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Title

Effect of perioperative neuromuscular electrical stimulation in patients undergoing cardiovascular surgery: A pilot randomized controlled trial

Authors

Hideki Kitamura[1], MD, Sumio Yamada[2], PhD, PT, Takuji Adachi[3], MS, PT, Kenichi Shibata[3, 4], MS, PT, Mototsugu Tamaki[1], MD, Yasuhide Okawa[1], MD, Akihiko Usui[5], MD, PhD

Affiliations

[1] Department of Cardiovascular Surgery, Nagoya Heart Center, Nagoya, Japan

[2] Department of Health Science, Nagoya University Graduate School of Medicine

[3] Program in Physical and Occupational Therapy, Nagoya University Graduate School of Medicine

[4] Department of Cardiac Rehabilitation, Nagoya Heart Center

[5] Department of Cardiac Surgery, Nagoya University Graduate School of Medicine

Conflicts of interest

The authors declare no conflicts of interest.

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Corresponding author

Sumio Yamada, PhD, PT

Department of Rehabilitation Science, Nagoya University Graduate School of Medicine

1-1-20 Daiko-minami Higashi-ku Nagoya 461-8673, Japan

Tel +81-52-719-1346; Fax +81-52-719-1346; Email yamadas@met.nagoya-u.ac.jp

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This study was approved by Nagoya Heart Center Ethics Committee (approval number: 8).

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Glossary of abbreviations

NMES = neuromuscular electrical stimulation

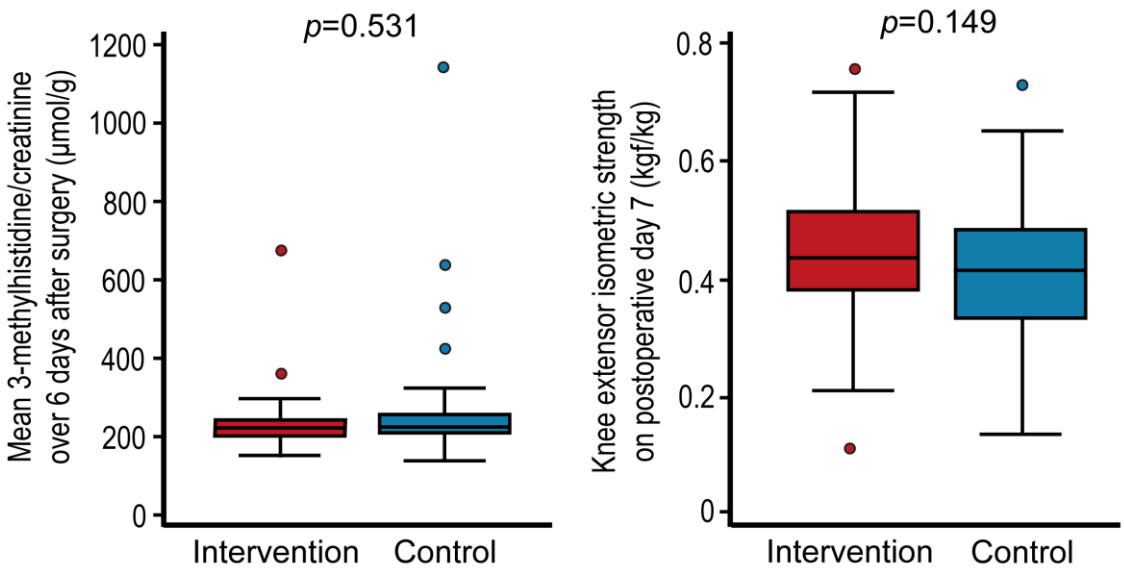
POD = postoperative day

KEIS = knee extensor isometric muscle strength

3-MH = 3-methylhistidine

Cre = creatinine

Central Picture



Central Picture Legend. Comparisons of primary outcomes between the intervention and control groups

Central message

We performed a randomized, controlled trial to examine the effects of neuromuscular electrical stimulation in patients who underwent cardiovascular surgery. The results did not show positive effects.

Perspective statement

As postoperative patients often have difficulty with sufficient voluntary muscle contraction, supplemental interventions to prevent muscle wasting immediately after surgery need to be developed. We performed a randomized, controlled trial to examine the effects of neuromuscular electrical stimulation in patients who underwent cardiovascular surgery, but we did not find any positive effects.

Abstract

Objectives

A randomized, controlled trial was conducted to examine the effects of perioperative neuromuscular electrical stimulation on muscle proteolysis and physical function using blinded assessment of physical function.

