論 文 題 目

糖尿病を併存する高齢心大血管術後患者を対象とした，神経筋電気刺激療法による術後早期筋力低下の抑制効果−多施設ランダム化比較試験−

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令和 3 年度学位申請論文

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CONTENTS

Abstract

Background: Cardiovascular surgery leads to postsurgical muscle weakness, probably because of muscle proteolysis and peripheral nerve dysfunction, which are augmented by aging and diabetes mellitus.

Objective: We examined the effect of neuromuscular electrical stimulation (NMES) on postsurgical muscle weakness in older individuals with diabetes mellitus.

Methods: We conducted a multicentre, randomized, controlled trial, and screened consecutive patients with diabetes who underwent cardiovascular surgery for eligibility (age ≥ 65 years). Those included were randomly assigned to the NMES or the sham group. The primary outcome was the percent change in isometric knee extension strength (%ΔIKES) from preoperative to postoperative day 7. Secondary outcomes were the percent change in usual (%ΔUWS), maximum walking speed (%ΔMWS), and grip strength (%ΔGS). A statistician who was blinded to group allocation used intention-to-treat analysis (student *t* test).

Results: Of 1151 participants screened for eligibility, 180 (NMES, n=90; sham, n=90) were included in the primary analysis. %ΔIKES was significantly lower in the NMES than sham group (NMES: mean -2%, 95% confidence interval [CI] -6 to 1; sham: -13%, 95% CI -17 to -9, $p < 0.001$). Among the secondary outcomes, %ΔMWS was

significantly lower and %ΔUWS and %ΔGS were lower, although not significantly, in the NMES than sham group.

Conclusions: A short course of NMES (< 1 week) mitigated postsurgical muscle weakness and functional decline in older persons with diabetes mellitus. NMES could be recommended as a part of postsurgical rehabilitation in older people with diabetes mellitus, especially those with a low functional reserve.

UMIN Clinical Trials Registry: UMIN000029940

要旨

背景

心大血管手術は，炎症性サイトカイン亢進による筋タンパク崩壊や末梢神経の微小循環障害によって術後筋力低下を引き起こす．糖尿病は，術後筋力低下を誘発させるインスリン抵抗性や糖尿病神経障害といった機序を有する．また，高齢者は若年者と比べて炎症反応の亢進が惹起されやすい．そのため，糖尿病併存の高齢心大血管術後症例に対しては，標準的な術後リハビリテーション以上の介入が求められる．心大血管術後症例において神経電気刺激療法（NMES）は，術後筋力低下の予防方策として注目されているが，ランダム化比較試験において，その効果は明らかとなっていない．

目的

本研究は，術後筋力低下が誘発されやすい糖尿病併存の高齢心大血管手術後患者に対象を絞り，NMES による術後筋力低下の抑制効果を明らかにすることとした．

方法

研究デザインは共同ランダム化並行群間比較試験とした．対象は待機的に心大血管手術が施行される 65 歳以上の糖尿病を併存した症例とした．性別，年齢（75 歳以上・未満）にてブロック層化ランダム化を行い，NMES 群とシャム群に分類した．NMES 群は術後リハビリテーション＋NMES（5 回/週，60 分/回）を，シャム群は NMES 群と同様なプロトコールとし，電気刺激のみシャム刺激を用いた．なお，NMES の電気刺激装置には，Solius

（ミナト医科学株式会社, 大阪, 日本）を使用した．本研究の主要アウトカムを等尺性膝伸展筋力，副次アウトカムを快適歩行速度，最大歩行速度，握力とした．アウトカムは，術前および術後 7 日目に測定し，術前から術後 7 日目の低下率を算出した．本研究におけるサンプルサイズは，先行研究の糖尿病併存例の結果より統計解析人数 150 例（Effect Size 0.42, β:0.8 , α:0.05）とし，2 割の脱落を考慮して 180 例の取り込みを行った．主解析を Intention to treat（ITT）とし, アウトカム欠損値の補完には Monte Carlo Markov chain 法を用いた．NMES 群とシャム群のアウトカムを対応のない T 検定を用いて比較した．

結果

2018 年 2 月 1 日から 2020 年 1 月 24 日の連続 1151 例の内，971 例を除外した 180 例が取り込まれ，NMES 群 90 例，シャム群 90 例に割り振られた．ITT 解析の結果，NMES 群の等尺性膝伸展筋力低下率が，シャム群と比較して有意に低かった（NMES 群 : -2.4% vs シャム群 : -13.0%, P< 0.001）．また副次アウトカムにおいても，NMES 群の最大歩行速度低下率がシャム群と比較して有意に低かった（NMES 群 : -13.9% vs シャム群 : -20.1% , P = 0.039）.

結論

糖尿病併存の高齢心大血管術後患者において，短期間の NMES は術後筋力低下および身体機能低下を抑制した．そのため，NMES は，高齢糖尿病患者の術後リハビリテーションの一部として推奨できる可能性がある.

1. Introduction

Neuromuscular electrical stimulation (NMES) triggers skeletal muscle contractions, inducing an increase in muscle protein synthesis and neural adaptation [1]. NMES has been reported to effectively strengthen skeletal muscle in people with chronic obstructive pulmonary disease and chronic heart failure [2]. NMES may also counter muscle weakness driven by acute systemic inflammatory reactions [3]. Postsurgical muscle weakness (PSMW) induced by systemic inflammation [4, 5] is becoming a major clinical concern as the proportion of older people undergoing cardiovascular surgery increases worldwide [6].

PSMW reduces the capacity to perform daily activities, especially in older persons with a low functional reserve. Muscle weakness induced by surgical stress may result from proteolysis caused by the postsurgical increase in levels of inflammatory cytokines [4, 7]. Increased levels of inflammatory cytokines also perturb the microcirculation within peripheral nerves [8] and impair motor neuron excitability [9]. The variability of PSMW suggests that these two pathways are influenced by pathophysiological factors. Diabetes mellitus (DM) can lead to PSMW via 2 mechanisms: insulin resistance and diabetic neuropathy, both are exacerbated by inflammatory cytokines [10, 11]. PSMW has been found greater in individuals with DM

than those without [12]. Furthermore, the impact of surgical stress on skeletal muscles is likely greater in older individuals with elevated insulin resistance [13]. To avoid PSMW, mobilization is initiated early; however, promoting an adequate level of muscle activity is difficult owing to hemodynamic instability in the immediate postsurgical period.

NMES may be used as a supplemental treatment along with early postsurgical mobilization to prevent PSMW. NMES is safe, even in the immediate postsurgical period [14] and may mitigate muscle proteolysis and PSMW [15]. However, recent randomized controlled trials (RCTs) found that NMES did not prevent PSMW or functional decline in persons undergoing cardiovascular surgery. These trials did not stratify for age or comorbidities [16]; they excluded participants ≥ 75 years [17], or included only those who stayed in the intensive care unit (ICU) for > 48 hr [18]. We hypothesised that NMES would prevent PSMW in specific populations. Therefore, this trial examined the effect of NMES on PSMW in older individuals with DM.

