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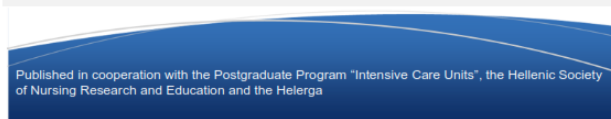
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RESEARCH ARTICLE

HIGH- VS MEDIUM-FREQUENCY NEUROMUSCULAR ELECTRICAL STIMULATION PROTOCOLS ON MUSCLE MASS IN INTENSIVE CARE UNIT PATIENTS, A PILOT STUDY

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Abstract

Aim: The aim of the present study was to investigate whether a high-frequency (HF) neuromuscular electrical stimulation (NMES) protocol could result in a smaller loss of muscle mass than a moderate-frequency (MF) protocol in ICU patients.

Methods and materials: In this randomized pilot control trial, patients of the two intervention groups followed daily NMES sessions from the day of ICU admission until the tenth day. All study groups received physiotherapy in terms of usual care. Muscle layer thickness was assessed with ultrasound in the vastusintermedius (VI) and rectus femoris (RF) muscle to evaluate changes in muscle mass.

Results: Totally 58 patients were allocated into three groups and 29 were finally analyzed (control: 10, MF: 12, HF: 7). Significant differences ($p=0.05$) between control and pooled NMES groups were observed for the right RF and VI. Significant differences in favor of HF vs MF group were observed for the left RF (3.6 ± 15.3 vs $7.2\pm7.9\%$ respectively, $p=0.04$). No differences were found regarding the number of sessions and presence of oedema ($p>0.05$), while strength of contraction during sessions tended to be somewhat higher in the HF ($p=0.09$).

Conclusion: HF may be more effective than MF to prevent muscle mass loss in ICU patients. More studies are needed to determine the optimal NMES characteristics.

Keywords: Early rehabilitation, muscle mass, NMES, frequency, electrical muscle stimulation, ICU.

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INTRODUCTION

A common complication in patients admitted in the Intensive Care Unit (ICU) is muscle wasting and weakness, observed from the very first days of hospitalization (1, 2). ICU acquired weakness (ICUAW), a type of skeletal muscle dysfunction related to overwhelming muscle wasting and weakness, is associated with delayed withdrawal from mechanical ventilation (MV), prolonged hospitalization, and poor prognosis (3, 4). Early mobilization has been increasingly applied to prevent ICUAW, shorten duration of ventilation and hospital stay, improve long-term patients' functionality, quality of life, and prognosis (5). Neuromuscular electrical stimulation (NMES), the percutaneous application of electric current that induces skeletal muscle contractions, has been suggested as a means of early mobilization, in unstable, uncooperating, or sedated patients to be applied from the first day of ICU admittance.

In ICU patients, NMES has been proposed as a potentially effective means of preventing or reducing muscle weakness and atrophy (6-9). NMES has been shown to reduce the incidence of ICUAW and the duration of MV (10) as it has the potential to induce acute systemic benefits on the microcirculation and endothelial function (11-13). NMES benefits have been additionally demonstrated in other sub-categories of critical illness, namely Chronic Obstructive Pulmonary Disease (COPD) (14,15) and Chronic Heart Failure (CHF) (16,17). In these studies, NMES frequency (the number of electrical pulses provided per second) ranged from 10 to 100 Hz. In general, when frequency is increased, higher tetanic force output and peak torque is expected, which consequently may influence NMES-evoked stimulus on muscle mass (18,19). To date, and to the best of knowledge, there is not any data on the effects of different-frequency NMES regimes on muscle mass in ICU patients.

It was hypothesized that a high-frequency NMES protocol would better affect muscle mass preservation than a medium-frequency regime. The primary purpose of this study was to provide preliminary data on the effect of two different NMES regimes, mainly including characteristic of frequency, on muscle mass maintenance in ICU patients.

MATERIALS AND METHODS

Study design, patients, and randomization

This was a randomized, pilot control study and the protocol was approved by the Ethics Committee of the Hospital participated. Written informed consent was obtained from all patients' next of kin.

