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Title: Could neuromuscular electrical stimulation improve the recovery of people with Covid-19 who require care in the intensive care unit? A narrative review

Authors

Louise C. Burgess (BSc)[1], Lalitha Venugopalan (PhD)[2], James Badger (MMedSc)[3], Tamsyn Street (PhD)[4,5], Gad Alon (PhD)[6], Jonathan C. Jarvis (PhD)[7], Thomas W. Wainwright (PgDip PgCert)[1,8], Tamara Everington (PhD)[9], Paul Taylor (PhD)[4,5], Ian D. Swain (PhD)[1]

Affiliations

1. Orthopaedic Research Institute, Bournemouth University, Bournemouth, UK
2. The Department of Biomedical Engineering, Saveetha Engineering College, Thandalam, Chennai, India
3. Department of Anaesthetics, University Hospital Southampton NHS Foundation Trust, Southampton, UK
4. National Clinical FES Centre, Salisbury NHS Foundation Trust, Salisbury, UK
5. Faculty of Health and Social Science, Bournemouth University, Bournemouth, UK
6. University of Maryland, School of Medicine, Department of Physical Therapy and Rehabilitation Science, Maryland, USA.
7. School of Sport and Exercise Science, Liverpool John Moores University, Liverpool, UK
8. Physiotherapy Department, University Hospitals Dorset NHS Foundation Trust, Bournemouth, UK.
9. Department of Haematology, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK.

Short title: NMES in Covid-19 patients admitted to the ICU

Abstract

The rehabilitation of Covid-19 patients after prolonged intensive care unit treatment is often complex and challenging. Patients may suffer a myriad of long-term multi-organ impairments affecting the respiratory, cardiac, neurological, digestive and musculoskeletal systems. Skeletal muscle dysfunction of respiratory and limb muscles, commonly referred to as intensive care unit acquired weakness, occurs in around 40% of all patients admitted to intensive care. The impact on mobility and return to activities of daily living is severe. Furthermore, many patients suffer ongoing symptoms of fatigue, weakness and shortness of breath in what is being described as "Long Covid". Neuromuscular electrical stimulation is a technique in which small electrical impulses are applied to skeletal muscle to cause contractions when voluntary muscle contraction is difficult or impossible. Neuromuscular electrical stimulation can prevent muscle atrophy, improve muscle strength and function, maintain blood flow and reduce oedema. This review examines the evidence, current guidelines, and proposed benefits of using neuromuscular electrical stimulation with patients admitted to the intensive care unit. Practical recommendations for using electrical muscle stimulation with Covid-19 patients are provided and suggestions for further research are proposed.

Keywords: critical care; rehabilitation; neuromuscular electrical stimulation; muscular atrophy; coronavirus infections; Covid-19

Lay Abstract

Many patients with Covid-19 who are admitted to the intensive care unit suffer ongoing symptoms of fatigue, weakness and shortness of breath. Neuromuscular electrical stimulation is a technique in which small electrical impulses are applied to skeletal muscle to cause contractions when voluntary muscle contraction is difficult or impossible. It can prevent muscle atrophy, improve muscle strength and function, maintain blood flow and reduce oedema. This review examines the evidence, current guidelines, and proposed benefits of using neuromuscular electrical stimulation with patients admitted to the intensive care unit. Practical recommendations for using electrical muscle stimulation with Covid-19 patients are provided and suggestions for further research are proposed.

Background

The COVID-19 (C-19) pandemic has seen unprecedented numbers of people being treated in Intensive Care Units (ICUs) throughout the world. Many patients have received artificial ventilation, and some have been ventilated for many weeks. Those that survive are often left with long term disabilities as a result of the effects of both the disease and of the treatments necessary to keep them alive. A myriad of multi-organ impairments is associated with C-19 including respiratory, cardiac, neurological, bowel and kidney dysfunction (1). The unexpectedly large number of C-19 patients requiring a prolonged ICU stay additionally increases the risk of dysfunction of both respiratory and skeletal muscle, commonly referred to as ICU acquired weakness (ICUAW). A conspicuous feature of C-19 is the persistence of symptoms, which may appear to resolve but then recur. As a result, many survivors are left needing significant rehabilitation at a time when such services are under great stress. This has led to the blanket term “Long Covid”, which describes ongoing fatigue, weakness and delayed recovery (2).