2. Methods

Study design and participants

We conducted a multicentre (Gifu Heart Centre, Toyohashi Heart Centre, Nagoya Heart Centre), parallel, two-arm, sham-controlled, randomized trial reported according to the CONSORT extension

for non-pharmacological treatments. Participants were consecutively screened at the time of elective cardiovascular surgery and were considered eligible if they were 65 years or older and had DM. DM was identified using the following criteria: current medications for DM, past diagnosis of DM, haemoglobin A1c level ≥ 6.5, fasting blood glucose level ≥ 126 mg/dL, or casual blood glucose level ≥ 200 mg/dL according to the guidelines of the Japan Diabetes Society. We excluded participants who (1) had dementia (Mini-Mental Statement Exam score < 18); (2) could not walk before surgery; (3) could not undergo the preoperative assessment; and (4) refused to participate in the study. All participants received information about the study and provided written consent for participation. The study was approved by the ethics committee of Gifu Heart Centre (approval No. 2017024), Toyohashi Heart Centre (approval No. 170402), and Nagoya Heart Centre (approval No. NHC2017-1113-03). The study was registered in the University Hospital Medical Information Network centre (registration No. UMIN000029940).

Randomization and masking

After enrolment, participants were randomly assigned (1:1) to the NMES group or the sham group using a computer-generated stratified block randomization (block sizes of 4). Randomization was performed using 4 strata based on 2 stratification factors: sex (male, female) and age (≥ 75 years, < 75 years). We blinded the trial physiotherapists to the primary and secondary outcomes but could not blind them to group allocation

because they delivered both the NMES and sham interventions. The participants, physicians, nurses, and the statistician who analysed the study data were all blinded to group allocation. The trial physiotherapists were instructed not to discuss interventions with the participants or the other investigators.

Procedures

The trial physiotherapists were all registered cardiac rehabilitation instructors certified by the Japanese Association of Cardiac Rehabilitation and all were trained in the use of NMES for the trial. The trial physiotherapists identified potentially eligible participants and collected informed consent. The researcher, who was not involved in collecting consents, randomly allocated participants to the NMES or sham group. Participants allocated to the NMES group underwent NMES from postoperative day (POD) 1 to POD7 in daily sessions of 60 min (maximum 5 sessions). A trial physiotherapist delivered NMES to each participant. NMES was applied with a variable-frequency train that began with high-frequency bursts (200 Hz), followed by low-frequency stimulation (20 Hz) by Solius (Minato Medical Science Co, Ltd, Osaka, Japan). This type of stimulation pattern has been reported to generate higher levels of force with lower levels of neuromuscular fatigue than a normal constant frequency train [19].

For the stimulation, self-adhering surface electrodes (60 × 90 mm^2) were

placed on the vastus lateralis, vastus medialis, and triceps surae bilaterally after cleaning the participant's skin. A direct electrical current with a symmetric and biphasic square waveform was delivered for 0.4 sec, followed by a 0.6-sec pause. Ten pulse trains (10 sec) were delivered to each muscle at 30-sec intervals for 60 min. NMES was set to trigger a visible muscle contraction at the maximum tolerated intensity. If the stimulation was perceived as painful, the intensity was reduced until it was tolerable. The feasibility and safety of this NMES protocol in participants immediately after cardiovascular surgery have been confirmed [14]. If the participant was intubated, the stimulation current was set just high enough to trigger a visible muscle contraction. We recorded the intensity of the electrical stimulation of the quadriceps femoris and triceps surae at each NMES session.

The quality of the contraction was rated using the scale presented in Table 1 to allow speculation regarding the mechanism of prevention of PSMW by NMES. Grades 0 to 4 have been previously described for both the quadriceps and triceps surae [20]. In this study, we added grades 5 and 6 for quadriceps, which corresponded to 10% and 20% maximal voluntary contractions (MVCs), respectively [16]. For the triceps surae, we defined grade 5 as a muscle contraction that could be overcome by manual resistance, and grade 6 as a contraction that could resist manual resistance. The

procedure for the sham stimulation was identical. The same monitor display was used for both groups: for the sham group, the amplitude shown on the screen was set at 20–30 mA, but the real amplitude was set at 0 mA, so that no electrical stimulation occurred. The physiotherapists told participants in the sham group that they were receiving a microcurrent that they would not feel. Participants in both groups underwent a physiotherapist-supervised postsurgical rehabilitation program according to the guidelines of the Japanese Circulation Society. Briefly, the early mobilization program involved sitting or standing on POD1, walking around the bed on POD2, and walking 100 m to 200 m in the corridor on POD3–4. Once participants could walk independently in the ward, they underwent aerobic exercise and resistance training in the gym until discharge. Aerobic training was initiated with an upright or recumbent-type cycle ergometer with the lightest load (5 to 10 watts) for 10 min at the first session, and then the duration was increased up to 20 min. Resistance training included leg extension with light resistance using a sandbag or resistance machines (< 30% of the one repetition maximum) and calf raises in standing. Both aerobic and resistance training began with 2 sets of 10 repetitions and increased to 3 sets of 10 repetitions.

Primary and secondary outcomes

The trial physiotherapists assessed the primary and secondary outcomes preoperatively

and at POD7. The primary outcome was isometric knee extensor strength (IKES) because this is a key outcome related to the capacity to perform daily activities following cardiovascular surgery and has been associated with both all-cause and cardiovascular mortality in persons with coronary artery disease [21]. IKES was measured using a hand-held dynamometer (μ-tas F1; Anima, Tokyo, Japan). The participant was seated with the knee and hip joints in 90° flexion. Two trials were completed for each leg and the higher value was used in the analysis.

The secondary outcomes were usual walking speed (UWS), maximum walking speed (MWS), and grip strength (GS). Walking speed was measured with the 10m-walk test, in which participants were asked to walk at their normal speed and then as fast as possible over 10 m. The trial physiotherapist walked behind the participant to avoid influencing their speed. The tests were performed twice at each speed, and the faster results were used for the analysis. GS was measured using a digital dynamometer (JAMAR Plus+ Digital Hand Dynamometer; Sammons Preston, Chicago, IL) set at the second handle position. Participants sat with their wrist in a neutral position and the elbow flexed at 90°. GS was measured twice for each hand, and the higher value was used for the analysis. All physiotherapists performed each test multiple times before the study so that the intra-rater and inter-rater reliability could be assessed for each test.

Trial physiotherapists whose reliability measured by the intraclass and interclass correlation coefficient of < 0.9 for some tests were instructed to train until they achieved an intraclass and interclass correlation coefficient of ≥ 0.9 in all tests. Outcomes were evaluated preoperatively and at POD7. The percent changes from the preoperative to POD7 assessment were calculated as follows: (value at POD7 minus the preoperative value) / preoperative value × 100 (%).

