can only be applied to the skin by using a conducting layer such as gel, a water-saturated sponge, or water-absorbent material. They further need to be held in place by tape, Velcro belts, or tight fitting clothing.

Electrode Size and Positioning

Larger electrodes are likely to stimulate a greater muscle cross-sectional area and hence to produce more force at a given level of discomfort. This is because there is a greater chance of covering the individually variable location of where the main nerve branches enter the muscle [67]. Positioning of electrodes on these muscle motor points maximizes muscle tension and muscle oxygen consumption and minimizes current intensity and discomfort [68-70]. When working with small electrodes, determination of motor point location before stimulation is crucial; therefore, an atlas of muscle motor points could be helpful for electrode positioning [71,72]. The larger the electrode, the greater the stimulation current has to be to achieve the same current density, which is the parameter that determines how deep the current penetrates the muscle [73-75] and also determines the level of discomfort. Smaller electrodes are needed when the aim is to stimulate only specific muscles in isolation, as may be required for treatment of muscle imbalances.

Pulse Form and Pulse Duration

Commercially available stimulators offer square or sinusoidal current compensated pulses (eg, no changes in resting potential of nerve and muscle cells under the electrode occur). Sinusoidal pulses were shown to be more effective than square pulses in preventing muscle atrophy in rats [76]. Some stimulators produce pulsed currents, where single pulses of a predefined pulse duration are produced at a chosen stimulation frequency, whereas the so-called "Russian stimulation" delivers bursts of set duration and set underlying frequency (typically 2.5-4 kHz) at a chosen frequency. For a given level of pain, pulsed currents produced larger muscle forces than currents using Russian stimulation [77].

Pulse durations chosen in most studies range from 0.2 to 0.5 ms. Longer pulse durations up to 1 ms have been shown to produce stronger contractions and to be less painful [78,79]. The latter is probably attributable to the fact that the current amplitude can be reduced with a longer pulse duration while still achieving the same charge and consequently contraction intensity.

Stimulation Intensity

Stimulation intensity is herein defined as pulse duration [ms] * current [A]. High currents are necessary to maximize the number of recruited muscle fibers, resulting in greater NMES-evoked forces and hence better training effectiveness [45]. The desired intensity mostly depends on the patient's disease/disorder, his or her physical condition, and the aims of the training program. Common stimulation prescriptions range from just-visible muscle contractions to maximally tolerable contractions. No universal guidelines regarding current amplitude can be given because of the individual differences in skin impedance, thickness of subcutateous fat layer and location of nerve branches [66]. Sensory and motor thresholds have been shown to be influenced by gender and age [80]. Like electrode positioning, current intensity also has to be determined for each subject individually. Because of the often-occurring muscle damage and DOMS at the beginning of the training program, less than maximally tolerable stimulation currents are recommended for the first 2-5 training sessions of a program, especially in patients who would poorly tolerate the side effects of muscle damage. Current can be increased successively thereafter. The most valid method for quantifying NMES intensity is obtained by expressing the force produced by NMES relative to MVC force (% MVC), which can easily be determined for knee extensors and flexors. A quasi-linear relationship was observed between activated muscle cross-sectional area and evoked torque, with 54% of the activated quadriceps cross-sectional area producing 75% MVC [67]. Unfortunately, many studies have not assessed and/or reported this %MVC [16], which makes the comparison between protocols used in different studies impossible.

Stimulation Frequency

There are 2 main frequency ranges that differ with regard to muscle tension and metabolic demand: non-tetanic frequencies (2-10 Hz, most commonly used are 4-6 Hz), which produce muscle twitches at low force and high metabolic demand (see the section "Effects on Muscle Fiber Type Composition") rather than fused tetanic contractions, and tetanic frequencies (20-100 Hz, most commonly used are 25-75 Hz), which produce fused tetanic contractions. Force increases linearly with increasing frequency up to a force plateau at approximately 70-80 Hz [21,22], depending on the fiber type composition of the stimulated muscle [23]. With NMES, greater stimulation frequencies are needed to achieve optimal force development than the physiological firing frequency of the nerves because of the synchronous MU firing pattern [24].

