Neuromuscular electrical stimulation may attenuate muscle proteolysis after cardiovascular surgery: A preliminary study

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ABSTRACT

Objective: To explore the efficacy of postoperative neuromuscular electrical stimulation (NMES) on muscle protein degradation and muscle weakness in patients after cardiovascular surgery.

Methods: Sixty-one patients underwent NMES daily from postoperative days (PODs) 1 to 5 in addition to postoperative mobilization program (NMES group), and 41 patients underwent postoperative mobilization program only (non-NMES group). The primary outcome was the concentration of 3-methylhistidine (3-MH) in 24-hour urine corrected for urinary creatinine content (3-MH/Cr) from PODs 1 to 5. The secondary outcomes were knee extensor isometric strength (KEIS) and handgrip strength at POD 7.

Results: Baseline characteristics such as age, sex, preoperative body mass index, hemoglobin, handgrip strength, KEIS, surgery type, cardiopulmonary bypass time, and immediate postoperative interleukin-6 were not different between the groups. Urinary 3-MH/Cr was increased significantly in both groups; however, urinary 3-MH/Cr in the NMES group peaked earlier compared with that in the non-NMES group. KEIS at POD 7 was significantly greater in the NMES group (median [interquartile range], 0.40 kg/weight [0.33-0.45] in the NMES group vs 0.23 kg/weight [0.15-0.36] in the non-NMES group; $P < .01$). Handgrip strength at POD 7 was also significantly greater in the NMES group (median [interquartile range], 32 kg [24.5-35.3] in the NMES group vs 24 kg [16.0-30.0] in the non-NMES group; $P < .01$).

Conclusions: This study demonstrated that NMES might attenuate skeletal muscle protein degradation and muscle weakness after cardiovascular surgery. A cause-effect relationship between NMES and functional preservation would be a future challenging issue. (J Thorac Cardiovasc Surg 2017;153:373-9)

Urinary 3-methylhistidine / creatinine from postoperative days 1 to 5 in the neuromuscular electrical stimulation (n = 61) and the non-neuromuscular electrical stimulation (n = 41) groups.

Central Message

Neuromuscular electrical stimulation reduced muscle proteolysis and preserved muscle strength in patients after cardiovascular surgery.

Perspective

Muscle protein catabolism after cardiovascular surgery induces postoperative muscle weakness and functional decline, for which no preventive tool has been established. Our study demonstrated the possibility of neuromuscular electrical stimulation to attenuate muscle protein degradation and muscle weakness in patients after cardiovascular surgery. These data provide a rationale for the application of neuromuscular electrical stimulation in postoperative rehabilitation.

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Surgical operation stress induces loss of muscle mass due to dysregulation in protein metabolism.^{1,2} Under this condition, protein degradation is accelerated whereas synthesis is suppressed, leading to a net loss of muscle protein. The concurrent reduction in muscle strength causes long-term impairments such as persistent muscle weakness.^{3,4} Currently, Iida and colleagues⁵ reported that

Scanning this QR code will take you to supplemental figure, table, and video for this article.

Abbreviations and Acronyms

Cre	= creatinine
IL-6	= interleukin-6
KEIS	= knee extensor isometric strength
3-MH	= 3-methylhistidine
MVC	= maximal voluntary contraction
NMES	= neuromuscular electrical stimulation
POD	= postoperative day

the cumulative urinary excretion of 3-methylhistidine (3-MH) in patients within 5 days after cardiac surgery was associated with an increase in interleukin-6 (IL-6) levels postoperatively and postoperative muscle weakness. 3-MH is a product of the methylation of peptide-bound histidine in actin and myosin and is released to the free amino acid body pool upon muscle protein breakdown.⁶ Because 3-MH is not reused for muscle protein synthesis or oxidized for energy,⁷ urinary 3-MH has been recognized as an index of muscle proteolysis rate.^{6,8} In addition, IL-6 traditionally is considered as a marker for surgical stress.^{9,10} Therefore, the prevention of muscle proteolysis induced by surgical stress at the early postoperative phase may be a potential intervention for the preservation of skeletal muscle strength after cardiovascular surgery.

