THE APPLICATION OF NEUROMUSCULAR ELECTRICAL STIMULATION TRAINING IN VARIOUS NON-NEUROLOGIC PATIENT POPULATIONS- A NARRATIVE REVIEW

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Abstract

In the last two decades, neuromuscular electrical stimulation has increasingly been used 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. There is insufficient clinical and basic knowledge 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-neurological patients, because training goals of neurological patients are specific to their functional deficits.

Key-words: neuromuscular electric stimulation, muscle weakness, muscular atrophy, resistance training.
1. Introduction

Since approximately the 1990s, neuromuscular electrical stimulation (NMES) has increasingly been used for the purpose of muscle strengthening in deconditioned patients, for example in orthopedic patients before and/or after surgery (1-3). More recently, NMES has been successfully implemented in intensive care unit (ICU) patients 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). While 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 due to a mostly small stimulated muscle mass the effects of NMES are generally smaller compared to 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, explains 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-neurological patients, because training goals of neurological patients are specific to their functional deficits.

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

3.1. 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 is usually 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 two reviews on healthy subjects and athletes, respectively (16,17), and is highly dependent on motivation of the subjects (17). In patient populations, MVC are generally 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 higher 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 are generally 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.

3.2. Metabolic stress

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

On the level of the contracting muscle, NMES-induced contractions may, however, lead to an exaggerate \(\text{VO}_2\) demand even at a relatively low mechanical load (28,29). When \(\text{VO}_2\) consumption during contractions of the knee extensors either by volitional or force-matched NMES-induced contractions was compared, \(\text{VO}_2\) consumption was higher with NMES (11 vs. 8 ml\(\text{min}^{-1}\text{kg}^{-1}\) at 46% MVC) (30). Similarly, in a study using positron emission tomography, Vanderthommen and coworkers measured a higher local oxygen consumption in NMES compared to volitional contractions (3.0 ± 2.3 vs. 0.7 ± 0.3 mL \(\text{O}_2\text{min}^{-1}\text{100 g}^{-1}\)) (29). The reason for a higher \(\text{VO}_2\) demand may be a reduced mechanical efficiency because of the synchronous motor unit activation...
imposed by NMES, which requires higher frequencies to reach comparable forces (31). However, compared to
volitional whole-body exercise, metabolic demand is relatively low (26), due to 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 to
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 highlights different possible reasons for the
increased metabolic demand, which are mainly based on the unique motor unit recruitment pattern associated to
NMES: continuous, synchronous and exhausting contractile activity in a spatially fixed pool of motor units (33).

We summarize that, despite an only moderate increase in systemic oxygen consumption during NMES, large
local metabolic demands can be achieved.

3.3. 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 when compared to 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 histological 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 is also 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.
3.4. Evidence of acute cellular responses to hypertrophy stimuli

In volitional exercise training, muscle hypertrophy is the result of increased post-exercise 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 are likely to differ. For example, at the same force output, serum growth hormone concentrations were higher after a NMES training session compared with volitional exercise (32).

Muscle protein synthesis as an acute response to 60 min of NMES (60 Hz, 3s on/3s off) was clearly demonstrated in elderly diabetic men (40). This protein synthesis rate was approximately 30% lower than the one achieved after 30 min 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 post-exercise protein synthesis increases as a consequence of NMES and, similarly to volitional training, depends on training parameters.

4. Chronic effects of NMES training

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

4.1 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 was also effective in improving muscle strength in patients with advanced disease, such as COPD and 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 to volitional training, results achieved by NMES were mostly inferior to volitional training (44,45).

The physiological adaptations leading to strength gains with NMES are, similarly to volitional exercise, of neuronal and myocellular nature. Increases in strength were found already after 4 weeks of NMES training,
while 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 has consistently been found to improve muscle strength. The gain in muscle force is
based on both neural and structural adaptations.

4.2 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 due 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 to 75 Hz
(48,58,59). In contrast, some studies have found an increase only in type I fiber CSA but a decrease in type II
fiber CSA (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 yet.

4.3 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), while such increases were absent in diabetic patients (65). Increases in maximal oxygen uptake may depend on selection of stimulation parameters and training protocol, however, they are also strongly affected by the stimulated muscle mass (i.e. 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.

5. Clinical recommendation for EMS applications

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

5.1. Variable parameters of NMES protocols

5.1.1. Electrode types

While most studies have used commercially available self-adhesive electrodes, a study by Lieber and Kelly has actually found that carbonized rubber electrodes produced the highest evoked torque of knee extensors (66). 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.

5.1.2. 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 higher the stimulation current has to be in order 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.

5.1.3. Pulse form and pulse duration

Commercially available stimulators offer square or sinusoidal current compensated pulses (e.g. 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, while 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 due 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.