We collected data on age, sex, body mass index, , comorbidity, left ventricular ejection fraction, medication, laboratory data, operative and postsurgical data (operation time, use of cardiopulmonary bypass, mechanical ventilation time and operative procedure) from medical records.

Statistical analysis

According to the results of the preliminary analysis in our pilot study [16], the effect size of the percent change in IKES between the 2 groups was assumed to be 0.42. A sample size of 75 participants per group was required to detect this effect size between the 2 groups with 80% power, using the Student *t* test with a two-sided 5% significance level. Allowing for a dropout rate of up to 20% based on pooled data from our pilot trial [16], we planned to recruit a total of 180 participants.

The primary analysis was by intention to treat. We handled missing data by a

multiple imputation approach (20 datasets), using a Monte Carlo Markov chain method. To impute the missing data, we constructed a multiple regression model that included variables potentially associated with the lost to follow-up and variables related to outcome [7]. Missing outcome imputation was based on age, sex, body mass index, the rate of participants on haemodialysis, left ventricular ejection fraction, haemoglobin level, the rate of brain natrium peptide ≥ 100 pg/ml or N-terminal pro-brain natriuretic peptide ≥ 400 pg/ml, use of cardiopulmonary bypass, operative time, mechanical ventilation time, operative procedure, the postsurgical complications and baseline outcomes.

Univariate plots (QQ plot, histograms), kurtosis, and skewness were used to determine whether the data were normally distributed. Participant baseline characteristics and outcomes are presented as mean (SD) and mean (95% confidence interval [CI]) for normally distributed data or median (interquartile range [IQR]) for non-normally distributed data for continuous variables. Categorical variables are presented as numbers and percentages. For primary and secondary outcomes, between-group differences in the percent change from the preoperative time point to POD7 was analysed with the Student *t* test. We conducted a per-protocol analysis (n=158) as a sensitivity analysis. This analysis included only participants with complete

paired preoperative and POD7 data.

For the subgroup analysis, we compared the primary and secondary outcomes between groups for participants ≥ 75 years with a post-hoc test because those participants may be particularly vulnerable to surgical stress on the skeletal muscles [13].

All statistical analyses were performed with SPSS Statistics Subscription version 28 for Windows (IBM Japan Inc.).

3. Results

The CONSORT diagram of participant flow through the study is presented in Figure 1. Between February 1, 2018, and January 24, 2020, 1151 participants underwent elective cardiovascular surgery and were screened; 209 met the eligibility criteria, of whom 180 were included: 90 were allocated to receive NMES plus the standard postsurgical rehabilitation, and 90 were allocated to receive sham stimulation plus the postsurgical rehabilitation. All 180 participants were included in the intention-to-treat analysis.

Baseline characteristics

The baseline characteristics of the study participants are shown in Table 2. The groups did not differ in rates of postsurgical complications. None of the participants

experienced postoperative artificial fibrillation or ventricular tachycardia during NMES. The median (IQR) number of NMES sessions from POD1 to POD7 did not differ between the NMES and sham groups: 5 (5–5) in the NMES group, and 5 (5–5) in the sham group. The number of postsurgical rehabilitation sessions before the performance test on POD7 was similar between groups (Table 2). In the NMES group, 52 participants (58%) underwent postsurgical exercise in the gym. Of these, 2 participants only underwent resistance training. In the sham group, 42 participants (47%) underwent postsurgical exercise in the gym. Among them, 3 only underwent resistance training. Of those who underwent postsurgical exercise in the gym (NMES group: n=52, sham group: n=42), 24 (46%) participants in the NMES group and 13 (31%) in the sham group were ≥ 75 years old. The median length of hospital stay from surgery to discharge was similar between groups, 12 (IQR 9-15) in the NMES group and 11 (9-18) in the sham group. The mean electrical stimulation intensities for the quadriceps and triceps surae were similar across the 5 sessions in the NMES group (Figure 2). In the NMES group, 59 participants underwent 5 sessions, 10 participants underwent 4 sessions, and 9 participants underwent 3 sessions.

Quality of the muscle contraction induced by NMES

The ratings of the quality of the muscle contractions for each NMES session in the quadriceps and triceps surae in the participants who underwent 5 sessions of NMES are shown in Figure 3. The ratings for the quadriceps during the last session were as follows: n=15 (22%) grade 5 or 6, n=37 (54%) grade 4, n=10 (15%) grade 3, and n=7 (10%) < grade 3. During the last session for the triceps surae, the grades were n=33 (55%) grade 5 or 6, n=16 (23%) grade 4, n=9 (13%) grade 3, and n=6 (9%) < grade 3.

The median duration of each NMES session was 60 (IQR 60-60) min. The number of participants who underwent NMES < 60 min for each session were n=10 during the 1st session, n=5 during the 2nd session, n=4 during the 3rd session, n=6 during the 4th session, and n=5 during the 5th session.

Effect of the intervention

For the primary outcome, the mean percent change in IKES from the preoperative time point to POD7 (%ΔIKES) was -2% in the NMES group and -13% in the sham group (treatment difference 11%) (Table 3). Similar results were found for the secondary outcomes; in particular, the percent change in MWS from the preoperative time point to POD7 (%ΔMWS) was significantly lower in the NMES than sham group. Percent change in UWS was lower in the NMES than sham group (Table 3). The absolute value of IKES at POD7 was also significantly greater in the NMES than sham group (Table 4).

The per-protocol analysis of participants with complete data sets (NMES group: n=78, sham group: n=80) showed similar results as the intention-to-treat analysis (Table 5).

In the subgroup analysis of participants ≥ 75 years, %ΔIKES was significantly smaller in the NMES than sham group. %ΔUWS was -11% in the NMES group and -19% in the sham group (Table 6).

4. Discussion

Short-term NMES administered to the lower extremity muscles immediately after cardiovascular surgery could mitigate PSMW in older individuals with DM. In addition to the reduction in PSMW, functional decline was reduced in the NMES group, although not significantly. These findings were stronger in participants ≥ 75 years, indicating that older individuals with DM who undergo cardiovascular surgery are likely to benefit from NMES. To the best of our knowledge, this is the first clinical trial to demonstrate the effects of NMES on PSMW and functional decline immediately after cardiovascular surgery.

Indication for NMES after cardiovascular surgery

We focused on older individuals with DM because, according to the potential underlying mechanisms of PSMW, NMES appeared to be indicated for this population.