Because immobilization, even of a short duration, is an important stimulus of muscle protein degradation,¹¹ promoting muscle activity is recognized widely as a countermeasure against muscle protein degradation. In the early postoperative phase after cardiovascular surgery, however, patients often have difficulty in producing sufficient muscle contractions as the result of their hemodynamic instabilities. Instead, neuromuscular electrical stimulation (NMES) can safely induce sufficient muscle activity without a patient's volitional efforts even immediately after cardiovascular surgery.¹² Data regarding the effect of postoperative NMES on skeletal muscle degradation (or weakness) in patients undergoing cardiovascular surgery, however, have been scarce. This study, therefore, aimed to explore the efficacy of postoperative NMES on muscle protein degradation and muscle weakness in patients after cardiovascular surgery.

MATERIALS AND METHODS

Participants and Data Collection

Adult patients who were scheduled for elective major cardiovascular surgery (coronary artery bypass, valvular, thoracic aorta, or combined surgery) at Nagoya University Hospital and Kainan Hospital were included consecutively. Exclusion criteria were chronic renal failure (estimated glomerular filtration rate < 30 mL/min/1.73 m²), peripheral arterial disease (Fontaine classification ≥ III), psychiatric disease, neuromuscular disease, dementia (Mini-Mental State Examination < 18 points), intubation more than 24 hour after surgery, and reoperation. Chronic renal failure of estimated glomerular filtration rate < 30 mL/min/1.73 m² was excluded

because of the uncertainty of measured urinary 3-MH, a marker of myofibrillar protein degradation.^{13,14} Patients who withdrew from the postoperative rehabilitation program and/or NMES also were excluded. Informed consent was obtained from each patient as approved by the Ethics Review Committee of the Nagoya University Graduate School of Medicine (approval number: 1272). This study was registered with the University Hospital Medical Information Network Center (registration number: UMIN000020221).

The following preoperative clinical data were collected from the patient's clinical record: age, sex, body mass index, and serum hemoglobin level. The intraoperative variables recorded included the type of surgical procedure (coronary bypass, valvular, thoracic aorta, or combined surgery), cardiopulmonary bypass time, and crossclamp time. Serum IL-6 immediately after surgery was assessed in both groups. We obtained patients' blood samples from a peripheral artery 4 hours after surgery to measure IL-6. Each sample was centrifuged at 2000g for 10 minutes, and the serum was collected in to small SRL vials (SRL, Inc, Tokyo, Japan) and frozen to -80°C for later analysis. The IL-6 level was measured with an automated chemiluminescent enzyme immunoassay system (SRL, Inc). Data for IL-6 were log-converted (natural logarithm) because of the skewed distribution.

Study Design

This study was conducted as a prospective, observational study. The patients from Nagoya University Hospital underwent a postsurgical rehabilitation program with NMES intervention from postoperative days (PODs) 1 to 5, and the patients from Kainan Hospital underwent postsurgical rehabilitation program only.

Intervention

The patients from Nagoya University Hospital underwent NMES on the bilateral quadriceps femoris and triceps surae daily from PODs 1 to 5 (5 sessions). During stimulation, self-adhering surface electrodes (62 × 62 mm) were positioned bilaterally on the vastus lateralis, vastus medialis, and triceps surae after the patient's skin was cleaned.¹² The waveform of NMES was a symmetric, biphasic square wave. The stimulator was configured to deliver a direct electrical current for 0.4 seconds followed by a pause that lasted 0.6 seconds. Pulse groups consisting of 10 impulse trains were delivered for each muscle at 30-second intervals during the session. Duration of the session was 30 to 60 minutes. The intensities of NMES were set to induce 10% and 20% of maximal

VIDEO 1. Neuromuscular electrical stimulation. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(16\)31154-0/addons](http://www.jtcvsonline.org/article/S0022-5223(16)31154-0/addons).