All patients admitted to the multidisciplinary ICU during the study period that were under mechanical ventilation were considered for inclusion in the study. The first assessment of the patients' muscle mass was done on the day of randomization (second day in the ICU) and the second assessment was done ten days later. Exclusion criteria were as follows: age under 18 years, obesity (body mass index $> 35 \text{ kg/m}^2$), ICU stay > 7 days (patient not on mechanical ventilation) before enrollment, patient on mechanical ventilation > 48 hours (at the ward) before ICU admission, pregnancy, preexisting neuromuscular disease or muscle weakness (e.g inability of moving from bed to seat), limitations not allowing NMES implementation (e.g lower extremities cancer, pelvis or legs fracture, cutaneous wounds at site of electrodes implementation), moribund $> 90\%$ (in-hospital mortality according to doctor's judgment), refusal of patient's closest relative or treating doctor, a pacemaker or defibrillator, pre-existing mental or psychological disease.

Patients satisfying inclusion/exclusion criteria at admission, were randomized after stratification to either one of two NMES intervention groups or the control group (CON). All patients received physiotherapy in terms of usual care. The NMES groups were a high- (HF) and a medium-frequency (MF) one. Stratification was made upon age (\leq or > 50 years of age, median value of patients' age, as observed in previous studies of our group (10) and severity according to Sequential Organ Failure Assessment (SOFA) score ($<$ or ≥ 8) (20). For each study site separately, block randomization (within blocks of 6, generated before the onset of the study) was performed by a blinded investigator, not involved in NMES application, outcome assessment and patient follow up.

Intervention

Patients of the NMES groups undertook daily NMES sessions of

both lower extremities (quadriceps femoris muscles, anterior tibialis muscles), from the 2nd day of ICU admission to 10 days after. Current characteristics of the HF and MF groups respectively were 75 Hz, 400µsec, 5 sec on – 21 sec off, 1.6 sec ramp up – 0.8 sec ramp down and 45 Hz, 400 µsec, 12 sec on – 6 sec off, 0.8 sec ramp up – 0.8 sec ramp down based on previous data (6,10,21). NMES sessions were delivered in addition to usual care.

NMES patients received daily sessions (7 days/week) lasting for 55 min. each and including a 5 min warm-up and another 5 min cool-down (10 Hz, 400 µsec). NMES implemented with 9x5 cm self-adhesive electrodes that were placed on motor points of the quadriceps and tibialis muscles. Before placing the electrodes, the skin area was properly prepared (shaved, if necessary, and cleaned). During the NMES sessions, the angle at the knee joint was approximately 30°-40° (0° corresponds to full extension of the knee). The portable, battery-powered stimulator unit (Rehab 4 Pro, Cefar Medical AB, Malmö, Sweden) delivered impulses at intensities able to cause visible contractions and be tolerated by the patients. In case of doubt, contraction was confirmed by palpation of the muscle involved. Current intensity, optimally aiming at full muscle contraction, was continuously increased during the sessions to counteract the contraction induced reduction in response to the current due to muscle fatigue. In non-sedated patients, intensity was initially set to the maximum tolerated level and was increased by 10 % (or less in case of discomfort) every 15 min till the end of the session. In sedated patients, starting intensity was set at 80% of that resulting in maximal response and increased by 10% every 15 min up to 100%. During the sessions, qualitative scores were employed to rate the contractions quality (0: no contraction, 1: palpable contraction, 2: visible contraction, 3: slight knee extension, 4: full knee extension) and the presence of edema (0: no edema, 1: barely detectable impression when finger is pressed into skin, 2: indentation ≤ 15 sec to rebound, 3: indentation ≤ 30 sec to rebound, 4: indentation > 30 sec to rebound) (21).

Control patients received only usual care and in terms of physiotherapy. Usual Care physiotherapy included exercises for the upper and lower limbs (from passive to strength exercises

against light resistance), transfer to seated position at the edge of the bed and from bed to chair, as well as respiratory physiotherapy.

Assessment of muscle mass

Muscle mass was evaluated as the muscle layer thickness of the rectus femoris (RF) and vastus intermedius (VI) and was assessed with ultrasonography (picture 1). These muscle groups were selected since they are easily accessible and correlate well with the lean muscle mass (23). Images were taken the day of randomization (2nd admission day) and 10 days after, specifically the measurement was made four hours after the application of NMES. Measurements were performed while patients were in the supine position with legs relaxed in full extension. The probe was placed midway between the anterior superior iliac spine and the midpoint of the patella, vertically to the transverse plane and perpendicular to bone surface. The exact location of the first measurements was marked by a permanent marker to ensure repeatability at follow-up. All the ultrasound examinations were performed on GE Vivid 7 Model ultrasound scanner, using a 7.5 MHz transducer with a 5 cm linear array footprint. Operators were blinded to the randomization and not involved in the data analysis. Evaluation of images was also made by a blinded researcher.