Strikingly, in the first seven months of 2020, there were more than 10,000 C-19 admissions to critical care in the United Kingdom (UK) National Health Service (NHS), which is four times greater than historic annual viral pneumonia cases (3). Our experience of C-19 in the UK is that critically unwell patients generally require a longer course of respiratory support, exacerbating other risk factors for ICUAW (Table 1) (3). At present, ICUAW is seen in around 20-50% of C-19 patients admitted to the ICU (4). General deconditioning, muscle atrophy, inflammation, and functional disability often necessitates transfer from the ICU to a long-term care facility. Exacerbations of chronic comorbidities and the cycle of prolonged bed rest, ongoing inflammation and malnutrition can lead to continued functional disability, immobility and continued ventilation support. Data from the UK Intensive Care National Audit and Research Centre (ICNARC) database indicates that older age, obesity, multiple deprivation, and the requirement for assistance in the activities of daily living are predictors for severe disease requiring admission to Critical Care (3). These risk factors are associated with a reduced level of background fitness, malnutrition and neuropathy. Infection with C-19 characteristically causes myalgia, lethargy and a loss of appetite likely to exacerbate this pre-morbid condition. Further deconditioning may result from constrained normal daily activities. This may be due to the disease itself, causing shortness of breath on exertion or delirium (5), or may be the result of supportive interventions and infection control measures. It is also noteworthy that proximal myopathy is associated with the use of therapeutic dexamethasone, a drug that has been shown to reduce 28 day mortality in C-19 (6).

After leaving hospital, almost 90% of survivors experience ongoing symptoms for more than two months, such as fatigue and shortness of breath, which are likely to limit rehabilitation and potentiate deconditioning (7). ICUAW is associated with worse outcomes, including a nearly two-fold increase in one-year mortality, and decreased quality of life (8, 9). A major challenge within current practice is how to ameliorate profound physical and functional deficits in C-19 survivors at a time where traditional services are stretched. Innovations that reduce the duration and improve the outcome of rehabilitation will alleviate the burden of suffering and economic damage caused by C-19.

Neuromuscular electrical stimulation (NMES) is the application of small electrical impulses to nerves supplying muscles using electrodes applied to the skin and has long been used as a treatment for muscle weakness (10). NMES can be used to induce a muscle contraction when it is difficult or impossible for the person to achieve this voluntarily thereby allowing effective exercise and the strengthening of muscles. NMES has been proposed as an intervention to address immobilisation and ICUAW in severe C-19 patients (11), however details on when and how to utilise NMES are lacking. As post-acute rehabilitation services respond to the increasing demand on services; recommendations are required to guide the delivery of rehabilitation models. This narrative review critically examines the evidence for using NMES in the ICU and offers suggestions for clinical practice among C-19 patients. This article provides practical recommendations using a continuum of care model for clinicians interested in using electrical stimulation for patients during and after prolonged ICU treatment.

Methodology

This narrative review was informed by the findings of a web-based literature search, completed in October 2020. The search aimed to identify studies that have investigated the role of electrical stimulation in the recovery of patients admitted to the ICU and published in the last ten years (January 2010-October 2020). A search strategy (supplementary material 1) was developed to capture randomised controlled trials or non-randomised clinical trials that have evaluated an intervention of electrical stimulation (FES or NMES) in patients admitted to the ICU. Specifically, we sought studies of adults (aged over 18 years), admitted to the ICU due to chronic illness or following non-elective surgery, who received an intervention of electrical stimulation, either i) during their stay in the ICU, ii) during the acute recovery phase in hospital, or iii) following discharge from hospital. The databases searched included: PubMed, EMBASE, Medline, CINAHL Complete, and The Cochrane Library. Articles were systematically reviewed by the research team to ensure they met the eligibility criteria (supplementary material 2) and were subsequently used to inform this critical analysis and recommendations for future practice. Studies were only included if they reported a replicable NMES protocol**.** In addition, recently published guidelines recommending the use of home based NMES for chronic respiratory conditions such as chronic obstructive pulmonary disease (COPD) from the National Institute of Clinical Excellent (NICE) were used to inform recommendations (12). A narrative review was considered the most appropriate methodology so that the research team could use a broad survey of the literature, in combination with expert opinion, to inform clinical recommendations. The research team is a multinational, multidisciplinary group of experts with many years clinical experience of NMES. The group includes biomedical engineers; physiotherapists; intensive care clinicians; physiologists and haematologists.