FIGURE 1. Flow diagram of study participants. *COPD*, Chronic obstructive pulmonary disease; *NMES*, neuromuscular electrical stimulation.

voluntary contraction (MVC), and the repetitions of 10%-10%-20% MVC were set throughout the session. NMES is shown in [Video 1](#). Daily NMES intervention started from POD 1. The safety of this NMES protocol in patients immediately after cardiovascular surgery has been reported elsewhere.¹² Patients in both groups underwent the postoperative mobilization program based on the guidelines of the Japanese Circulation Society under the supervision of a physical therapist ([Table E1](#)).

Outcomes

The primary outcome in this study was time trend of the 3-MH concentration in 24-hour urine corrected for urinary creatinine (Cre) content (3-MH/Cre) after surgery. The ratio of 3-MH to urinary Cre was used for normalizing the data for lean body mass differences among patients. Collection of 24-hour urine samples started at operative time and continued until POD 5. Urine was collected during 24 hours and stored into bottles containing hydrochloric acid to avoid bacterial hydrolysis of urea. At the end of the daily urine collection, we gathered a urine sample from the pooled urine after immixture of the collected urine and stored at -80°C until processing. The 3-MH concentration was determined by high-performance liquid chromatography¹⁵ (SRL, Inc). The value of 3-MH and Cre in urine samples was multiplied by the 24-hour urine volume to produce a value for daily 3-MH/Cre excretion.

Secondary outcomes were knee extensor isometric strength (KEIS) and handgrip strength. Both muscle strengths were measured the day before surgery (baseline) and POD 7. KEIS was measured by an isometric dynamometer ($\mu\text{Tas F-1}$; ANIMA Corp, Tokyo, Japan). Patients sat in a chair with their hips and knee at 90° to measure KEIS. Their shin was strapped into a cuff, and they performed 3 maximal isometric contractions against a fixed resistance for each leg with a 3-minute interval. During measurement, identical verbal encouragement was given, and force generated was measured in kilogram force. The greatest value among 3 measurements was selected for analysis.^{16,17} Handgrip strength was measured with a JAMAR dynamometer (5030J1; Sammons Preston, Rolyon, Bolingbrook, Ill) set at the second grip position.¹⁸ Measurements were made thrice on the nondominant hand, and the greatest value (in kilograms) was selected for analysis.¹⁶ An image of the measurement of both muscle strengths is shown in [Figure E1](#). Both muscle strengths were measured by

well-trained physical therapists who showed good test-retest reliability (intraclass correlation coefficients of >0.85).

Statistical Analysis

We used the Wilk-Shapiro test to assess the normality of distribution of the data. Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range) in cases of non-normal distribution. Categorical data were reported as percentages. Group baseline characteristics were compared by use of the *t* test (or Mann-Whitney *U* test) for continuous variables and χ^2 test for categorical variables. To assess the effect of NMES on urine 3-MH/Cre level from PODs 1 to 5, we used linear mixed models for repeated measurement. Fixed effects of interest were group (NMES/non NMES), time (PODs), and interaction between group and time. In addition, because the urine 3-MH/Cre level on POD 1 varied between the groups, we used the value on POD 1 as a covariate. Between-group and within-group comparisons for muscle strength parameters were performed with the Mann-Whitney *U* test and Wilcoxon test, respectively. A *P* value $< .05$ was considered statistically significant. All analyses were calculated with SPSS, ver 16.0 (SPSS Inc, Chicago, Ill).

RESULTS

Study Participants

This study included 68 and 41 patients from Nagoya University Hospital and Kainan Hospital, respectively ([Figure 1](#)). No differences were found in the baseline characteristics between the groups, except for the crossclamp time ([Table 1](#)). In addition, although immobilization after surgery is an important stimulus for muscle proteolysis,¹¹ days from surgery to initial mobilization were not significantly different between the groups.