On-Off Time and Duty Cycle

On-off time usually is defined as the duration of active stimulation and the recovery time without active stimulation and is mostly indicated as x seconds on/y seconds off. Duty cycle is indicated as the ratio between on-time and total time, eg, x:(x + y) [3]. In general, a greater duty cycle (greater on- than off-time) is associated with greater metabolic stress [8,81]. With regard to muscle fatigue, at long on-times, such as 10 seconds, intracellular acidosis because of the long contraction time leads to greater fatigue at greater duty cycles (eg 1:1 versus 1:5) [81]; however, at short on-times, it seems that total contraction time determines fatigue rather than duty cycle, meaning that the same fatigue is reached after a shorter time period with a greater duty cycle, but after the same number of contractions [82,83]. The choice of duty cycle largely depends on the target population and the goal of the training program (see the section "Effects on Exercise Capacity"). Although healthy subjects can sustain a large percentage of MVC with NMES at a duty cycle of 1:1 over a period of 30-60 minutes, frail persons will fatigue quickly and, hence, a duty cycle of 1:2 may be preferable. The addition of a ramp both at the start and end of the on-time adds to patient comfort and may therefore allow the use of greater stimulation intensities.

Limb Position

Most NMES protocols are conducted in isometric conditions. This allows specific limb positioning and control of NMES-evoked torque according to intended goals. Muscle hypertrophy can be optimized when maximizing muscle tension, which can be increased when the muscle is stimulated in a lengthened position [84], which also avoids painful muscle cramping. Recent findings suggest that NMES with eccentric contractions is a promising technique for improving muscle strength [85]; however, DOMS is greater at longer muscle length and more so with eccentric contractions and can be reduced when NMES isometric or concentric contractions are performed at shorter muscle lengths [38]. Therefore, we recommend completing the first few NMES training sessions of a program at the muscle length that produces maximal isometric force, which may be increased successively over the weeks to achieve greater muscle tension with progressive training. Functional goals need to be defined at the start of the training program because gains in isometric force may be specific to the joint angle at which NMES training is performed [46,55].

Training Frequency and Duration

A wide spectrum of training durations and frequencies has been used in published NMES studies. Training volumes have ranged from 30 minutes per week [86] to 28 hours per week [19], and training frequencies from 1.5 sessions per week [86] to (twice) daily [19,87]. NMES training frequency should be determined according to training goals, similar to volitional training. Prescription for volitional resistance training with the aim of increasing maximal muscle force are 2-3 times per week depending on the target population [88]. For example, in a NMES study with healthy subjects 3 sessions/week had better results on muscle strength than 2 sessions/week [89]. If the goal is to increase muscle endurance by increasing muscle aerobic capacity, weekly training frequency should be 5 times/week [90]. Providing sufficient recovery time between training sessions have been found to be important [91]. Considering the scarcity of NMES studies that have compared different frequencies with the same stimulation parameters [9], training volume and target population, we suggest to determine the frequency of a NMES program according to recommendations for volitional training with the same training goal. With regard to the total number of training sessions, the same recommendations apply as with volitional training [90]. Unless the condition of the patient changes (eg, critically ill patients, orthopedic patients), for lasting benefits the training needs to be performed indeterminably.

Training Goals

Few studies have stated clear training goals, and even fewer studies have justified their choice of stimulation parameters, NMES training volume, and frequency according to their training goals. Although some

NMES studies in athletes have defined clear goals and have assessed them with appropriate methods [92,93], goals in patient groups often are more general and include all kinds of functional improvements [20,64]. In this section we summarize findings on NMES parameters and protocols with regard to the achievement of predefined goals.