Recommendations

Physiological considerations

Fundamental to the treatment with NMES is an understanding of the electrophysiological mechanisms associated with skeletal muscle function. Skeletal muscles, including diaphragm and accessory respiratory muscles, are made up of long, multinucleate, approximately cylindrical cells containing sarcomeres in which the contractile proteins actin and myosin interact to generate force and shortening. Skeletal muscle powers voluntary movement, including speech and breathing, buffers circulating glucose, and is surprisingly labile. Disuse during bedrest causes loss of muscle mass by active cellular mechanisms. This presents a severe problem in ventilated patients. The domed diaphragm muscle normally flattens by shortening to generate a lower than atmospheric pressure in the pleural space, so the lungs inflate. During mechanical ventilation it quickly loses mass so that after ventilatory assistance, diaphragm function is reduced (13). The extreme reduction in activity from contraction during every breath, to zero, may explain why the diaphragm loses mass more quickly than, say, the pectoral muscles. In healthy persons, growth of muscle is often considered to be slower than the loss of muscle with disuse; to gain 1kg of leg muscle might take 12 weeks of resistance training, whereas 1kg of mass is lost in one week with complete disuse (14). The magnitude of the difference in activity before and after is very different in these scenarios, so prevention of atrophy with early activity-based methods may reduce the human and financial cost of rehabilitation after critical illness.

To activate muscle contractions from outside the body, action potentials must be generated in the muscle membrane. Stimulation is usually applied where the nerve that contains the target motor neurones is most accessible. Muscles respond to single action potentials with a brief period of activation then relaxation. The force response to a single stimulus is a very brief twitch with a low force. To produce stronger contractions, successive activations must be applied before the relaxation of the prior stimulus, and so frequencies in humans of 20-50 impulses per second are used (20-50Hz). Muscles require a continuous supply of oxygen and glucose to generate sustained work, and therefore contractions must be intermittent, because blood flow is excluded during strong contractions. The activity/rest cycle and the number of contractions in a session provides a huge number of possible combinations. Exercise is often prescribed in terms of a number of sets of repetitions (single contractions), with a rest period between sets. As a result, unless otherwise stated, cyclic electrical stimulation was used in the articles considered in this review, rather than any other NMES (for example, EMG-triggered stimulation).

Neuromuscular electrical stimulation and intensive care unit acquired weakness

The application of NMES to treat ICUAW is well documented within the evidence-base (15-18). The primary objective of interventions has been to induce intermittent muscle contractions with electrical stimulation to minimize the loss of muscle mass and excitability, to strengthen these muscles and to enhance the recovery of mobility during and after discharge from the ICU (19). The findings from pre-clinical work on underlying electrophysiological mechanisms from healthy participants and data from critical care patients suggest that to prevent ICUAW, an NMES program should begin in the ICU as soon as medically feasible. This is particularly relevant to people with C-19, as early intervention is advised due to the often-prolonged stay and risk for subsequent long-term ICUAW. Reducing initial muscle atrophy is preferable to extending rehabilitation due to the extended amount of time it takes to recover pre-ICU muscle strength (20). Those with risk factors for ICUAW should be prioritised because there is a small amount of evidence that NMES can reduce the prevalence of ICUAW (21).

Many studies have activated the quadriceps (Figure 1) along with another muscle group such as the hamstrings, whereas others have targeted the abdominal musculature. Stimulation parameters commonly used are a frequency between 30-50Hz, pulse duration of 250-400 μs and an intensity adjusted up to maximum sensory tolerance so that contractions are easily visible and palpable. Most studies have included one hour-long session or two 30 minutes sessions per day. There has been enough commonality to conduct systematic reviews and a meta-analysis using the Medical Research Council's (MRC) score for muscle strength as an outcome measure. Liu et al. (15) found a significant improvement in muscle strength for NMES over control (mean difference (MD)=1.78, 95% CI 0.44, 3.12 (p = 0.009)). All studies included in the review used the MRC scale to evaluate the strength of the surrounding muscles, with a score of <48 to diagnose ICUAW (22-26). Several previously conducted systematic reviews in the area are largely consistent with these findings (16-18).