3-MH/Cre

Time course of urinary 3-MH/Cre from PODs 1 to 5 is shown in [Figure 2](#). Urinary 3-MH/Cre level peaked on POD

TABLE 1. Patients' characteristics of NMES and non-NMES group

	NMES, n = 61	non-NMES, n = 41	P value
Age, y	69 (62-74)	70 (65-75)	.77
Female, n (%)	16 (26.2)	10 (24.4)	.83
BMI, kg/m ²	23.3 ± 3.5	23.4 ± 3.5	.90
Preoperative hemoglobin, g/dL	12.9 (11.9-14.1)	12.4 (11.5-13.5)	.05
Preoperative grip strength, kg	36 (29-41)	33 (27-41)	.63
Preoperative KEIS, kg/wt	0.42 (0.35-0.48)	0.39 (0.24-0.49)	.26
Operative procedure			
Coronary artery bypass, n (%)	25 (40.9)	19 (46.3)	.16
Valvular, n (%)	20 (32.8)	15 (36.6)	
Thoracic aorta, n (%)	10 (16.4)	1 (2.4)	
Combined, n (%)	6 (9.8)	6 (14.6)	
CPB time, min	169 (111-196)	178 (139-202)	.13
Crossclamp time, min	108 (0-138)	127 (88-153)	<.05
log IL-6, pg/dL	2.2 ± 0.4	2.3 ± 0.3	.10
Days from surgery to initial mobilization	3 (2-3)	2 (2-3)	.34

Data are expressed in mean ± standard deviation or median (interquartile range). NMES, Neuromuscular electrical stimulation; BMI, body mass index; KEIS, knee extensor isometric strength; CPB, cardiopulmonary bypass; log IL-6, logarithmic interleukin-6.

3 in the NMES group, whereas the level showed a sustained increase until POD 4 in the non-NMES group. Significant main effect for time ($F = 173.7$, $P < .01$) and group $\times$ time interaction ($F = 12.1$, $P < .01$) were found by the use of linear mixed models for repeated measurement. In contrast, the main effect for group was not significant ($F = 1.01$, $P = .31$).

Change in Muscle Strength

Change in KEIS from baseline to POD 7 is shown Figure 3. KEIS decreased significantly from baseline to POD 7 in both groups. The value at POD 7 in the NMES group was, however, significantly greater than that in the non-NMES group (median, 0.40 [0.33-0.45] kg/weight vs median, 0.23 [0.16-0.36]; $P < .01$). Handgrip strength also reduced from baseline to POD 7 in both groups (Figure 4). The value at

POD 7 in the NMES group was, however, significantly greater than that in the non-NMES group (median, 32.0 [24.5-35.3] kg vs median, 25.0 [16.0-30.0]; $P < .01$).

DISCUSSION

The present findings support our hypothesis that NMES performed immediately after cardiovascular surgery is effective in reducing sustained elevation of muscle protein degradation and preserving muscle strength. To the best of our knowledge, this is the first study that demonstrates the possibility of using NMES to attenuate postoperative muscle protein degradation and muscle weakness in patients after cardiovascular surgery.

FIGURE 2. Time trend of urinary 3-MH/Cr from PODs 1 to 5 in NMES (n = 61) and non-NMES (n = 41) groups. Cr, Creatinine; NMES, neuromuscular electrical stimulation; 3-MH/Cr, 3-methylhistidine/creatinine ratio; POD, postoperative day.

FIGURE 3. KEIS at baseline and POD 7 in NMES (n = 61) and non-NMES (n = 41) groups. *Significant between-group difference ($P < .01$). KEIS, Knee extensor isometric strength; NMES, neuromuscular electrical stimulation; POD, postoperative day.

FIGURE 4. Handgrip strength at baseline and POD 7 in NMES ($n = 61$) and non-NMES ($n = 41$) groups. *Significant between-group difference ($P < .01$). NMES, Neuromuscular electrical stimulation; POD, postoperative day.