Statistical analysis

The Shapiro-Wilk test was used to test distribution normality. Paired samples t-test or Wilcoxon signed-rank test (in case of not normal distribution) was employed to assess within-group differences. T-test for independent samples or Mann-Whitney signed-rank test, as appropriate, evaluated between-group differences. Categorical variables were compared with the chi-square test. Differences between groups over time were assessed with factorial analysis of variance (ANOVA) 2 × 2 (time × group). Statistical significance was set as $p \leq 0.05$. Continuous variables are reported as mean ± standard deviation (SD). Statistical analyses were performed with IBM SPSS 25 software.

RESULTS

A total of 751 patients met the study entry criteria and 693

were excluded. Fifty-eight patients were randomized, 18 in the CON, 20 in the HF and 20 in the MF group. Finally, 10 patients in the CON, 7 patients in the HF and 12 patients in the MF group, were evaluated on both baseline and follow-up measurements and included in the analysis (Figure 2). Baseline characteristics of the patients finally evaluated are presented in Table 1 and 2. The study was conducted between 2014 and 2016.

No difference ($p>0.05$) between control and pooled NMES groups was observed for the demographic and clinical variables assessed at ICU admission (Table 1). No difference ($p>0.05$) between MF and HF groups was observed for age, gender, and SOFA score. APACHE II score tended to differ ($p=0.07$), and there was a significant difference in terms of SAPS III score ($p=0.04$) at baseline.

In relation to the control vs pooled NMES group comparison (table 3), the muscle layer thickness was decreased in all the muscle groups evaluated ($p<0.05$). Significant between-group differences were observed for the right lower extremity ($p=0.05$, figure 3), but not for the left one ($p>0.05$).

In concern to the MF- vs HF-group comparisons (table 4), the muscle layer thickness of all the muscle groups evaluated diminished ($p<0.05$) or tended to diminish ($p=0.07$) in the MF, which was not the case in the HF ($p>0.05$). Significant differences between groups were observed for the left RF ($p=0.04$), but not for the rest of the muscle groups (right RF: $p=0.30$, right VI: $p=0.48$, left VI: $p=0.99$) (figures 4 and 5).

Not any significant difference was found for control vs NMES or MF vs HF comparisons at all the muscle groups evaluated at baseline ($p>0.05$). Finally, not any differences between the MF and HF groups were also observed (table 5) for NMES sessions completed, and presence of edema ($p>0.05$). Strength of contraction during these sessions tended to be somewhat higher in the HF ($p=0.09$).

In terms of safety, not any adverse effects related to the NMES application were observed (i.e., skin irritation or burn, haemodynamic instability).

DISCUSSION

The main finding of this study was that a HF protocol may be

more effective than a MF protocol to preserve muscle mass in critically ill patients. To the best of knowledge, this is the first randomized controlled study to compare effects of medium- vs high-frequency NMES on muscle mass in these patients.

NMES has been an alternative means of training in patient populations not able to be involved in conventional exercise rehabilitation. In previous years, there have been various studies in critically ill populations, namely CHF (17,24,25), COPD (26-28) and ICU (7-10,29) patients, suggesting beneficial effects of NMES on quality of life, aerobic capacity, muscle mass preservation and cachexia. Different protocols have been utilized, with frequencies varying from 10 Hz to 100 Hz, covering the low- to high-frequency spectrum. Still, there has been limited data comparing effects of different frequencies. Chaplin et al compared changes in muscle strength after two different medium-frequency NMES (50 and 35 Hz) in individuals admitted to hospital with an acute COPD exacerbation and they did not observe any significant difference between the two groups (30). Sillen et al (31) showed similar effects of low- (15 Hz) vs high-frequency (75 Hz) on oxygen uptake, ventilation, and symptom perception during a single NMES session on quadriceps of COPD patients. In an intervention study with COPD patients to compare the efficacy of high- (75 Hz) and low-frequency (15 Hz) NMES on quadriceps muscle weakness, Sillen et al observed higher increase in muscle strength and endurance after the high-frequency regime (32). However, the comparison of the results from the above studies is not possible since the protocols differed in terms of the characteristics used, such as frequency.

Higher frequencies are expected to generate higher peak torque than lower frequencies, because of enhanced twitch summation during muscle contraction (19,33). As a result, HF NMES may result in improved local muscle adaptations in ICU patients, such as less muscle mass loss and strength improvement. In a study with healthy participants, HF NMES (60 Hz) acutely induced a higher rise in molecular indices of muscle hypertrophy in comparison to LF NMES (20 Hz) regime (19). Benefits related to prevention of muscle wasting have been observed with MF and HF NMES (6,11). Interestingly in this study, HF tended to induce higher strength of contraction than

MF, an observation confounded by the lower APACHE II and SAPS severity/morbidity scores in the HF group at admission. The observation that RF thickness was mostly affected, could be explained by the potentially different degree of activation of the RF and VI muscle groups during NMES exercise (34).