The current most commonly protocols on the ICU, suggest that NMES at this stage for a limited amount of time might be sufficient to maintain muscle volume but not increase it. In one of the larger studies conducted, Dall'Acqua et al. (27) did not find a significant improvement in abdominal muscle thickness for NMES but interestingly found a significant decline in the control. Further support for this hypothesis is suggested in a recent study from Nakamura et al, (28) who examined the effects of a 20-minute daily dose of NMES (171 contractions per day) on femoral muscle volume. Researchers found a significant decrease in muscle volume for both the control and intervention group; however, the mean rate of muscle volume reduction was significantly less for the NMES group (NMES (standard deviation (SD)=10.4% (SD 10.1%), control=17.7% (SD 10.8%) (p=0.04)). The data from these studies and longer-term treatment, for example, up to nine weeks (29) suggests that NMES can be used in the ICU to slow down muscle wasting but it is necessary for participants to then use home based NMES to maintain and strengthen muscles post-ICU. Interestingly, recent research by Nakashini et al. (30) suggests that identifying the motor-point to elicit the strongest contraction, as well as increasing the number of contractions in a session, may maintain muscle strength more effectively. Researchers included a 30-minute daily session (180 contractions) for five days to the NMES group while the control had usual care. A significant difference in muscle volume and strength was found but no difference in ICUAW was found. This suggests that further research should be conducted into optimal dosing for ICU patients and is supportive of a period of post ICU NMES treatment for maintenance and recovery of strength.

Neuromuscular electrical stimulation in chronic obstructive pulmonary disease

As Covid-19 is a chronic respiratory condition, patients may share some similarities with COPD patients in terms of symptoms and complications (for example, shortness of breath, respiratory infection, heart problems and peripheral muscle weakness) and thus it is beneficial to review the evidence for NMES within COPD patient groups. Recently published NICE guidelines for the use of NMES to strengthen muscles in patients with chronic respiratory disease recommend that for those who are unable to exercise, evidence supports the use of electrical muscle stimulation. However, standard arrangements must be in place for clinical governance, consent and audit (12). A meta-analysis of nine studies including 276 patients with moderate-to-severe COPD found improvement in quadriceps muscle strength (standardised mean difference (SMD)=1.12, 95% CI 0.64 to 1.59 (p<0.001); 6 studies of 207 patients) with NMES (31). In a recent Cochrane review, improvements were found for peripheral muscle endurance (SMD=1.36, 95% CI 0.59 to 2.12, (p<0.001); 2 studies of 35 patients) and these improvements translated into improved 6-minute walking distance (MD=39.26m, 95% CI 16.31 to 62.22, (p<0.001); 2 studies of 72 patients) (32). An improvement in exercise endurance was also found (MD=3.62 minutes, 95% CI 2.33 to 4.91, (p<0.001); 3 studies of 55 patients) and days to first transfer out of bed was decreased for the NMES group (MD=-4.98 days, 95% CI -8.55 to -1.41, (p=0.006); 2 studies of 44 patients) (32). However, NMES was not associated with improvements to health-related quality of life (32), and thus the actual value of NMES for improved quality of life remains uncertain (31).

NMES stimulation parameters for COPD vary considerably among studies, with stimulation frequency set to a median value of 50Hz (range 15-75 Hz), pulse duration 400µs (200-700), target duty cycle 33% (13-75), session length 30 minutes (18-240), session frequency 5 times (2-7) each week, and programme duration 6 weeks (4-11) (31). All studies set stimulation amplitude to elicit a visible muscle contraction within the participant's tolerance and most found that the amplitude could be increased over the course of the programme. However, the high variability in length of time, parameters and different type of outcome measures used in the studies made comparison difficult.

Neuromuscular electrical stimulation to wean critically ill patients off ventilators

Neuromuscular electrical stimulation may be considered to help wean critically ill patients off ventilators and is advantageous when the patient cannot participate in voluntary exercise. Preliminary work supporting the added value of an NMES program to wean patients from dependence on ventilators is supportive of further research in this area. McCaughey et al. (33) provided the most credible, albeit preliminary data, that earlier weaning is possible. They applied NMES over the posterior-lateral abdominal wall to activate the transversus abdominis and internal and external oblique muscles during exhalation, automatically synchronized with the participant's breathing pattern. Stimulation was applied for 30 minutes, twice per day, five days per week, until discharge from the ICU. The study compared an active group receiving stimulation that caused a strong visible muscle contraction (30Hz frequency and a pulse-width of 350 μsec) to a control group that received sensory level stimulation (10 Hz frequency and 350 μsec pulse-width, but with an amplitude sufficient to be felt on the skin but not to cause muscle contraction). A survival analysis found ICU length of stay (median 11 versus not estimable days, (p=0.011)) and ventilation duration (median 6.5 versus 34 days, (p=0.039)) were shorter in the intervention compared to the control group. Dall'Acqua and colleagues (27) stimulated the pectoral and rectus abdominis muscles bilaterally for 30 min daily, using 300 μsec phase duration, 50 Hz pulse rate to induce a 3 second contraction followed by 10 seconds of relaxation and compared it to a sensory threshold stimulation group. Time to weaning off the ventilator was not recorded but the length of ICU stay was shorter in the NMES group (mean: 10 ± 4 days) compared to the control group (mean: 16 ± 9) (p=0.045). Other investigators used NMES to activate the deltoid and quadriceps muscles bilaterally, applied concurrently with active exercises or without exercises or exercise only and found no difference between groups in terms of time to discharge from the ICU (34). None of these three groups of investigators reported any adverse response or interference with the recovery of and discharge from the ICU.