Improvement or Preservation of Maximum Muscle Force

If the aim of a NMES training program is a gain in muscle force or its preservation when a patient is immobilized, then the training should produce high muscle tension, metabolic stress, and/or muscle damage [10,94]. The use of high-stimulation frequencies and high duty cycles (1:1 or 1:2), with on-time of at least 2 seconds to evoke high muscle tension, on a large part of the muscle cross-section (by using high stimulation currents) would favor hypertrophy. However, effects of NMES training regimes on muscle force comparing different stimulation frequencies so far have only been assessed in 1 study. This study has shown that there was a significantly greater increase in knee extension torque after 8 weeks of NMES training at 75 Hz compared with the same training volume at 15 Hz in patients with COPD [9]. A different approach to optimize muscle strength gains has been suggested by a recent study, which indicated that the NMES force-time integral has to be maximized [8]. Force-time integral depends on the choice of stimulation parameters and is maximized when fatigue is minimized.

Reduction of Muscle Fatigue

Chronic continuous NMES at low frequencies successfully increases fatigue resistance [95-97], but with extreme protocols it can also lead to a reduction in maximal muscle force [98].

Most NMES protocols that have achieved an increase in maximum muscle force and also measured muscle endurance have found a concomitant increase in muscle endurance [99-101].

Improvement of Cardiopulmonary Exercise Capacity, Glucose Uptake, or Insulin Sensitivity

Although tetanic frequency stimulation with short on-off times (1 second on/1 second off) has been found to improve glucose metabolism in healthy subjects [27,102], the use of nontetanic frequency stimulation (4-12 Hz), which produces muscle twitches rather than fused contractions, has been used commonly for maximizing energy consumption in obese and/or diabetic subjects and to alleviate hyperglycemia [103]. Minogue et al [104] have found maximal oxygen consumption when stimulating at 5 Hz, as this was the maximal frequency with complete relaxation between muscle twitches and tolerable discomfort. Complete relaxation between muscle twitches seems to be important to achieve maximal energy consumption as the shortening of the muscle fibers (actin myosin cross bridge cycle) consumes more ATP than the sustainment of the shortened muscle length [105]. Furthermore, nontetanic stimulation has been shown to be less fatiguing than tetanic stimulation at comparable oxygen consumptions [106].

In summary, to maximize metabolic effects and energy consumption, the stimulated muscle mass should be maximized by including several large muscle groups (such as upper and lower legs, torso, and arms), by increasing electrode size, and by setting the current intensity to maximally tolerable. Stimulation frequency should be set at 4-6 Hz according to individual preference, session time should be as long as possible (60-120 minutes), and training frequency as high as possible (5-7 times per week).

Target Populations

The following section summarizes NMES parameters and protocols used in specific patient populations who conducted NMES with the purpose of increasing muscle force and mass as well as improving muscle function and physical capacity. For patient populations for whom a variety of stimulation parameters and protocols has been used with no consensus on the optimal NMES program, we give recommendations based partly on scientific evidence and partly on own experience (Table 1). We have omitted patient populations with very sparse and inconsistent scientific evidence on efficacy of NMES, such as cancer [43,107,108] and hemophiliac patients [109].

Critically Ill Patients

Two recent systematic reviews on effects of NMES for preventing muscle weakness and wasting in critically ill patients have found NMES to be effective [4,110]. The mechanical ventilation weaning period was significantly shorter and NMES prevented the development of critical illness polyneuromyopathy in a randomized controlled study by Routsi et al [111]. One restriction may be that in very acute intensive care unit patients NMES may be unable to prevent muscle atrophy because of excessive inflammation [112]. Nevertheless, a further potential benefit of using NMES during immobilization may be the prevention of the loss of myonuclei and satellite cells, thus maintaining a viable satellite cell pool for subsequent muscle regeneration [113].

Because of the scarcity of studies in critically ill patients recommendations on how to stimulate these patients cannot be based on comparative data. Caution may be advisable in very acute patients with high systemic inflammation not to induce muscle damage that would produce further inflammation [114]. It may be safer to use nontetanic stimulation initially (eg, 4 Hz) to avoid any form of DOMS and then introduce tetanic

Table 1
Summary of recommended stimulation parameters, protocols, and set-ups for different patient groups