5.1.4. 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 higher 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 due to individual differences in skin impedance, thickness of subcutaneous 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, also current intensity has to be determined for each subject individually. Due to 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.

5.1.5. Stimulation frequency

There are two main frequency ranges which 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 section 4.2.) 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 EMS, higher 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).

5.1.6. On-off time and duty cycle

On-off time is usually defined as the duration of active stimulation and the recovery time without active stimulation and is mostly indicated as x s on/y s off. Duty cycle is indicated as the ratio between on-time and total time, e.g. x:(x+y) (3). In general, a higher duty cycle (greater on- than off-time) is associated with higher metabolic stress (8,81). With regard to muscle fatigue, at long on-times, such as 10 s, intracellular acidosis due to the long contraction time leads to greater fatigue at higher duty cycles (e.g. 1:1 vs. 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 higher 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 Section 4.3.). While healthy subjects can sustain a large percentage of MVC with NMES at a duty cycle of 1:1 over a period of 30-60 min, 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 higher stimulation intensities.

5.1.7. 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 to complete 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 in order to achieve greater muscle tension with progressive training. Functional goals need to be defined at the start of the training program as gains in isometric force may be specific to the joint angle at which NMES training is performed (46,55).

5.1.8. Training frequency and duration

A wide spectrum of training durations and frequencies have been used in published NMES studies. Training volumes have ranged from 30 min per week (86) to 28 h 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). In the absence of NMES studies that have compared different frequencies with the same stimulation parameters, 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 (e.g. critically ill patients, orthopedic patients), for lasting benefits the training needs to be performed indeterminably.

5.2. 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. While some NMES studies in athletes have defined clear goals and have assessed them with appropriate methods (92,93), goals in patient
groups are often 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.

5.2.1 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 s in order 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 have so far only been assessed in one 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 to the same training volume at 15 Hz in COPD patients (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.

5.2.2 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).

5.2.3 Improvement of cardiopulmonary exercise capacity, glucose uptake or insulin sensitivity

While tetanic frequency stimulation with short on-off times (1 s on/1 s off) has been found to improve glucose metabolism in healthy subjects (27,102), the use of non-tetanic frequency stimulation (4-12 Hz) - which produces muscle twitches rather than fused contractions - has commonly been used for maximizing energy consumption in obese and/or diabetic subjects, and to alleviate hyperglycemia (103). Minogue and colleagues 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 (104). 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, non-tetanic 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 min) and training frequency as high as possible (5-7 times per week).

5.3. 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 have 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).

5.3.1. 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 and colleagues (111). One restriction may be that in very acute ICU patients NMES may be unable to prevent muscle atrophy due to 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).

Due to 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 which would produce further inflammation (114). It may be safer to use non-tetanic stimulation initially (e.g. 4 Hz) in order to avoid any form of DOMS, and then introduce tetanic contractions with rather low frequencies (e.g. 20-25 Hz) and short duty cycles (e.g. 2 s on/2 s off). Session time may be gradually increased from day to day (e.g. from 10 to 60 min).
5.3.2. Geriatric patients

Sarcopenia in the elderly is characterized by a pronounced reduction in cross-sectional area of type II muscle fibers (115). While 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 $\geq$ 70 yrs), 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, strength improvements were found greater with whole body NMES (NMES of trunk, upper arms, buttocks and thighs) compared to no training in weak, but otherwise healthy elderly women (117). However, strength improvements were inferior to those achieved by volitional strength training in orthopedic patients (118). 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 (119).

Stimulation duration and intensity should be low during the first sessions in order 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.

5.3.3. Patients with congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD)

Muscle dysfunction in CHF and COPD patients is characterized by an abnormally low aerobic capacity (120-123). 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 $\text{VO}_2\text{peak}$ were smaller with NMES (124).

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.
The general recommendation in CHF patients is that high blood pressure should be avoided (126). Therefore, long on times (>4 s) may be contraindicated when stimulating a large muscle mass.

5.3.4. Patients with an electrical device

Long-term NMES training of lower extremity muscles has been found to be safe in implantable cardiac defibrillator (ICD) patients (127) and in patients with pacemakers (128). In a case study, NMES did not interfere with left ventricular assist device performance (129). Contrary to NMES, due to the use of much higher frequencies, transcutaneous electrical nerve stimulation is not recommended in patients with ICD (130).