Neuromuscular electrical stimulation and venous thromboembolism prevention

Venous thromboembolism (VTE), encompassing pulmonary embolism (PE) and deep venous thrombosis (DVT), is a common and severe complication of critical illness (35, 36). Many critically ill patients have multiple risk factors that predate ICU admission; including, recent surgery or trauma, sepsis, malignancy, immobilisation, increased age and cardiac or respiratory failure (37). Once admitted, patients that need treatment on the ICU are exposed to additional VTE risk factors, including prolonged immobilisation, pharmacological paralysis, central venous catheterisation, haemodialysis and treatment with vasopressors (37-39). In four recent meta-analyses of hospitalised C-19 patients, incidence of thrombotic complications was reported between 22.7%-31%, and risk persisted even in those receiving anticoagulation (40-43).

Prophylaxis aims to combat the three predisposing factors to VTE; venous stasis, hypercoagulability and endothelial injury (44). Traditional prevention strategies include pharmacological agents such as unfractionated heparin, low molecular weight heparin (LMWH) direct oral anticoagulants, and mechanical devices such as graduated compression stockings or intermittent pneumatic compression of the limbs (45). Interim guidance for C-19 recommends treatment with LMWH administered at prophylaxis doses pending the emergence of additional data and guidance (46). Despite receiving anticoagulation for thromboprophylaxis, a high rate of VTE has been observed among C-19 patients admitted to the ICU (43). NMES has been approved by NICE as an alternative prophylaxis when other mechanical and pharmacological methods of prophylaxis are impractical or contraindicated (47, 48). The transcutaneous application of electrical impulses stimulates the common peroneal nerve to generate dorsiflexion in the lower limb, which in turn activates the calf muscle pump emulating the normal physiological response achieved by walking, without the patient having to mobilise. NMES has been shown to be effective in reducing fibrinogen, D-Dimer and tPA levels, and increasing venous, arterial and microcirculatory flow, thus preventing venous stasis and oedema (49-58). Moreover, clinical evidence has shown effectiveness of NMES for reducing the incidence of DVT in hospitalised patients (59-66).

In line with recommendations from NICE, NMES should be considered as an alternative or adjunct prophylaxis in C-19 patients where other mechanical and pharmacological prophylaxis are impractical (47). It may be most effective when used prior to the formation of oedema, to prevent venous stasis and reduce VTE risk. Devices should be used in accordance with guidance (47) and the individual instructions for use of specific devices. If NMES is used for other treatment aims (such as muscle strengthening), it should be acknowledged that a circulatory effect will be delivered simultaneously, and so competing treatment aims may be balanced by preferentially aiming NMES settings for muscle strengthening parameters. Furthermore, NMES may provide the most benefit to patients who are immobilised or positioned where the leg is lower than the body.

Neuromuscular electrical stimulation and the continuum of care model

Neuromuscular electrical stimulation may be advantageous in C-19 as it can be used throughout the patient's recovery to address a number of physiological and clinical deficits (Figure 3) in a continuum of care model. Example applications of NMES for patients admitted to the ICU with C-19 are illustrated in Figure 4.

While minimising the amount of stimulation is pragmatic on the ICU unit, following discharge, similarly to any exercise programme, NMES can be progressively increased subject to patient tolerance and measurable benefits. As the patients begin to mobilize out of bed, a structured mobility program has been recommended (67). Adding the NMES to a structured physical exercise program appears advisable compared to applying the NMES in isolation (68). From a practical perspective, as long as the patient is non-responsive to verbal commands the NMES can be combined with passive range of motion (PROM) exercises. Once responsive, the patient should be encouraged to add volitional contraction and active range of motion (AROM) combined with the NMES. In studies with neurological patients, volitional contraction has been found to be more effective at inducing useful therapeutic improvements (69).