The value of urinary 3-MH/Cre peaked significantly earlier in the NMES group than in the non-NMES group. Ninety percent of the whole body protein bound to 3-MH is present in actin and myosin of the skeletal muscle.¹⁹ The use of the ratio to urinary Cre normalizes the data for lean body mass differences among patients. Iida and colleagues²⁰ reported that preoperative handgrip strength, body mass index, hemoglobin, cardiopulmonary bypass time, and IL-6 level 4 hours after surgery are independent predictors of the amount of 3-MH/Cre after cardiovascular surgery.²⁰ In this study, these variables were not significantly different between the groups. The results in this study, therefore, suggest that NMES may attenuate the sustained elevation of muscle proteolysis after cardiovascular surgery.

Our results correspond with those observed in previous studies.^{21,22} In an early study involving patients in the intensive care unit,²¹ NMES was reported to decrease 3-MH excretion. In that study,²¹ however, all participants underwent NMES at least 8 days after hospitalization, when the level of metabolic stress would be low. The present study demonstrated the preventive effect of NMES on the elevation of 3-MH/Cre levels within 5 days after cardiovascular surgery, suggesting that NMES can reduce muscle proteolysis even in patients in a hypercatabolic state. Another study has reported that postoperative NMES reduced muscle protein degradation in patients immediately after abdominal surgery.²² Although they showed that NMES attenuated the activity of the ubiquitin-proteasome system,²² which is the main pathway of protein degradation in catabolic situations,^{23,24} it remains unclear whether this molecular biologic alteration actually leads to measurable change in muscle strength. Our results add to the evidence that reduction in muscle

proteolysis induced by NMES were accompanied by preservation of muscle strength. The mechanism of the reduction in 3-MH/Cre levels induced by NMES remains unclear. As noted previously, because the ubiquitin-proteasome pathway physiologically plays an important role in protein degradation, we assume that the possible mechanisms of the reduction in 3-MH/Cre levels induced by NMES include suppression of the ubiquitin-proteasome pathway.

KEIS decreased after surgery in both groups; however, KEIS at POD 7 in the NMES group was significantly greater compared with that in the non-NMES group, whereas no difference was found in the baseline value between the groups. In the non-NMES group, comparable levels of reduction were observed in KEIS (35.1%) and handgrip strength (30.2%) on POD 7. In contrast, the reduction in KEIS, which were the target muscles of NMES, was 5.3% in the NMES group, whereas handgrip strength decreased by 14.9%. NMES implemented for more than 4 weeks has been reported to improve quadriceps muscle strength in stable patients with chronic obstructive pulmonary disease^{17,25} and chronic heart failure.^{16,26} In this study, NMES for less than 1 week (5 days) preserved quadriceps muscle strength of patients in a hypercatabolic state immediately after cardiovascular surgery. The results of this study suggest that, even in short-term, NMES intervention immediately after cardiovascular surgery might be effective in preventing postoperative muscle weakness.

One explanation about the mechanism for preservation of muscle strength could be the reduction in myofibrillar degradation observed in the NMES group. Other mechanisms may include maintaining the stimulus of protein anabolism through insulin-like growth factor 1 excretion²⁷ because the NMES used in our study induced 20% of MVC, wherein most previous NMES could not achieve. In addition, a previous study reported that the increases in muscle strength after NMES for less than 4 weeks were accounted for the neural adaptations without muscle hypertrophy in healthy young adults.²⁸ Further studies will be needed to clarify the mechanisms for preservation of skeletal muscle strength induced by NMES under the hypercatabolic state.

Interestingly, handgrip strength also was preserved in the NMES group compared with the non-NMES group, whereas stimulation was only applied to the lower-extremity muscles. NMES implemented to the unilateral leg has been reported to increase muscle strength in the contralateral, nonstimulated leg.^{29,30} In addition, a previous study reported that NMES improved the sum score of the upper- and lower-extremity muscle strength in critically ill patients.³¹ The spread effect of NMES on nontarget muscles should be explored in future studies.