It is well known that the increase in levels of inflammatory cytokines following surgery may lead to increased insulin resistance, which in turn causes hyperglycemia [10]. Moreover, an increase in levels of inflammatory cytokines may exacerbate muscle protein breakdown and alter nerve function, particularly in older people [22, 23]. This observation led us to postulate that older individuals with DM were at risk of PSMW. We also speculated that these effects might have contributed to the lack of an effect of NMES in recent RCTs [16, 17]. Indeed, the decrease in IKES at POD7 in the sham group was greater than that reported in the RCT by Kitamura et al. [16]: in that study, consecutive participants were enrolled with no stratification for age or haemodialysis. Another RCT that found no effect of NMES in participants who underwent valve replacement included younger individuals (mean age: 42 years). [17]. Furthermore, an RCT of participants who underwent cardiovascular surgery and stayed in the ICU for > 48 hr found that NMES did not maintain muscle mass measured by ultrasonography [18]. However, in the subgroup analysis, NMES was associated with recovery of the secondary outcome: PSMW rated on the Medical Research Council scale. Similar results were found in a recent RCT that focused on critically ill participants [24]. In another RCT, NMES improved the medical research council score in participants with ICU-acquired weakness [24]. However, the improvement in Medical Research Council

score did not differ significantly between the NMES and control groups, which suggests that NMES may prevent the progression of the underlying mechanisms that lead to ICU-acquired weakness. These results and the findings of our study suggest that NMES may be of value to mitigate PSMW, particularly in fragile populations.

Possible mechanism of mitigation effect of NMES on PSMW

The positive results we found for NMES may result from the suppression of surgery-induced catabolism. Immediately after abdominal surgery, NMES was found to reduce muscle protein degradation and attenuate the activity of the ubiquitin-proteasome system, which is the main protein degradation pathway in catabolic situations [25]. In a non-RCT of people undergoing cardiovascular surgery, Iwatsu et al. reported that NMES may attenuate muscle protein degradation measured by urinary 3-methylhistidine level [15]. In addition, NMES increased skeletal muscle protein synthesis during the 4 hr after stimulation in older people with type 2 DM [26]. However, it has been suggested that a minimum level of 10% to 20% MVC should be induced to counteract skeletal muscle degradation [27]. In the present study, the induced quadriceps femoris contraction was lower than grade 5 (10% MVC) in approximately 80% of the participants, which implies that another mechanism led to the positive effect of NMES on PSMW.

NMES may induce considerable neural adaptation by increasing motor unit recruitment through reflex pathways. Older individuals [28] and individuals with diabetic neuropathy [29] often have a loss of motor units, which causes muscle weakness. NMES triggers action potentials in intramuscular nerve branches and induces force production through 2 pathways: 1) directly by activation of motor axons and 2) indirectly by reflex recruitment of spinal motor neurons [30]. This reflex recruitment may be disturbed by antidromic transmission within motor axons that block signal transmission through high NMES amplitudes with intense muscle contractions (grade 5 or 6 in this study) [30, 31]. Reflex recruitment might have been augmented because of the waveform applied in this study. We applied NMES with a variable-frequency train that began with high-frequency bursts followed by low-frequency stimulations, which may augment reflex pathways [31]. Our data showed that the short duration (5 sessions) of NMES reduced PSMW even in the participants who did not receive all 5 NMES sessions because of the safety criteria. After only 1 week, NMES improved motor unit recruitment in the quadriceps [32]. In addition, the loss of GS in our study was lower in the NMES than sham group, possibly because of neural adaptation with cross-education [33]. For these reasons, the neural adaptation induced by the NMES may have been the main underlying mechanism of the findings in this study. Further studies of

minimum-intensity NMES that triggers reflex pathways are required to increase understanding of the mitigating effects of NMES on PSMW and functional decline.

Mitigation effect of NMES on functional decline

The rate of functional decline was lower in the NMES than sham group. This finding was stronger in participants ≥ 75 years, which suggests that NMES may be particularly beneficial for individuals with a lower skeletal muscle functional reserve. NMES maintained MWS as well as IKES in all participants. Stronger correlations have been reported between IKES and MWS than UWS [34]. The subgroup analysis showed a treatment difference of 8% for UWS in participants ≥ 75 years as compared with only 4% in the whole sample. When functional reserve is low, a small change in muscle strength may result in increased relative work, which may in turn reduce functional decline and help to maintain UWS. According to the findings of our subgroup analysis, NMES may be particularly indicated for those with a greater risk of functional deterioration due to surgical stress.

Clinical implications

NMES provided in addition to usual postsurgical rehabilitation mitigated PSMW and functional decline in older individuals with DM, particularly those ≥ 75 years, probably because of the effects of the neural stimulation. Furthermore, among the participants

who were able to train in the gym, the proportion of those ≥ 75 years was greater in the NMES than sham group, which suggests that NMES may particularly enhance the effects of postsurgical rehabilitation in older people.

NMES has the potential to be widely applied to mitigate functional decline in people undergoing cardiovascular surgery. In this RCT, the dropout rate in the NMES group was 4%, which was as low as in a recent RCT (4% to 10%) that also focused on cardiovascular surgery [16-18]. Considering this level of adherence and the neural adaptation suggested by the results of this RCT, a low dose of NMES (< 10%MVC) may be sufficient for older participants with DM. According to the number of eligible participants in this study, we estimate that the proportion of patients for whom NMES may be indicated is approximately 25%; this number will likely increase with advances in surgical techniques and the growing population of older people with DM who undergo cardiovascular surgery [6]. Therefore, NMES should be included as part of standard postsurgical rehabilitation in selected populations.

Study limitations

Although we blinded the participants, physicians, nurses, and the statistician who analysed the study data, we could not blind the trial physiotherapists because of the visibility of NMES-induced muscle contractions. Nevertheless, this RCT provides novel

findings that will contribute to advancing postsurgical rehabilitation.

5. Conclusions

The short duration of NMES, less than one week, mitigated PSMW and functional decline in older persons with DM after cardiovascular surgery. NMES could be recommended as a part of postsurgical rehabilitation for older people with DM, especially those with a low functional reserve.

6. Acknowledgments

We thank all the medical staff and cardiac surgeons at Gifu, Nagoya, and Toyohashi Heart Center for their cooperation in this study. We are also deeply grateful to Dr. Yuki Iida, Dr. Kotaro Iwatsu, and Dr. Hideki Kitamura and their colleagues for conducting a series of clinical studies on the mechanisms and preventive effect of NMES on PSMW.

7. References

[1] Maffiuletti NA. Physiological and methodological considerations for the use of neuromuscular electrical stimulation. Eur J Appl Physiol 2010; 110: 223-34.

[2] Jones S, Man WDC, Gao W, Higginson IJ, Wilcock A, Maddocks M. Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. Cochrane Database Syst Rev 2016; **10**: CD009419.

[3] Trethewey SP, Brown N, Gao F, Turner AM. Interventions for the management and prevention of sarcopenia in the critically ill: A systematic review. J Crit Care 2019; 50: 287–95.