Following discharge from hospital, ongoing use of NMES may also be considered to address persistent symptoms and functional limitations. NMES can be applied independently in the home environment and is considered an attractive adjunct to enhance the hypertrophic effect of traditional exercise (10). Likewise, following discharge it may be appropriate to consider the ongoing use of NMES to increase blood flow and prevent oedema or DVT. Nonetheless, one of the main shortcomings of current research on NMES in the ICU is the lack of long-term follow-up because most studies only use NMES for the duration of hospital stay (5-14 days). This may be reflective of the lack of long-term rehabilitation and follow-up for these patients once they leave the ICU and hospital. Further research including long term follow-up should be conducted as currently it is unknown whether patients who appear to benefit during their stay in ICU continue to benefit after a relatively short period of treatment. Further research should also examine the potential benefits of home based NMES post-ICU as part of a continuum of care. Using NMES for a period of nine weeks such as in previous investigations (29) or for a minimum of six weeks as in many of the COPD studies may lead to sustained longer-term benefits (31).

Practical considerations

Early rehabilitation has been generally accepted as a safe and effective intervention in Critical Care (70-74). However, there are several practical issues that make the implementation of these interventions challenging, especially in those with C-19. Such issues include deep sedation for facilitating mechanical ventilation; delirium; prone positioning; access to appropriate number or type of personnel; physiological stability and obesity. An observation study in France demonstrated that 65% of those with C-19 admitted to Critical Care experienced delirium and therefore a significant number of patients presumably would have been unable to safely/successfully participate in active physiotherapy regimes while affected (75).

Furthermore, even passive interventions such as in-bed cycle ergometry are restricted to those in the supine position, rendering them unsuitable for C-19 patients for whom prone positioning for more than 12 hours per day is a widely accepted strategy for improving oxygenation (76). In addition, in-bed cycling is purely passive and although it will help maintain range of movement it will not increase muscle bulk or strength. Another consideration is weight restrictions on rehabilitation equipment, which may preclude the 7.9% of morbidly obese patients (3) admitted to Critical Care with C-19 from receiving a number of interventions. Finally, accepting that C-19 has resulted in an increase in intensive care admissions and physiotherapy demand, more efficient rehabilitation interventions and use of staff is required.

Safety considerations

Common equipment in an ICU includes mechanical ventilators to assist breathing through an endotracheal tube or a tracheostomy tube; monitors of cardiac functions; equipment for the constant monitoring of bodily functions; a web of intravenous lines, feeding tubes, nasogastric tubes, suction pumps, drains, and catheters; syringe pumps; and a wide array of drugs to treat the primary condition(s) of hospitalization. Accordingly, the clinical team must verify the compatibility of the stimulation system to ensure there is no interference with the electronic systems such as ECG and EEG monitors, pacemakers, defibrillators, or other implanted stimulators. Iwatsu et al. (77) provided evidence assuring the safety of stimulation in the ICU. Furthermore, none of the other published clinical trials that used non-invasive electrical stimulation in the ICU reported interference with the ICU equipment (27, 28, 30, 33, 34, 78). Interference with pacemakers and implantable cardioverter defibrillators appears to depend on the proximity of the electrodes to the implanted device; lower limb stimulation in particular appears safe in this group, but clinicians must be aware of, and monitor for, such an interaction (79) especially if stimulation of respiratory muscles is indicated. In addition, the stimulation system must meet all hygiene, disinfection and sterilization standards required by the hospital. When applying the electrical stimulation, clinicians must not apply the electrode over open wounds and should avoid any contact of the electrodes with external fixation hardware. In contrast, applying NMES over internal hardware appears safe (80, 81). Electrical stimulation is known to increase muscle perfusion and oxygen consumption in a similar way to light intensity exercise. Given that changes are small and reversible, it is likely to be safe in those receiving cardiovascular support, and studies in this cohort have not reported any adverse effects (78). Finally, when applying electrical stimulation to those with reduced consciousness, special care must be taken over skin integrity as the patient will not be able to report pain.