Our group has also employed the protocols used in this study to explore the NMES acute effects in the ICU setting. A single session on both lower extremities, with either MF or HF NMES, acutely mobilized endothelial progenitor, an index of the endothelium restoration potential, and beneficially affected local and systemic muscle microcirculation (12,13). Both protocols were found similarly effective.

Technically speaking, a couple of additional points can also be highlighted. Beyond frequency, duty cycle was also considered to control for level of fatigue; this was 67% and 12% for MF and HF, respectively. Also, for the reason of preventing fatigue and maintaining strength of contraction, intensity was increasingly adapted throughout the sessions (by 20%), in both sedated and cooperating patients.

Taken both frequency protocols together, NMES was able to induce better results on muscle mass preservation than controls, without completely alleviating muscle wasting. This finding is in line with some previous studies, but not with others. Gerovasili et al (7) observed NMES to relate with a lower degree of muscle mass loss, as assessed with ultrasonography measurements of the cross-sectional diameter of the rectus femoris and vastus intermedius. In another study, that of Dirks et al (34), NMES resulted in not any changes on type 1 and 2 muscle fiber cross-sectional area as well as enhanced phosphorylation of key proteins participating in the regulation of muscle protein synthesis, as evaluated with muscle biopsies. In any case, alleviation of muscle wasting has been associated to ICUAW prevention. NMES, acting as an anabolic stimulus to the muscle, has the potential to reverse the catabolic effects of critical illness and immobilization (35,36). Muscle mass is also connected, up to an appreciable extent, to muscle strength, which has been also demonstrated to improve with NMES intervention (33,38). The rate of muscle mass loss reported in this study may be considered comparable to rates previously observed (6-13% to 12.5%) in another study of our group (7).

Lower rates, within 4%, have also been observed (38).

From a clinical perspective, muscle weakness is a common complication of ICU hospitalization, associated with increased rate of muscle mass loss starting at the first days after admission, and entailing serious implications in weaning, length of stay in the ICU/hospital, and incidence of the post intensive care syndrome. NMES has been an important means of early mobilization with advantages including cost-benefit effectiveness, ability to apply in the first 1-2 days from admission, and ability to apply in sedated, non-cooperative or physiologically unstable patients. Therefore, defining the current characteristics to optimize benefits sounds clinically relevant and interesting.

Some limitations need to be addressed. A limitation was the sample size, and the results were underpowered to reach definite conclusions. In fact, this was a pilot study to serve as a basis for further exploration. Another limitation comes from the fact that patients randomized to the MF group presented with higher severity/morbidity scores (i.e APACHE II and SAPS III), suggesting more severe clinical condition, than those in the HF group. This issue is likely an indirect effect of the small sample size, since the SOFA score at admission was a criterion of the stratified randomization. In addition, there was not any difference in SOFA score at admission between MF- and HF-group. Finally, there was an increased number of drop-out patients.

Future studies are warranted to further explore the optimal NMES frequency and characteristics to mostly benefit muscle mass, strength and related variables and outcomes, in ICU populations.

CONCLUSIONS

In conclusion, a high-frequency protocol was observed to better preserve muscle mass of ICU patients than a medium-frequency protocol during the first 10 days of hospitalization. Further studies are necessary to define the optimal NMES frequency level in this population.

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Authors contribution

CG: formal analysis, investigation, writing – original draft; EKat: formal analysis, investigation, writing – original draft; EP: methodology, investigation, data curation, writing – review and editing; GS: investigation, data curation, writing – review and editing; IV: writing – review and editing, supervision; EM: methodology, writing – review and editing, supervision; SN: conceptualization, methodology, writing – review and editing, project administration; EK: methodology, formal analysis, writing – review and editing, visualization, project administration.

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Conflicting Interest

The authors declare that they have no conflicts of interest.

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ANNEX

Figure 1. Ultrasound image of rectus femoris (RF) and vastus intermedius (VI) to assess muscle layer thickness.



Table 1. Demographic and clinical characteristics of patients at ICU admission.