[4] Iida Y, Yamada S, Nishida O, Nakamura T. Body mass index is negatively correlated with respiratory muscle weakness and interleukin-6 production after coronary artery bypass grafting. J Crit Care 2010; 172: 1–8.

[5] Bloch SA, Lee JY, Wort SJ, Polkey MI, Kemp PR, Griffiths MJD. Sustained elevation of circulating growth and differentiation factor-15 and a dynamic imbalance in mediators of muscle homeostasis are associated with the development of acute muscle wasting following cardiac surgery. Crit Care Med 2013; 41: 982-9.

[6] Barreto-Filho JA, Wang Y, Dodson JA, Desai MM, Sugeng L, Geirsson A, et al. Trends in aortic valve replacement for elderly patients in the United States, 1999–2011.

J Am Med Assoc 2013;310: 2078-85.

[7] Iida Y, Yamazaki T, Arima H, Kawabe T, Yamada S. Predictors of surgery-induced muscle proteolysis in patients undergoing cardiac surgery. J Cardiol 2016; 68: 536-41.

[8] Fenzi F, Latronico N, Refatti N, Rizzuto N. Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. Acta Neuropathol 2003; 106: 75-82.

[9] Nardelli P, Khan J, Powers R, Cope RC, Rich MM. Reduced motoneuron excitability in a rat model of sepsis. J Neurophysiol 2013; 109: 1775-81.

[10] Shoelson SE, Lee J, Goldfine AB, Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance Review series Inflammation and insulin resistance. J Clin Invest 2006; 116: 1793-801.

[11] Zhou J, Zhou S. Inflammation: Therapeutic targets for diabetic neuropathy. Mol Neurobiol 2014; 49: 536–46.

[12] Nishitani M, Shimada K, Sunayama S, Masaki Y, Kume A, Fukao K, et al. Impact of diabetes on muscle mass, muscle strength, and exercise tolerance in patients after coronary artery bypass grafting. J Cardiol 2011; 58: 173-80.

[13] Basu R, Breda R, Oberg AL, Powell CC, Man CD, Basu A, et al. Mechanisms of the age-associated deterioration in glucose tolerance: Contribution of alterations in

insulin secretion, action, and clearance. Diabetes 2003; 52: 1738-48.

[14] Iwatsu K, Yamada S, Iida Y, Sampei H, Kobayashi K, Kainuma M, et al. Feasibility of neuromuscular electrical stimulation immediately after cardiovascular surgery. Arch Phys Med Rehabil 2015; 96: 63-8.

[15] Iwatsu K, Iida Y, Kono Y, Yamazaki T, Usui A, Yamada S. Neuromuscular electrical stimulation may attenuate muscle proteolysis after cardiovascular surgery: A preliminary study. J Thorac Cardiovasc Surg 2017; 153: 373-9.

[16] Kitamura H, Yamada S, Adachi T, Shibata K, Tamaki M, Okawa Y, et al. Effect of perioperative neuromuscular electrical stimulation in patients undergoing cardiovascular surgery: A pilot randomized controlled trial. Semin Thorac Cardiovasc Surg 2019; 31: 361-7.

[17] Fontes Cerqueira TC, Cerqueira Neto ML, Pereira Cacau LA, Oliveira GU, Silva Júnior WM, Carvalho VO, et al. Ambulation capacity and functional outcome in patients undergoing neuromuscular electrical stimulation after cardiac valve surgery A randomised clinical trial. Med 2018; 97: e13012.

[18] Fischer A, Spiegl M, Altmann K, Winkler A, Salamon A, Themessl-Huber M, et al. Muscle mass, strength and functional outcomes in critically ill patients after cardiothoracic surgery: Does neuromuscular electrical stimulation help? The Catastim 2

randomized controlled trial. Crit Care 2016; 20: 1-13.

[19] Lee SCK, Becker CN, Binder-Macleod SA. Catchlike-inducing train activation of human muscle during isotonic contractions: Burst modulation. J Appl Physiol 1999; 87: 1758-67.

[20] Segers J, Hermans G, Bruyninckx F, Meyfroidt G, Langer D, Gosselink R. Feasibility of neuromuscular electrical stimulation in critically ill patients. J Crit Care 2014; 29: 1082-8.

[21] Kamiya K, Masuda T, Tanaka S, Hamazaki N, Matsue Y, Mezzani A, et al. Quadriceps Strength as a Predictor of Mortality in Coronary Artery Disease. Am J Med 2015; 128: 1212-9.

[22] Iorio AD, Cherubini A, Volpato S, Sparvieri E, Lauretani F, Franceschi C, et al. Markers of inflammation, vitamin E, and peripheral nervous system function: the InCHIANTI study. Neurobiol Aging 2006; 27: 1280-8.

[23] Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol 2004; 39: 687-99.

[24] Patsaki I, Gerovasili V, Sidiras G, Karatzanos E, Mitsiou G, Papadopoulos E, et al Effect of neuromuscular stimulation and individualized rehabilitation on muscle strength in Intensive Care Unit survivors: A randomized trial. J Crit Care 2017; 40:

76-82.

[25] Strasser EM, Stättner S, Karner J, Klimpfinger M, Freynhofer M, Zaller V, et al. Neuromuscular electrical stimulation reduces skeletal muscle protein degradation and stimulates insulin-like growth factors in an age- and current-dependent manner: A randomized, controlled clinical trial in major abdominal surgical patients. Ann Surg 2009; 249:738-43.

[26] Wall BT, Dirks ML, Verdijk LB, Sniders T, Hansen D, Vranckx P, et al. Neuromuscular electrical stimulation increases muscle protein synthesis in elderly type 2 diabetic men. Am J Physiol - Endocrinol Metab. 2012; 303: 614-23.

[27] Natsume T, Ozaki H, Kakigi R, Kobayashi H, Naito H. Effects of training intensity in electromyostimulation on human skeletal muscle. Eur J Appl Physiol 2018;118: 1339-47.

[28] Piasecki M, Ireland A, Jones DA, McPhee JS. Age-dependent motor unit remodelling in human limb muscles. Biogerontology. 2016; 17: 485-96.

[29] Allen MD, Kimpinski K, Doherty TJ, Rice CL. Length dependent loss of motor axons and altered motor unit properties in human diabetic polyneuropathy. Clin Neurophysiol. 2014; 125: 836-43.

[30] Bergquist AJ, Clair JM, Lagerquist O, Mang CS, Okuma Y, Collins DF.

Neuromuscular electrical stimulation: Implications of the electrically evoked sensory volley. Eur J Appl Physiol 2011; 111: 2409-26.

[31] Collins DF, Burke D, Gandevia SC. Sustained contractions produced by plateau-like behaviour in human motoneurones. J Physiol 2002; 538: 289-301.

[32] Newsam CJ, Baker LL. Effect of an electric stimulation facilitation program on quadriceps motor unit recruitment after stroke. Arch Phys Med Rehabil. 2004; 85: 2040-5.