Summary

Innovations that save time and improve the outcome of rehabilitation will alleviate the burden of suffering and economic damage caused by C-19. Current evidence suggests that NMES can reduce the rate of muscle atrophy for patients admitted to the ICU. Whilst the evidence for increasing muscle mass is less clear, reduction of atrophy is a worthwhile goal in the pursuit of expedited recovery and return to independence. For the immobilised patient, NMES increases blood flow, reduces oedema and can be used as an alternative prophylaxis in cases where traditional methods are contraindicated. Evidence suggests NMES may play a role in the weaning of patients from ventilators and should be continued in the post-acute and longer-term phases of recovery. As such, NMES may be a suitable treatment modality to implement within rehabilitation pathways for C-19, with consideration of the practical and safety issues highlighted within this review. Future research endeavours should aim to evaluate the specific application of NMES to C-19 patients, the longer-term effect of NMES and the most effective parameters to influence underlying electrophysiological mechanisms.

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Table I. Risk factors for deconditioning and ICU associated weakness in C-19 in comparison to viral pneumonia(3)

Risk Factor for deconditioning/ICU associated weakness	C-19 (N=10,557)	Viral Pneumonia, 2017-19 (N=5,782)
Duration of advanced respiratory support, median days (IQR)	13 (7,23)	9 (4,17)
Multi-organ failure, %	40.8	26.3
Age, mean (SD)	58.8 (12.7)	58 (17.4)
Very severe comorbidities, %	13.6	24
Dependency prior to hospital admission, %	10.3	26.4

ICU=intensive care unit; C-19=Covid-19

Figure legends

Figure 1. Electrode positioning for electrical stimulation of the quadriceps (mannequin)

Figure 2. Electrode position for electrical stimulation of the peroneal stimulation for increased blood flow to the lower limb (mannequin)

Figure 3. Characteristics of a patient admitted to intensive care unit with Covid-19

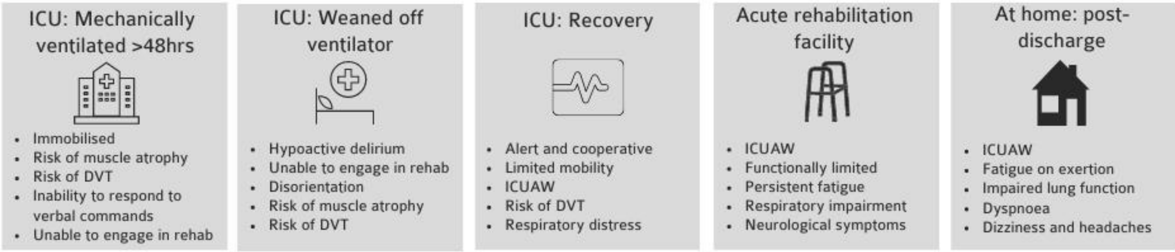
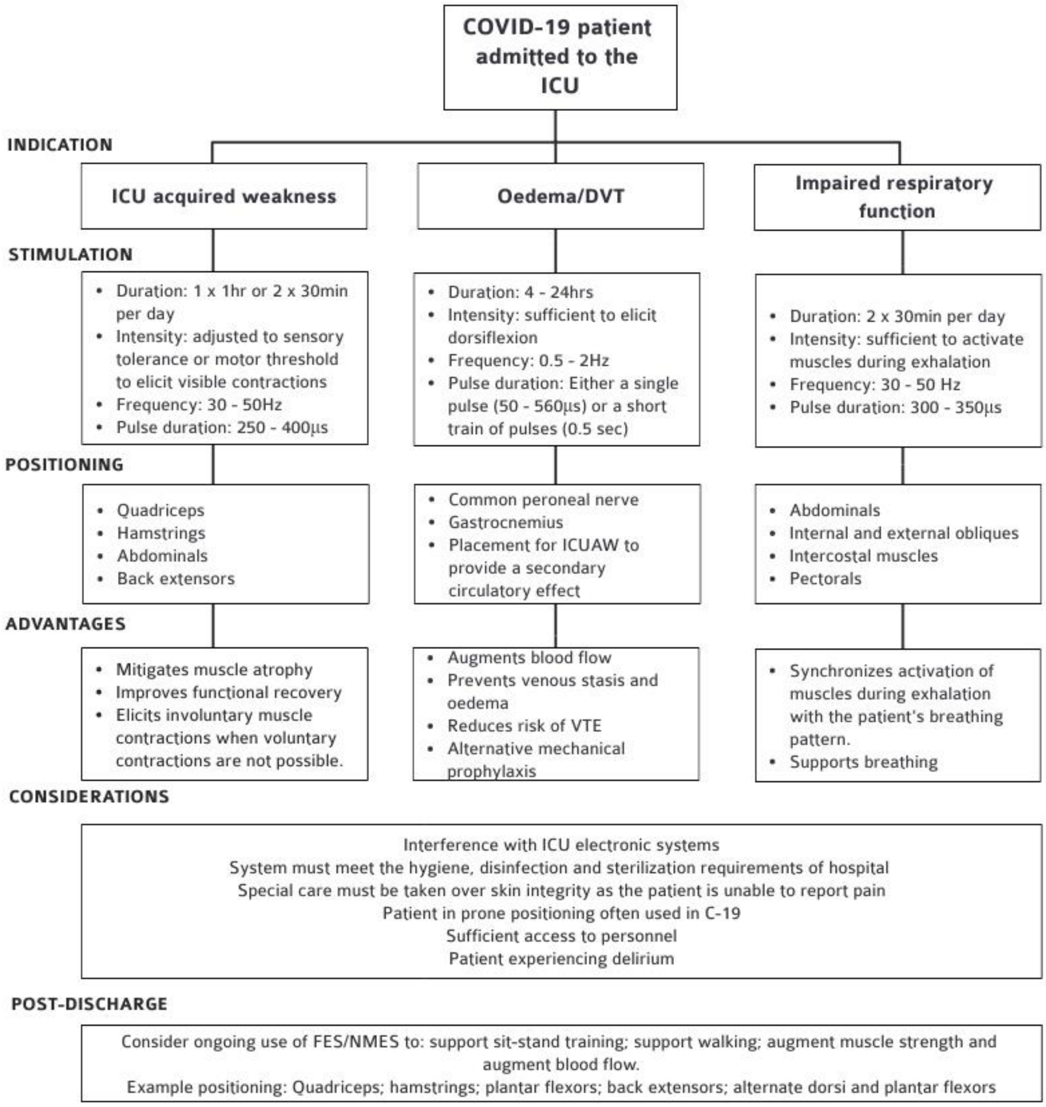