	Control group	NMES group	p	MF group	HF group	p
n	10	19		12	7	
age (years)	45±25	55± 16	0.27	55±15	55±13	0.91
gender (male/female)	7 / 3	13 / 6	0.99	7 / 5	6 / 1	0.33
height (m)	1.71 ± 0.12	1.71 ± 0.11	0.95	1.71 ± 0.13	1.69 ± 0.5	0.64
body mass (kg)	73 ± 11	75 ± 12	0.58	76 ± 13	74 ± 10	0.83
body mass index (kg/m ²)	24.9 ± 2.2	25.7 ± 2.5	0.39	25.6 ± 2.5	25.8 ± 2.7	0.85
SOFA	6 ± 3	7 ± 3	0.56	7 ± 3	6 ± 3	0.23
APACHE II	13 ± 8	13 ± 6	0.92	15 ± 6	10 ± 6	0.07
SAPS	46±15	54±15	0.18	60 ±12	46±15	0.04

SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation; SAPS III: Simplified Acute Physiology Score; NMES: neuromuscular electrical stimulation; MF: medium-frequency; HF: high-frequency

Table 2. Post-surgery status, diagnostic category and comorbidities of the patients finally included in the analysis at ICU admission.

	post-surgery pa- tient	diagnostic category	comorbidities ^
Control			
1	yes	neurological	none
2	yes	neurological	none
3	yes	gastrointestinal	respiratory, cardiovascular, gastrointestinal, hematological
4	yes	gastrointestinal	none
5	yes	gastrointestinal	none
6	yes	trauma	none
7	no	neurological	other
8	yes	trauma	none
9	no	cardiovascular	cardiovascular
10	no	sepsis	None
MF group			
1	yes	sepsis	respiratory, cardiovascular
2	yes	trauma	respiratory, diabetes
3	no	respiratory	none
4	yes	neurological	other
5	no	neurological	gastrointestinal, hepatic
6	yes	trauma	none
7	no	neurological	other
8	no	respiratory	cardiovascular
9	yes	sepsis	cardiovascular
10	yes	gastrointestinal	cardiovascular, other
11	yes	trauma	none
12	no	trauma	none
HF group			
1	no	sepsis	other
2	no	respiratory	cardiovascular, diabetes
3	yes	trauma	none
4	yes	neurological	respiratory
5	no	respiratory	cardiovascular, diabetes
6	yes	trauma	other
7	yes	neurological	respiratory

MF: medium frequency; HF: high frequency; F: female; M: male; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score

^ 9 categories of comorbidities were considered: respiratory disease, cardiovascular disease, diabetes mellitus, gastrointestinal disease, haematological disease, hepatic disease, renal disease, other, none

Table 3. Muscle layer thickness of control and pooled NMES groups.

	Control group				Pooled NMES groups				P ^b
	ICU admission	post	change (%)	p ^a	ICU admission	post	change (%)	p ^a	
RF right (cm)	1.54± 0.54	1.33± 0.48	-13.3±9.3	0.01	1.46± 0.41	1.37 ± 0.39	-5.9± 11.0	0.01	0.05
VI right (cm)	1.05± 0.40	0.75± 0.25	-25.3±15.3	0.01	0.85± 0.21	0.73± 0.21	-6.6 ± 27.3	0.02	0.05
RF left (cm)	1.50± 0.51	1.35± 0.50	-10.3± 11.0	0.02	1.36 ± 0.37	1.29± 0.35	-4.7±12.4	0.05	0.31
VI left (cm)	1.24± 0.66	1.02± 0.53	-17.7± 12.6	0.06	0.90± 0.31	0.80± 0.30	-11.0± 14.4	0.01	0.16

RF: rectus femoris; VI: vastusintermedius; NMES: neuromuscular electrical stimulation

^a within-group difference; ^b between-group difference

Table 4. Muscle layer thickness of medium- and high-frequency groups.

	Medium-frequency group				High-frequency group				p ^b
	ICU admission	post	change (%)	p ^a	ICU admission	post	change (%)	p ^a	
RF right (cm)	1.49 ± 0.44	1.38 ± 0.39	-7.2 ± 7.9	0.01	1.41 ± 0.38	1.37 ± 0.43	-3.6 ± 15.4	0.83	0.30
VI right (cm)	0.83 ± 0.19	0.68 ± 0.17	-17.0 ± 16.6	0.02	0.88 ± 0.25	0.80 ± 0.26	-6.6 ± 27.3	0.44	0.48
RF left (cm)	1.36 ± 0.31	1.20 ± 0.40	-22.8 ± 12.9	0.06	1.36 ± 0.31	1.38 ± 0.31	1.5 ± 8.8	0.67	0.04
VI left (cm)	0.99 ± 0.28	0.88 ± 0.32	-11.5 ± 10.2	0.07	0.83 ± 0.34	0.72 ± 0.28	-10.4 ± 18.1	0.13	0.99

RF: rectus femoris; VI: vastusintermedius; ^a within-group difference; ^b between-group difference

Table 5. Strength of contraction, edema, current intensity applied, and sessions performed within 10 days.