Patient Group	Authors	Stimulation Frequency, Hz	On-Off Times, s/s	Stimulation Intensity	Session Duration, min	Sessions per Week	Stimulated Muscle Group
Critically ill patients	Maffiuletti et al [4], Routsi et al [111], Gruther et al [112]	4-25	2/2	Avoid high intensities	10-30	2-3	Quads
Geriatric patients	Gremeaux et al [116], Maggioni et al [5], Wall et al [40], Kemmler et al [86]	25-75	2/2-6/6	Maximally tolerable	20-60	2-5	Functionally important muscle groups (quads, gluts)
CHF/COPD	Sbruzzi et al [123], Quittan et al [101], Sillen et al [9,57]	4-75	Avoid long on times (>4 s)	Maximally tolerable	30-60	3-5	Major muscle groups of the legs
Obese/DMT2	Hamada et al [27,102], Miyamoto et al [103]	4-5	n.a.	Maximally tolerable	At least 60	≥7	Maximally possible muscle mass
Orthopedic patients	Bade and Stevens-Lapsley [1], Levine et al [134], Wright et al [135]	25-75	4/4-10/10	Maximally tolerable	30-60	3-5	Quads (and gluts after hip surgery)
Nephrologic patients	Di Iorio et al [138], Dobsak et al [137], Farese et al [136]	4-5 or 25-75 depending on training goal	4/4-10/10	Maximally tolerable	30-60 (during hemodialysis)	2-3	Major muscle groups of the legs
PAD	Abraham et al [142], Anderson et al [141]	4-5	n.a.	Avoid pain from ischemia	1-2 × 20	3-7	Quads and calves

CHF = congestive heart disease; COPD = chronic obstructive pulmonary disease; DMT2 = diabetes mellitus type 2; quads = quadriceps muscles; gluts = gluteal muscles; PAD = peripheral arterial disease; n.a. = not available.

contractions with rather low frequencies (eg, 20-25 Hz) and short duty cycles (eg, 2 seconds on/2 seconds off). Session time may be gradually increased from day to day (eg, from 10 to 60 minutes).

Geriatric Patients

Sarcopenia in elderly patients is characterized by a pronounced reduction in cross-sectional area of type II muscle fibers [115]. Although volitional specific recruitment and training of type II fibers is difficult for frail, elderly people, NMES offers a training modality by which type II fibers (at least some of them) can be recruited in addition to type I fibers, which may lead to an improvement in maximal force and functional activities, such as rising from a chair or walking upstairs.

Similar to critically ill patients, there is only a small number of NMES studies that have focused on elderly, mostly orthopedic, subjects (mean age ≥70 years), with equivocal results. Some studies have found an increase in muscle force after NMES training in hospitalized patients with various pathologies, which was greater than what was achieved with conventional rehabilitation training [5,116]. Unsurprisingly, greater strength improvements were found with whole-body NMES (NMES of trunk, upper arms, buttocks, and thighs) compared with no training in weak but otherwise-healthy elderly women [86]. However, strength improvements were inferior to those achieved by volitional strength training in orthopedic patients [117]. Similarly, a review on muscle strengthening in elderly patients with knee osteoarthritis found favorable outcomes with NMES training with limited evidence that NMES was better than other rehabilitation programs [118].

Stimulation duration and intensity should be low during the first sessions to avoid muscle damage. Stimulation intensity should then gradually be set to the maximum tolerable and increased whenever possible. A training frequency of 2-3 times per week to allow for sufficient regeneration may be applicable.

Patients with CHF and COPD

Muscle dysfunction in CHF and COPD patients is characterized by an abnormally low aerobic capacity [119-122]. Therefore, in these patient groups NMES was used not only to successfully improve muscle force and power but also fatigue resistance. A recent meta-analysis in patients with CHF found that NMES training was as effective as volitional aerobic training in improving muscle strength and 6-min walking distance but gains in VO_2peak were smaller with NMES [123].

In CHF and COPD patients, both tetanic and non-tetanic frequencies have been used in NMES training programs, with most studies demonstrating benefits in both muscle maximum force as well as endurance [9,20,99-101,124]. The general recommendation in patients with CHF is that high blood pressure should be avoided [125]. Therefore, long on times (>4 seconds) may be contraindicated when stimulating a large muscle mass.