Figure 4. Example neuromuscular electrical stimulation application for patients admitted to intensive care unit with Covid-19 by indication



Supplementary material 1 – Search strategy

((heart failure) OR (chronic kidney disease) OR (critically ill) OR (critical illness) OR (multiple organ failure) OR (intensive care unit) OR (critical care) OR (ICU) OR (CCU) OR (intensive therapy unit) OR (ITU) OR (acute respiratory failure) OR (acute respiratory distress) OR (ARDS) OR (multiorgan failure) OR (mechanical ventilat*) OR (mobili*) OR (sepsis) OR (septic) OR (deep vein thrombosis) OR (DVT) OR (COPD) OR (COAD) OR (chronic obstruct* pulmonary disease) OR (chronic obstruct* airway disease) OR (chronic obstruct* airflow disease) OR (chronic obstruct* pulmonary disorder) OR (chronic obstruct* airway disorder) OR (chronic obstruct* airflow disorder) AND ((muscle strength) OR (muscle dysfunction) or (muscle atrophy) or (muscle degeneration) or (muscle deteriorate*) OR (intensive care unit acquired weakness) OR (ICUAW)) AND ((electrical stimulation) OR (neuromusc* stimulation) OR (function* stimulation))

Supplementary material 2 – Inclusion/exclusion criteria

Inclusion Criteria	Exclusion Criteria
Patient Population	
• Patients being treated for ICU-acquired weakness with NMES • Patients with Chronic Illness such as COPD, heart failure, and CKD that were being treated using NMES/FES to improve muscle mass and prevent muscle atrophy • Patients that were being treated using NMES/FES to improve blood flow and oedema.	• Patients with ICU-acquired weakness after an elective surgery. • Patients with stroke, multiple sclerosis, and spinal cord injuries.
Intervention	
• Functional Electrical Stimulation or Neuromuscular Electrical Stimulation	• Transcutaneous electrical nerve stimulation
Outcome	
• Stimulation parameters and the protocol used for the therapy	• Studies that did not clearly specify the protocol or the FES/NMES intervention
Methodology	
• Randomised controlled trials, systematic reviews and meta-analyses, and clinical studies that used NMES for the intended patient group. • Studies reporting a replicable NMES protocol	
Publication	
• Published in the last 10 years • Published in the English language • Studies with human participants • Access to full texts	• Animal studies • Conference abstracts • Protocols and non-clinical studies