	Medium-frequency	High- frequency	p
strength of contraction	2.3 ± 0.7	2.9 ± 0.7	0.09
edema	0.2 ± 0.4	0 ± 0	0.38
current intensity – start (mA)	29 ± 20	30 ± 23	0.54
current intensity – end (mA)	36 ± 24	36 ± 24	0.54
sessions (number)	7.6 ± 1.8	8.3 ± 1.1	0.48
sessions (%)	89.2 ± 19.2	95.2 ± 20.2	0.16

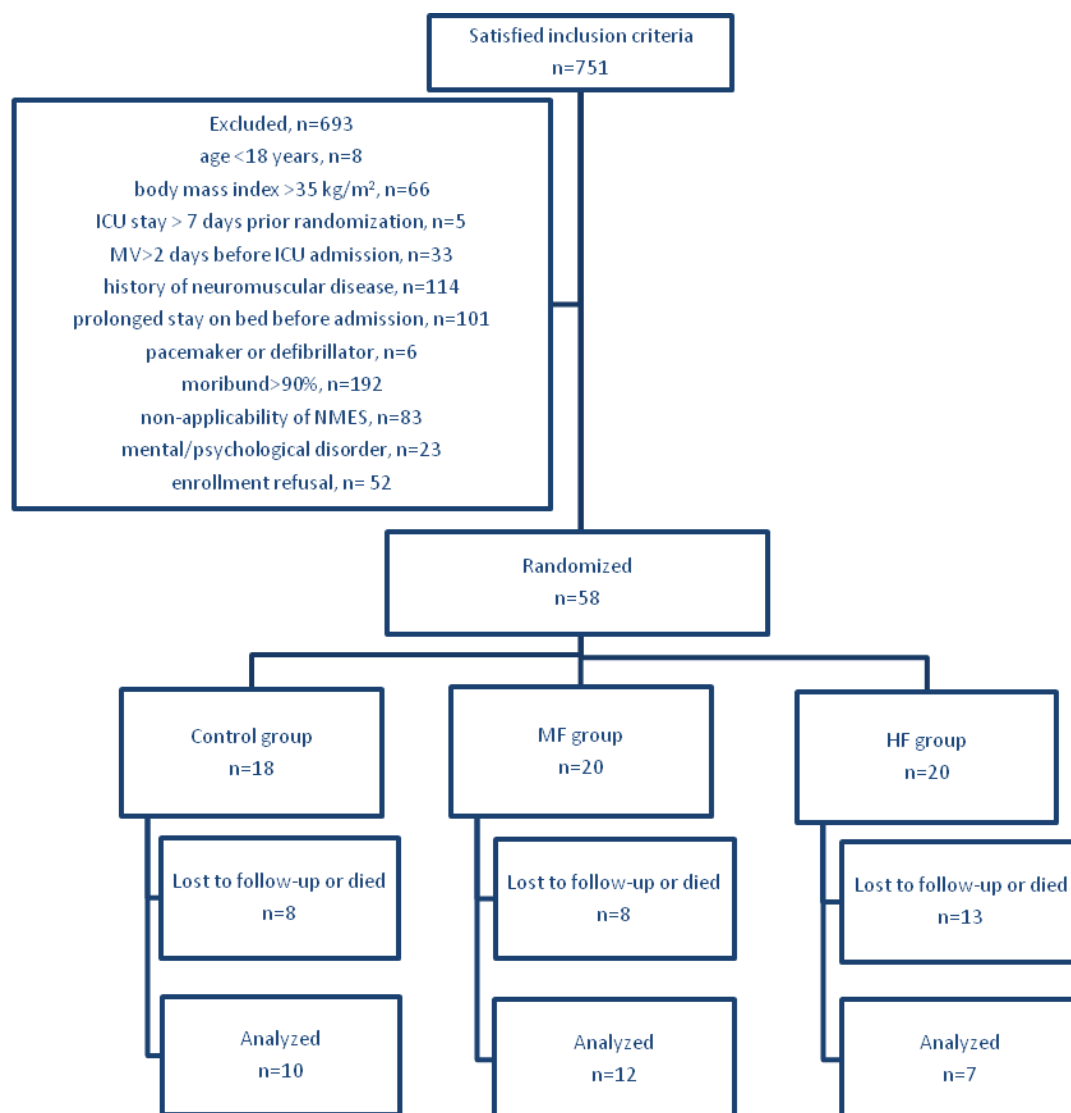
Figure 2. Flow diagram of the study

Figure 3. Muscle layer thickness pre- and post-intervention values of the right (a) rectus femoris and (b) vastusintermedius for control and pooled NMES group.