Methods

Consecutive patients undergoing cardiovascular surgery were screened for eligibility as study subjects. Participants were randomly assigned to receive either neuromuscular electrical stimulation or the usual postoperative mobilization program. The intervention group received neuromuscular electrical stimulation on bilateral legs 8 times before and after surgery. The primary outcomes were the mean 3-methylhistidine concentration corrected for urinary creatinine content from baseline to postoperative day 6, and knee extensor isometric muscle strength on postoperative day 7. Secondary outcomes were usual walking speed and grip strength. Physical therapists blinded to patient allocation performed measurements of physical function.

Results

Of 498 consecutive patients screened for eligibility, 119 participants (intervention group, n=60; Control group, n=59) were enrolled. In the overall subjects, there were no differences in any outcomes between the intervention and control groups.

Conclusions

The results demonstrated no significant effects of neuromuscular electrical stimulation on muscle proteolysis and physical function after cardiovascular surgery, suggesting the need

to explore indications for neuromuscular electrical stimulation and to clarify the effects in terms of the dose-response relationship.

Word count: 198

Introduction

After cardiovascular surgery, muscle wasting is induced by systemic inflammation[1]. This acute inflammatory response accelerates protein catabolism and decreases protein synthesis, resulting in increased muscle proteolysis[2,3]. In addition, perioperative immobilization or physical inactivity also promotes muscle wasting[4]. Since this postoperative muscle wasting results in muscle weakness and functional decline, postoperative rehabilitation mainly aims to prevent muscle loss and weakness as well as postoperative complications. To avoid this, early mobilization has been introduced, but muscle proteolysis markedly accelerates within 48 h after cardiovascular surgery[5], and it is often difficult for postoperative patients to initiate sufficient muscle activities due to hemodynamic instability. Supplemental interventions to prevent muscle wasting immediately after surgery thus need to be developed.

Neuromuscular electrical stimulation (NMES) is an intervention modality that can induce sufficient muscle contraction without the patient's volitional efforts. Iwatsu and colleagues previously reported that NMES could be safely applied to patients even immediately after cardiovascular surgery[6]. In addition, a subsequent trial demonstrated favorable effects of NMES on skeletal muscle proteolysis and muscle weakness[7]. However, a cause-effect relationship has yet to be established because of the lack of randomization and blinded assessment of muscle strength.

Therefore, a pilot randomized, controlled trial was performed to examine the effects of perioperative NMES on muscle proteolysis and physical function and to collect data for sample size calculation for future trials.

Methods

Study design and participants

The present study was conducted as a single-center, randomized study. Consecutive patients who underwent cardiovascular surgery at Nagoya Heart Center from May 2014 to September 2016 were approached. Exclusion criteria for this study included the following: 1) emergency cases; 2) renal dysfunction, defined as estimated glomerular filtrating rate < 30 ml/min/1.73 m^2 before surgery; 3) chronic hemodialysis before surgery or patients who require new hemodialysis after surgery; 4) neurological dysfunction before or after surgery including postoperative delirium; or 5) disagreement with participation in the study.

This study was approved by Nagoya Heart Center Ethics Committee (approval number: 8) and written informed consent was obtained from each patient for participation in this study. This study was registered in the University Hospital Medical Information Network (UMIN) center (Registration Number: UMIN000018542).

Randomization and masking

Participants were randomly assigned in a 1:1 ratio to undergo NMES after surgery or to receive the usual postoperative mobilization program using a computer-generated stratified block randomization (block sizes of 10). Randomization was performed using four strata based on two stratification factors: sex and planning of cardiopulmonary bypass, because cardiopulmonary bypass time was independently associated with muscle proteolysis[8]. Study participants were assigned to one of four strata according to their sex and planning of

cardiopulmonary bypass and then allocated to NMES or usual care. During the study period, off-pump surgery was planned for coronary artery bypass grafting, whereas cardiopulmonary bypass was planned for other cardiovascular surgeries including concomitant coronary artery bypass grafting.

Study participants and physical therapists were not blinded to the group allocations; that is, this was an open-label trial. In contrast, measurements of physical function before and after surgery were performed by two examiners who worked outside of Nagoya Heart Center and were blinded to the group allocation; that is, blinded outcome assessment was performed regarding physical function. To maintain the blinded assessment, examiners were instructed not to discuss interventions with the participants, doctors, physical therapists, and the cardiac rehabilitation team. Additionally, assessments were performed after 5 PM at a time distant from the therapy intervention. All statistical analyses were conducted by examiners who worked outside our institution and were blinded to group allocation.