The present study has several limitations. The main limitation of this study was the absence of randomization. In

this study, NMES intervention was split between 2 different hospitals. This practical choice could have led to some potential bias. Crossclamp time in the NMES group was actually shorter than that in the non-NMES group; however, patient characteristics, which have been reported as predictive factors for postoperative muscle proteolysis,²⁰ were not different between the groups. In addition, postoperative early mobilization protocol during the study period was similar in the 2 hospitals (Table E1). Therefore, the risk of bias in this study would be low.

Another limitation was the unblinded testers of muscle forces, which might lead to measurement bias that is usually avoided by methodology. Although identical encouragement was used in the pre- and postoperative measurements, and the maximal force value was accepted from the 3 successive measurements performed by the patients, we assume that the results of muscle force in this study still have a possibility to overestimate the effect of NEMS. To clarify this, a blinded randomized controlled trial focused on the efficacy of NEMS on postoperative muscle degradation and force reduction will be needed. Nevertheless, the findings of this study provide fundamental data regarding the possibility of NMES to overcome postoperative skeletal muscle hypercatabolism and, in turn, muscle weakness.

CONCLUSIONS

This study is the first exploratory research to suggest an anticatabolic effect of NMES in patients immediately after cardiovascular surgery. The findings of this study provide a rationale, not only for a larger blinded randomized controlled trial, but also for a study that would explore who should be prescribed with NMES for postoperative functional preservation after cardiovascular surgery. A cause-effect relationship between NMES and functional preservation would be a future challenging issue.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: electric stimulation therapy, skeletal muscle, proteolysis, muscle weakness, cardiovascular surgical procedures, rehabilitation

EDITORIAL COMMENTARY

A new weapon in the fight against postcardiac surgery muscle catabolism

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Systemic inflammatory response syndrome is a complex pathophysiologic event following cardiac surgery, and is the result of surgical stress, altered end-organ blood flow during cardiopulmonary bypass, and neuroendocrine alterations.¹

This proinflammatory milieu is characterized by perioperative increased plasma levels of cytokines such as interleukin 6 and tumor necrosis factor alpha and contributes to the establishment of a catabolic phase that occurs during the postoperative course.^{2,3}

The subsequent muscle wasting and muscle weakness appears early in critically ill patients, negatively influencing outcomes.⁴⁻⁶ In this scenario, patient-related factors, such as preoperative nutritional status, body mass index, hemoglobin level, and endocrine alterations interact with procedure-related determinants.⁷

Iwatsu and colleagues⁸ conducted a prospective study to evaluate the efficacy of neuromuscular electrical

Andrea Montisci, MD, and Antonio Miceli, MD, PhD

Central Message

Neuromuscular electrical stimulation is a potential solution to attenuate postcardiac surgery proteolysis and muscle weakness.

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stimulation (NEMS) in attenuating postcardiac surgery proteolysis and muscle weakness.⁸ Specifically, 61 patients underwent daily NEMS up to postoperative day 5, whereas 41 patients received standard therapy. The levels of urinary 3-methylhistidine, a parameter of protein breakdown, were significantly lower in the NEMS group. Moreover, knee extensor isometric strength and handgrip strength—2 specific muscular strength tests—were higher in the NEMS group compared with the non-NEMS group on postoperative day 7. These results highlight the

Measurement of KEIS

Measurement of handgrip strength

FIGURE E1. Measurement of muscle strength.

TABLE E1. Postoperative mobilization protocol form PODs 1 to 7 in each hospital

	NMES group	Non-NMES group
POD 1	Sitting on the edge of the bed	Sitting on the edge of the bed
POD 2	Standing at bedside walking around the bed	Standing at bedside walking around the bed
POD 3	Walking in the corridor 50 m	Walking in the corridor 100 m
POD 4	Walking in the corridor 100 m	Walking 100 m
POD 5	Walking 200 m	Walking 300 m
POD 6	Walking 300 m	Walking 300 m
POD 7	Aerobic exercise using cycle ergometer	Aerobic exercise using cycle ergometer

NMES, Neuromuscular electrical stimulation; POD, postoperative day.