[33] Hortobágyi T, Scott K, Lambert J, Hamilton G, Tracy J. Cross-education of muscle strength is greater with stimulated than voluntary contractions. Motor Control. 1999; 3: 205-19.

[34] Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. Age Ageing 1997; 26: 15-9.

8. Tables

Table 1. Scale for rating the quality of muscle contractions.

Grade 0	No palpable or visible contraction
Grade 1	Just palpable but no visible contraction
Grade 2	Just palpable and just visible contraction
Grade 3	Palpable and visible contraction (partial muscle bulk)
Grade 4	Palpable and visible contraction (full muscle bulk; no joint motion)
Grade 5	Palpable and visible contraction (full muscle bulk; joint motion - Quadriceps: heel lifts off the bed, Triceps surae: foot cannot resist manual resistance)
Grade 6	Palpable and visible contraction (full muscle bulk; joint motion - Quadriceps: calf lifts off the bed, Triceps surae: foot can resist manual resistance)

Table 2. Characteristics of the study participants with neuromuscular electrical stimulation (NMES) and sham treatment

	NMES (n=90)	sham (n=90)
Age, years, mean (SD)	74 (5)	74 (5)
Age ≥ 75 years	43 (48)	41 (46)
Body mass index, kg, m2, median (IQR)	19.8 (18.0-21.8)	19.3 (18.2-20.8)
Men	61 (68)	63 (70)
Comorbidity		
Hypertension	70 (78)	66 (73)
Dyslipidemia	49 (54)	50 (56)
Haemodialysis	14 (16)	13 (14)
Years of diabetes mellitus, years, median (IQR)	10 (3-25)	8 (2-20)
Preoperative echocardiogram		
LVEF, % median (IQR)	56.0 (47.0-65.0)	54.4 (43.3-63.0)
Preoperative medication		
ACE/ARB	51(57)	57 (63)
Calcium channel blocker	37 (41)	42 (47)
Beta blocker	38 (42)	34 (38)
Oral inotropic agent	3 (3)	5 (6)
Statin,	52 (58)	44 (49)
Anticoagulants	25 (28)	17 (19)
Antiplatelet drugs	45 (50)	44 (49)
Diuretic	40 (44)	40 (44)
Insulin therapy	9 (10)	13 (14)
Dipeptidyl peptidase-4 inhibitor	49 (54)	56 (62)
Glucagon like peptide-1 receptor agonist	0 (0)	2 (2)
Sodium glucose cotransporter 2 inhibitor	11 (12)	10 (11)
α-Glucosidase inhibitor	16 (18)	18 (20)
Sulfonylurea	15 (17)	14 (16)
Thiazolidine derivatives	2 (2)	4 (4)

Biguanide	14 (16)	17 (19)
Rapid-acting insulin secretagogue	4 (4)	6 (7)
Preoperative laboratory data		
Hemoglobin, d/ml, median (IQR)	12.7 (11.4-14.0)	13.3 (12.1-14.0)
BNP ≥ 100 pg/ml or NT-Pro BNP ≥ 400 pg/ml	51 (65)	51 (64)
hs-CRP	0.12 (0.03-0.63)	0.15 (0.06-0.56)
Hemoglobin A1c, % median (IQR)	6.8 (6.4-7.3)	6.80 (6.4-7.5)
Use of cardiopulmonary bypass	53 (59)	61 (68)
Operation time, min	254 (69)	285 (80)
Mechanical ventilation time, min	721 (589-1002)	756 (631-1097)
Operative procedure		
CABG	35 (39)	31 (34)
Valvular	20 (22)	15 (17)
Thoracic aorta	5 (6)	7 (8)
Other	2 (2)	2 (2)
Combined	26 (29)	34 (38)
Postsurgical complications		
Acute kidney injury	4 (4)	4 (4)
Low output syndrome	2 (2)	1 (1)
Delirium	15 (17)	17 (19)
Respiratory complications	7 (8)	7 (8)
Atrial fibrillation	22 (24)	22 (24)
Central nervous disorder	4 (4)	3 (3)
Preoperative outcome		
IKES, kgf, mean (SD)	26.0 (9.9)	25.7 (9.2)
UWS, m/s, mean (SD)	1.04 (0.27)	1.05 (0.24)
MWS, m/s, mean (SD)	1.39 (0.40)	1.43 (0.33)
GS, kg, mean (SD)	25.9 (9.7)	27.0 (9.1)
POD for initial sitting, median (IQR)	1 (1-1)	1 (1-2)
POD to resume 100-m walking, median (IQR)	3 (2-4)	3 (2-5)
Achieved 100-m walking, median (IQR)	79 (88)	82 (91)
Number of postsurgical rehabilitation sessions before testing on POD7,	4 (4-5)	4 (3-5)

median (IQR)		
Proportion of participants who underwent exercise in the training room before testing on POD7	52 (58)	42 (47)

Data are n (%) unless otherwise indicated.

ACE: Angiotensin converting enzyme inhibitor; ARB: Angiotensin II receptor antagonist; BNP: Brain natriuretic peptide; CABG: Coronary artery bypass; GS: Grip strength; hs-CRP: high-sensitive C-reactive protein**;** IKES: Isometric knee extension strength; LVEF: Left ventricle ejection fraction; MWS: Maximum walking speed; NMES: Neuromuscular electrical stimulation; NT-pro BNP: N-terminal pro-brain natriuretic peptide; POD: Postoperative day; UWS: Usual walking speed.

Table 3. Differences between NMES and sham groups in primary and secondary outcomes.

	NMES (n=90)	sham (n=90)	Treatment difference	P value
%ΔIKES	-2.4 (-5.9 to 1.1)	-13.0 (-16.7 to -9.3)	10.5 (5.4 to 15.7)	<0.001
%ΔUWS	-12.9 (-17.6 to -8.2)	-17.2 (-21.7 to -12.7)	4.3 (-2.1 to 10.7)	0.18
%ΔMWS	-13.9 (-18.0 to -9.8)	-20.1 (-24.4 to -15.8)	6.2 (0.3 to 12.1)	0.04
%ΔGS	-8.2 (-11.1 to -5.3)	-11.8 (-14.9 to -8.7)	3.6 (-0.7 to 7.9)	0.10

Missing data were imputed using a multiple imputation approach (20 datasets) (Monte Carlo Markov chain method).

Values are mean (95%CI).

%ΔGS: percent change in grip strength from preoperative to postoperative day 7; %ΔIKES: percent change in isometric knee extension strength from preoperative to postoperative day 7; %ΔMWS: percent change in maximum walking speed from preoperative to postoperative day 7; NMES: Neuromuscular electrical stimulation; %ΔUWS: percent change in usual walking speed from preoperative to postoperative day 7.

Table 4. Comparisons of the absolute values at postoperative day 7 between NMES and sham group.