5.3.5. 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 $8.7 \pm 1.3 \text{ ml*min}^{-1}\text{*kg}^{-1}$ (47% of VO$_2$peak) and energy expenditure $318.5 \pm 64.3 \text{ kcal/h}$ during a 5 Hz stimulation, which corresponded to the energy expenditure recommended in weight management programs (131). In healthy subjects with stimulation of lower and upper body muscles, values as high as $40 \text{ ml*min}^{-1}\text{*kg}^{-1}$ (10 fold increase) can be achieved with NMES (132,133). Further, whole body glucose uptake was enhanced until at least 90 min after exercise cessation (greater than after volitional training) (27,102).

Energy consumption can be maximized by using non-tetanic 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 higher current intensities (134).

5.3.6. 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 non-affected limb. Here, NMES can assist in maintaining muscle mass and muscle force (1,135,136). 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. Since an increase in muscle force is desired, stimulation frequency should produce tetanic contractions (25-75 Hz), and on times of at least 4 s should be used. Stimulation can be performed every day for 30-60 min.

5.3.7. Nephrology patients
There are few studies on NMES training during hemodialysis in chronic kidney disease patients. NMES has been found to stabilize blood pressure during hemodialysis (137) and to improve dialysis efficacy(138,139). Also, improved exercise capacity has been found (138). The two only studies using NMES in hemodialysis patients have used stimulation frequencies of 9-10 Hz and on times of 15-20 s. 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 (140,141).

5.3.8. Peripheral arterial disease (PAD)

In patients with PAD, low frequency NMES of the calf muscles significantly increased pain-free and maximum walking distance (142). 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 (142). Furthermore, NMES of the calf muscle in PAD patients increased arterial inflow without measurable muscle ischemia or pain (143). Given the sparse scientific evidence of NMES efficacy in PAD patients, 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.

6. Conclusions

This review summarizes scientific evidence of using 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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Table 1. Summary of recommended stimulation parameters, protocols and set-ups for different patient groups.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Authors</th>
<th>Stimulation frequency (Hz)</th>
<th>On-Off times (s/s)</th>
<th>Stimulation intensity</th>
<th>Session duration (min)</th>
<th>Sessions per week</th>
<th>Stimulated muscle group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critically ill patients</td>
<td>Maffiuletti et al. (4), Routsi et al. (110), Gruther et al. (111)</td>
<td>4-25</td>
<td>2/2</td>
<td>Avoid high intensities</td>
<td>10-30</td>
<td>2-3</td>
<td>Quads</td>
</tr>
<tr>
<td>Geriatric patients</td>
<td>Gremeau et al. (115), Maggioni et al. (5), Wall et al. (40), Kemmler et al. (85)</td>
<td>25-75</td>
<td>2/2 – 6/6</td>
<td>Maximally tolerable</td>
<td>20-60</td>
<td>2-5</td>
<td>Functionally important muscle groups (quads, gluts)</td>
</tr>
<tr>
<td>CHF/COPD</td>
<td>Sbruzzi et al (123), Quittan et al. (100), Sillen et al. (9,56)</td>
<td>4-75</td>
<td>Avoid long on times (&gt;4s)</td>
<td>Maximally tolerable</td>
<td>30-60</td>
<td>3-5</td>
<td>Major muscle groups of the legs</td>
</tr>
<tr>
<td>Obese/DMT2</td>
<td>Hamada et al. (27,101), Miyamoto et al. (102)</td>
<td>4-5</td>
<td>n.a.</td>
<td>Maximally tolerable</td>
<td>At least 60</td>
<td>≥ 7</td>
<td>Maximally possible muscle mass</td>
</tr>
<tr>
<td>Orthopedic patients</td>
<td>Bade &amp; Stevens-Lapsley (2), Levine et al. (134), Wright et al. (135),</td>
<td>25-75</td>
<td>4/4 – 10/10</td>
<td>Maximally tolerable</td>
<td>30-60</td>
<td>3-5</td>
<td>Quads (and gluts after hip surgery)</td>
</tr>
<tr>
<td>Nephrologic patients</td>
<td>Di Iorio et al. (139), Dobsak et al. (138), Farese et al. (136)</td>
<td>4-5 or 25-75 depending on training goal</td>
<td>4/4 – 10/10</td>
<td>Maximally tolerable</td>
<td>30-60 (during hemodialysis)</td>
<td>2-3</td>
<td>Major muscle groups of the legs</td>
</tr>
<tr>
<td>PAD</td>
<td>Abraham et al. (143), Anderson et al. (142)</td>
<td>4-5</td>
<td>n.a.</td>
<td>Avoid pain from ischemia</td>
<td>1-2 x 20</td>
<td>3-7</td>
<td>Quads and calves</td>
</tr>
</tbody>
</table>

CHF: Congestive heart disease; COPD: Chronic obstructive pulmonary disease; DMT2: Diabetes mellitus type 2; PAD: Peripheral arterial disease; Quads: Quadriceps muscles; Gluts: Gluteal muscles.