*within-group difference ($p < 0.05$)

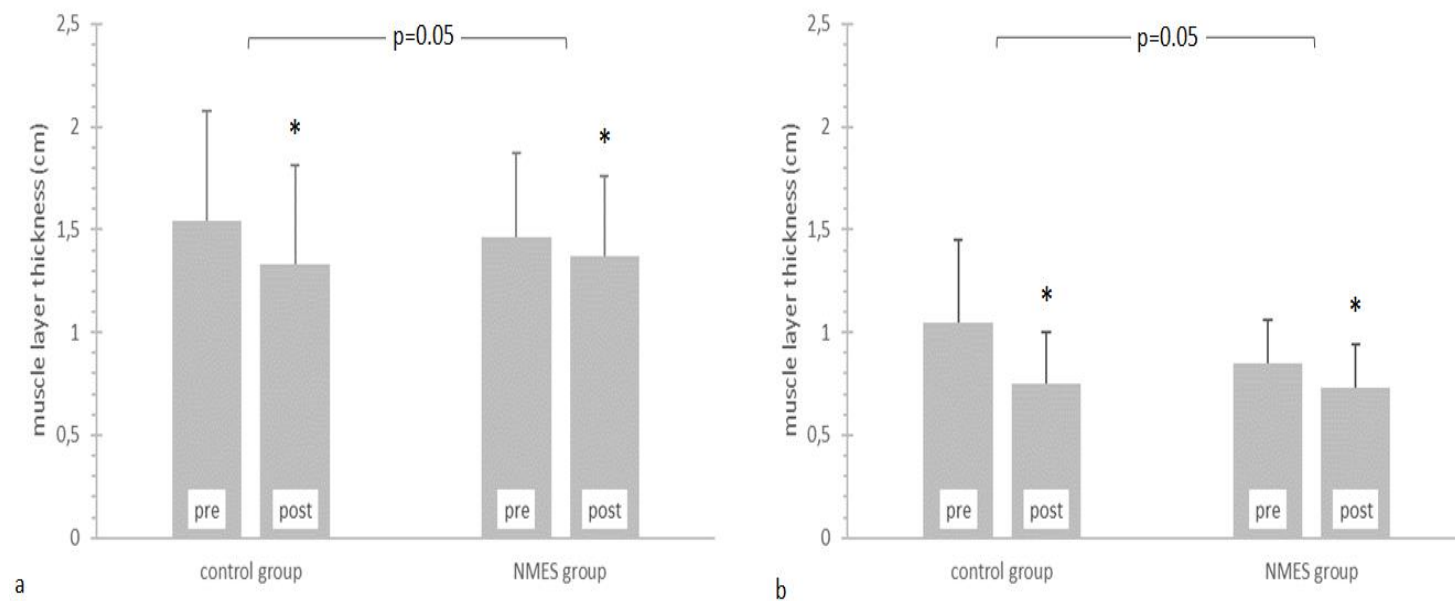


Figure 4. Muscle layer thickness at ICU admission (pre) and 10 days after (post) of the right (a) rectus femoris and (b) vastus intermedius for medium- and high-frequency groups.

*within-group difference ($p < 0.05$)