Patients with an Electrical Device

Long-term NMES training of lower-extremity muscles has been found to be safe in patients with an implantable cardiac defibrillator [126] and in patients with pacemakers [127]. In a case study, NMES did not interfere with left ventricular assist device performance [128]. Contrary to NMES, because of the use of much greater frequencies, transcutaneous electrical nerve stimulation is not recommended in patients with an implantable cardiac defibrillator [129].

Obese and Diabetes Mellitus Type II Patients

In obese and diabetic patients, NMES can be used to improve muscle strength and endurance but also to enhance energy consumption. In obese subjects, oxygen consumption reached 8.7 ± 1.3 mL*min^{-1}*kg^{-1} (47% of VO_2peak) and energy expenditure 318.5 ± 64.3 kcal/h during a 5 Hz stimulation, which corresponded to the energy expenditure recommended in weight management programs [130]. In healthy subjects with stimulation of lower and upper body muscles, values as high as 40 mL*min^{-1}*kg^{-1} (10-fold increase) can be achieved with NMES [131,132]. Furthermore, whole-body glucose uptake was enhanced until at least 90 minutes after exercise cessation (greater than after volitional training) [27,102].

Energy consumption can be maximized by using nontetanic stimulation (4-5 Hz) of a maximally large muscle mass for a time duration of at least 1 hour per day. Pulse durations of at least 0.5 ms should be used in obese subjects, because the large impedance of the skin and subcutaneous fat requires high current intensities [133].

Orthopedic Patients

Before or after orthopedic surgery (most commonly hip or knee arthroplasty, anterior cruciate ligament surgery), patients often experience extended periods of immobilization, which lead to muscle atrophy in the affected and sometimes also in the nonaffected limb. Here, NMES can assist in maintaining muscle mass and muscle force [1,134,135]. The NMES training should be started as soon as possible, preferably before surgery if pain permitting. Isometric contractions by simultaneous contraction of agonists and antagonists will prevent joints from further damage and pain. Because an increase in muscle force is desired, stimulation frequency should produce tetanic contractions (25-75 Hz), and on times of at least 4 seconds should be used. Stimulation can be performed every day for 30-60 minutes.

Nephrology Patients

There are few studies on NMES training during hemodialysis in patients with chronic kidney disease. NMES has been found to stabilize blood pressure during hemodialysis [136] and to improve dialysis efficacy [137,138]. Also, improved exercise capacity has been found [137]. The only 2 studies on NMES in hemodialysis patients that have used stimulation frequencies of 9-10 Hz and on-times of 15-20 seconds. The training goal in these patients is to counteract extensive muscle wasting, which would most likely be achieved with a NMES hypertrophy training (high current intensity, high stimulation frequency, long on-times, high duty cycle) combined with nutritional supplements and anabolic hormones [139,140].

Peripheral Arterial Disease (PAD)

In patients with PAD, low-frequency NMES of the calf muscles significantly increased pain-free and maximum walking distance [141]. Low-frequency NMES did not induce an increase in the albumin:creatinine ratio and resulted in an 81% smaller increase in activated leucocyte than a standard treadmill test [141]. Furthermore, NMES of the calf muscle in patients with PAD increased arterial inflow without measurable muscle ischemia or pain [142]. Given the sparse scientific evidence of NMES efficacy in patients with PAD, it is too early to provide recommendations for NMES training, other than the prospect that low-frequency stimulation (4-5 Hz) of calf and upper leg muscles may provide a promising therapeutic regimen in these patients.

Conclusions

This review summarizes scientific evidence of the use of NMES in deconditioned patient populations for the purpose of increasing muscle force as well as improving muscle function and exercise capacity. Potential underlying mechanisms are deducted from established knowledge on volitional training.

Effectiveness of NMES in improving muscle force and muscle function as well as exercise capacity in deconditioned patients can be enhanced by appropriate choice of stimulation parameters according to specific training goals and tailored to patients' diseases.

This review is the first to give an overview of clinical NMES application over a wide range of disease conditions all leading to deconditioning. Clinicians may find our practical recommendation with regard to the choice of stimulation protocols and parameters for specific patient populations helpful.

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Disclosure

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