	NMES (n=90)	sham (n=90)	P value
IKES (kgf)	24.7 (22.7 to 26.7)	22.0 (20.3 to 23.7)	0.03
UWS (m/s)	0.90 (0.85 to 0.95)	0.87 (0.81 to 0.93)	0.45
MWS (m/s)	1.18 (1.10 to 1.26)	1.14 (1.06 to 1.22)	0.56
GS (kg)	23.9 (21.9 to 25.9)	23.8 (22.0 to 25.6)	0.94

Missing data were imputed using a multiple imputation approach (20 datasets), using a Monte Carlo Markov chain method.

Values are mean (95%CI).

GS: Grip strength; IKES: Isometric knee extension strength; MWS: Maximum walking speed; NMES: Neuromuscular electrical stimulation; UWS: Usual walking speed.

Table 5. Differences between NMES and sham group in outcomes by per-protocol analysis.

	NMES (n=78)	sham (n=80)	Treatment difference	P value
%ΔIKES	-2.7 (-6.2 to 0.8)	-13.6 (-17.3 to -10.0)	10.9 (5.9 to 15.9)	<0.001
%ΔUWS	-12.5 (-16.5 to -8.5)	-17.5 (-21.6 to -13.4)	5.1 (-0.6 to 10.8)	0.08
%ΔMWS	-13.1 (-17.4 to -8.8)	-20.2 (-21.6 to -13.4)	7.1 (1.1 to 13.1)	0.02
%ΔGS	-8.3 (-11.1 to -5.5)	-12.0 (-14.8 to -9.2)	3.7 (-0.2 to 7.6)	0.07

Values are mean (95% CI).

%ΔGS: percent change in grip strength from preoperative to postoperative day 7; %ΔIKES: percent change in isometric knee extension strength from preoperative to postoperative day 7; %ΔMWS: percent change in maximum walking speed from preoperative to postoperative day 7; NMES: Neuromuscular electrical stimulation; %ΔUWS: percent change in usual walking speed from preoperative to postoperative day 7.

Table 6. Differences between NMES and sham groups in primary and secondary outcomes for participants ≥ 75 years (post-hoc analysis) (n=76)

	NMES（n=38)	sham（n=38)	Treatment difference	P value
%ΔIKES	-2.5 (-8.0 to 3.0)	-13.0 (-19.1 to -7.0)	10.5 (2.5 to 18.6)	0.01
%ΔUWS	-10.8 (-15.9 to -5.8)	-19.1 (-24.3 to -14.0)	8.3 (1.2 to 15.4)	0.02
%ΔMWS	-13.4 (-19.1 to -7.6)	-20.8 (-26.8 to -14.7)	7.4 (-0.8 to 15.6)	0.08
%ΔGS	-5.0 (-9.4 to -0.6)	-11.6 (-15.7 to -7.5)	6.6 (0.7 to 12.5)	0.03

Values are mean (95%CI).

%ΔGS: percent change in grip strength from preoperative to postoperative day 7; %ΔIKES: percent change in isometric knee extension strength from preoperative to postoperative day 7; %ΔMWS: percent change in maximum walking speed from preoperative to postoperative day 7; NMES: Neuromuscular electrical stimulation; %ΔUWS: percent change in usual walking speed from preoperative to postoperative day 7.

9. Figures

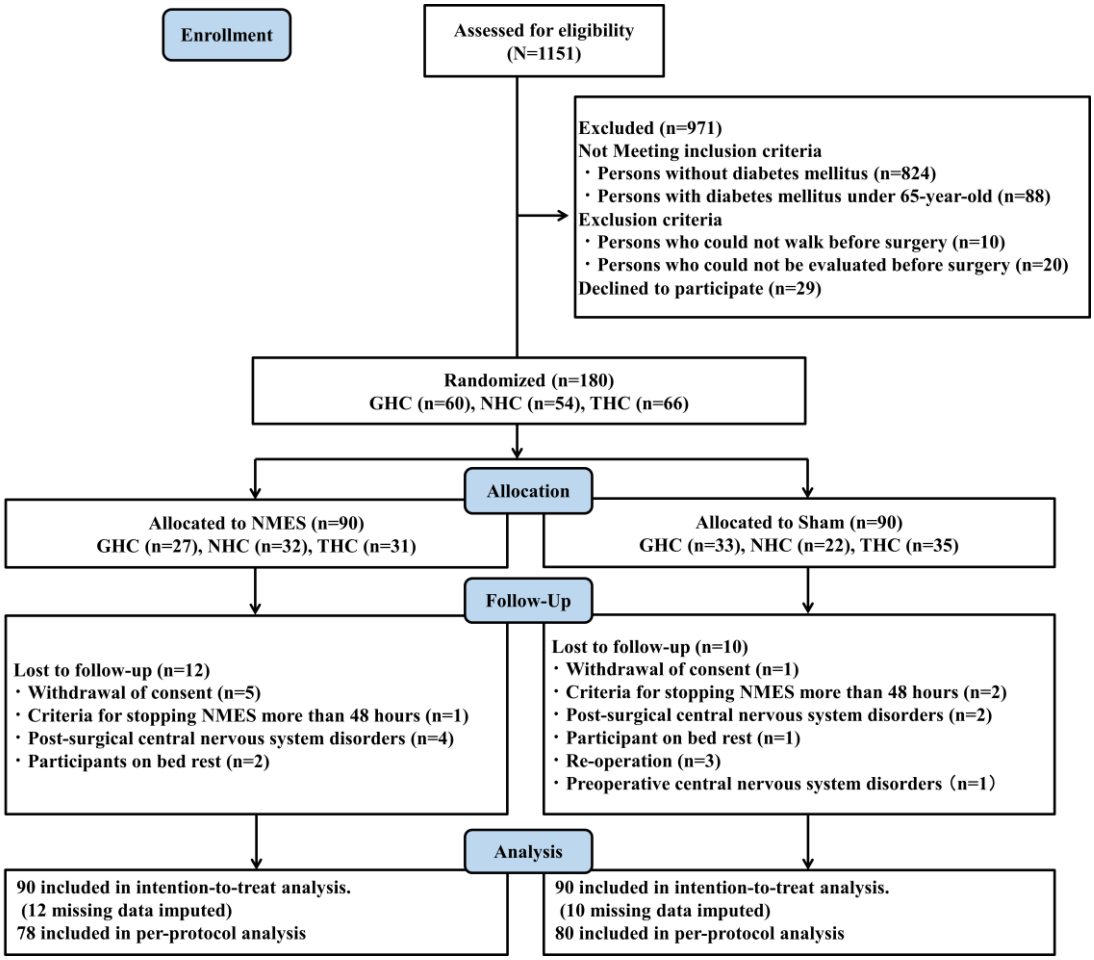

Figure 1. CONSORT diagram of participant flow through the study. GHC: Gifu Heart Center; NHC: Nagoya Heart Center; THC: Toyohashi Heart Center; NMES: Neuromuscular electrical stimulation