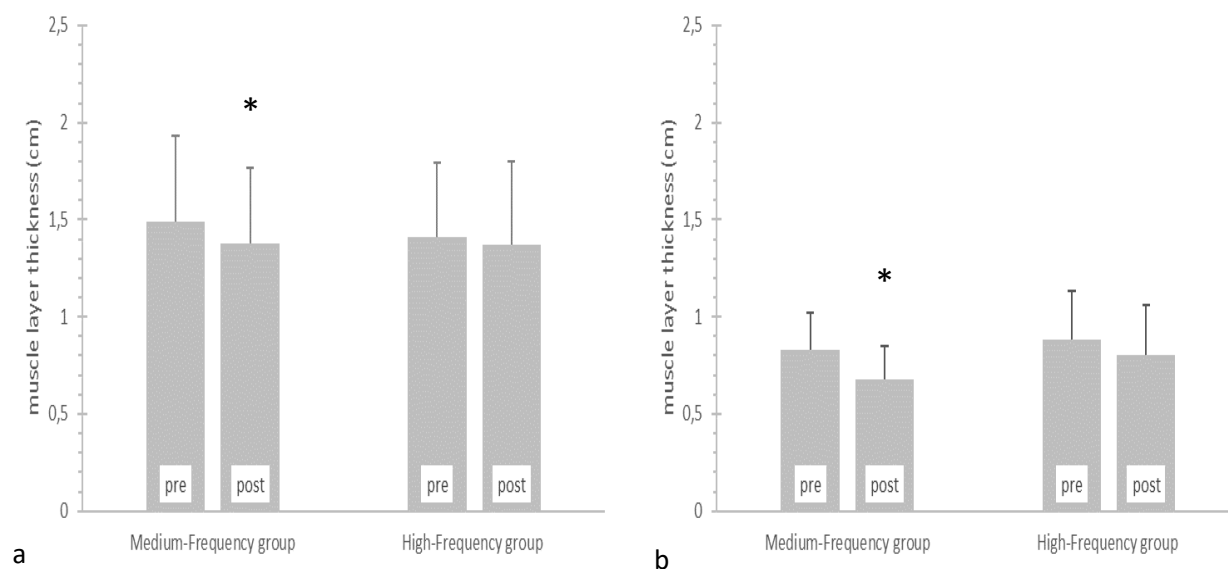
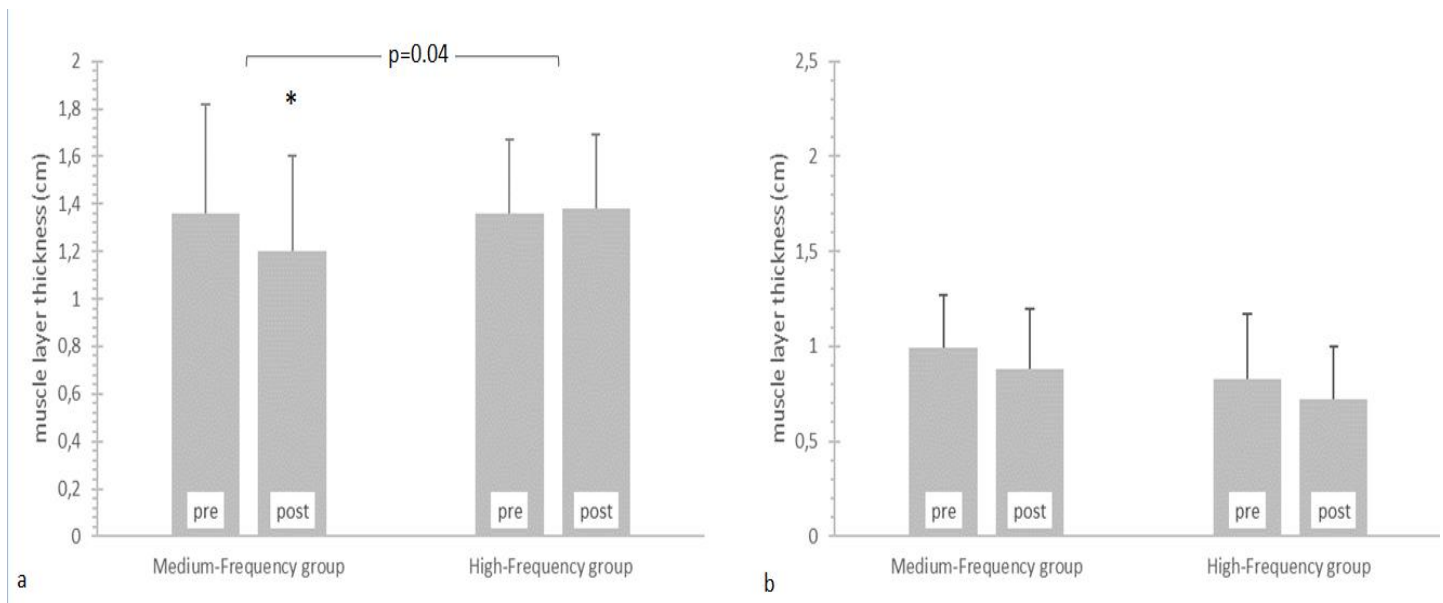


Figure 5. Muscle layer thickness at ICU admission (pre) and 10 days after (post) of the left (a) rectus femoris and (b) vastus intermedius for medium- and high-frequency groups.



*within-group difference ($p < 0.05$)