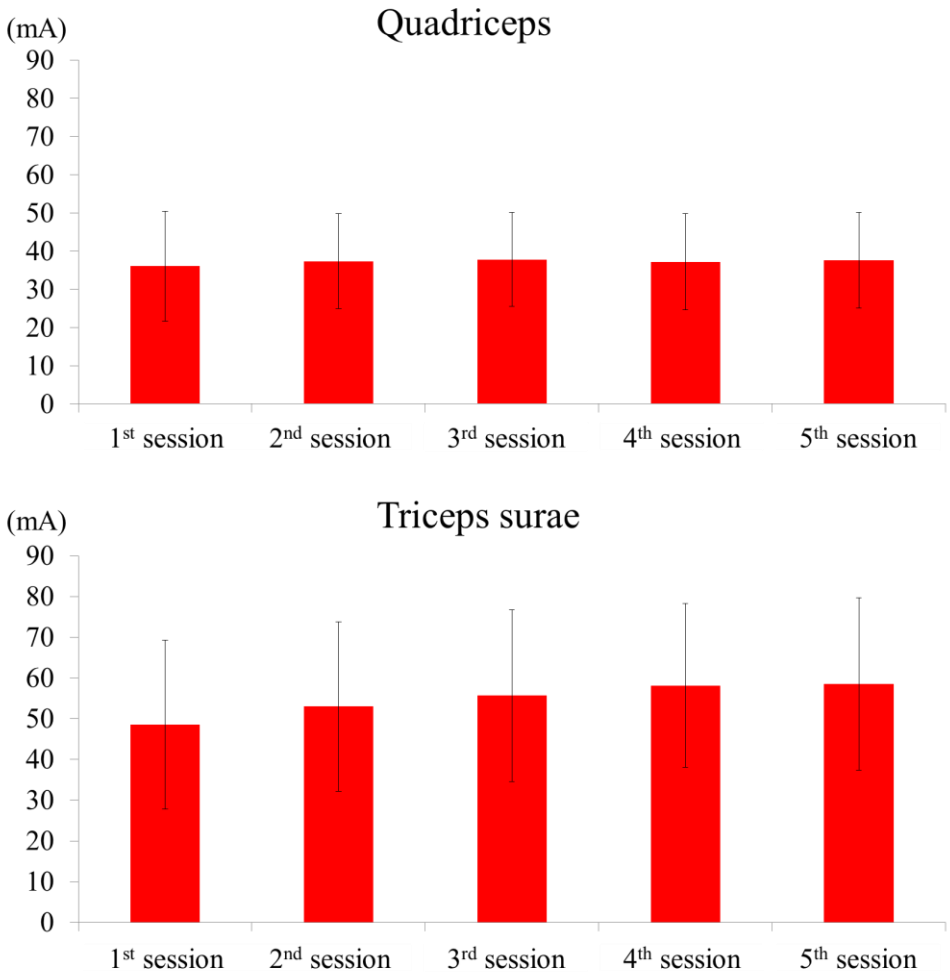

Figure 2. Average intensity of electrical stimulation in quadriceps and triceps surae for each neuromuscular electrical stimulation (NMES) session in the NMES group (n = 78). Electrical intensity is expressed as mean (SD).

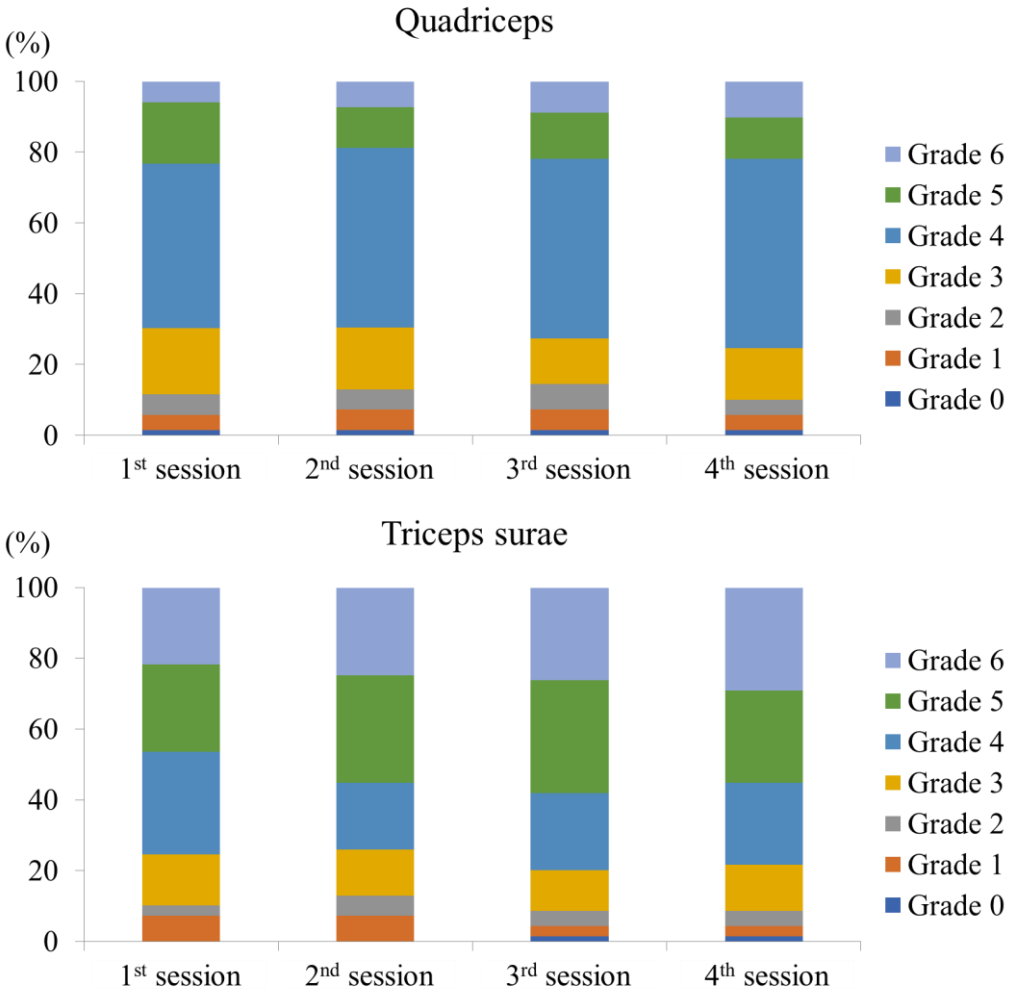

Figure 3. Ratings of the quality of the quadriceps and triceps surae muscle contractions for each NMES session in participants who underwent > 4 sessions of NMES (n=69).