Intervention

Patients randomized to the intervention group underwent NMES on bilateral quadriceps femoris and triceps surae muscles for 3 days prior to surgery and daily from postoperative day (POD)1 to POD5 (total, 8 sessions). NMES was delivered to each patient by a physical therapist in the Department of Cardiac Rehabilitation at Nagoya Heart Center. NMES after surgery is shown in Video 1. During stimulation, self-adhering surface electrodes (62 × 62 mm^2) were placed on the vastus lateralis, vastus medialis, and triceps surae bilaterally after

cleaning the patient's skin. A direct electrical current with a symmetric and biphasic square waveform was delivered for 0.4 seconds followed by a 0.6-second pause. Ten pulse trains (10 seconds) were delivered to each muscle with 30-second intervals and repeated for 30 minutes of a session. The intensities of NMES were set at 10 and 20% of maximal voluntary contraction estimated by the degree of elevation of the stimulated leg. As Video 1 shows, NMES to induce approximately 20% of maximal voluntary contraction provides full knee extension. Because, in our experiences, 30% of NMES-induced maximal voluntary contraction will bring muscle pain or soreness that patients cannot tolerate, we considered 20% of maximal voluntary contraction as an appropriate intensity to maintain knee extensor isometric strength (KEIS), a primary outcome, for postoperative patients who could not achieve sufficient voluntary muscle contraction. The repetitions of 10%-10%-20% maximal voluntary contraction were set throughout the session. If the subjects suffered from wound pain due to NMES, the intensity was reduced to 10%-10%-15% maximal voluntary contraction. The feasibility and safety of this NMES protocol in patients immediately after cardiovascular surgery were confirmed and reported elsewhere[6].

Patients in both groups underwent a postoperative rehabilitation program according to the guidelines of the Japanese Circulation Society, under the supervision of physical therapists. In Nagoya Heart Center, the early mobilization program began with dangling or standing up on POD1, walking around the bed or 100 m if possible on POD2, walking in the corridor 300 m or aerobic exercise training using a cycle ergometer on POD3. After independent walking in the ward, patients performed resistance training and aerobic

exercises every day until discharge.

Outcomes

Primary outcomes in this study were the mean concentration of 3-methylhistidine concentration corrected for urinary creatinine (Cre) content (3-MH/Cre) from POD1 to POD6, and KEIS on POD7.

KEIS is a key muscle function for resuming early daily activities in patients following cardiovascular surgery. In our previous study, the postoperative decrease in KEIS was correlated with the postoperative 3-MH/Cre level[1], which is an objective measure of muscle proteolysis. By measuring KEIS and 3-MH/Cre as primary outcomes, the effects of NMES were explored in terms of both muscle function and muscle proteolysis.

KEIS was measured using a hand-held dynamometer (μ-tas F1; Anima, Tokyo, Japan). The participant was positioned in a seated position with the knee and hip joints in 90° of flexion. Two trials were completed for each leg, and the ratio of the strongest value to body weight was used for analysis.

The ratio of 3-MH to urinary Cre was used to normalize data for body mass differences among patients. Collection of 48-h urine samples was started from the beginning of the operation to POD6. All collected 48-h urine was stored in bottles containing hydrochloric acid to avoid uric hydrolysis by bacteria. After 48-h collection of urine, a sample was gathered from the bottle and stored at -80°C until processing. The concentration of 3-MH was measured by high-performance liquid chromatography (SRL, Tokyo, Japan). The value of 3-MH and Cre in urine samples was multiplied by the 48-h

urine volume to produce a value for 48-h 3-MH/Cre excretion. The mean concentration of 3-MH/Cre over 6 days after surgery was calculated using three 48 h urine samples (POD1-2, POD3-4, POD5-6) and used for the analysis.

Usual walking speed and grip strength were also assessed as secondary outcomes. Usual walking speed was measured with a 10-m walk test[9]. The test was performed twice, using the faster result for analysis. Grip strength was measured using a digital dynamometer (JAMAR® Plus+ Digital Hand Dynamometer; Sammons Preston, Chicago, IL) set at the second handle position. Participants sat with the wrist in a neutral position and the elbow flexed at 90°. Grip strength was measured twice for each hand, and the highest value was used for analysis. NMES implemented to the unilateral leg has been reported to increase muscle strength in the contralateral, nonstimulated leg[10,11]. Added to this, a previous study has demonstrated that NMES improved the sum score of upper and lower extremity muscles in critically ill patients[12]. Furthermore, grip strength is particularly important in early mobilization postsurgical rehabilitation; therefore, grip strength was assessed as a secondary outcome in the present study.

In this study, two physical therapists outside of Nagoya Heart Center who were blinded to patient allocations performed measurements of physical function before and after surgery. Prior to starting measurements, intra- and interclass correlation coefficients >0.9 on each indicator were examined.

Statistical analysis

An examiner who worked outside of our institution and was not informed of group

allocation conducted all statistical analyses, as described before.

The Wilk-Shapiro test was used to assess the normal distribution of data. Continuous variables are presented as means ±standard deviation, or as medians and interquartile range in cases of non-normal distributions. Categorical data are presented as percentages.

The mean concentration of 3-MH/Cre over 6 days after surgery and physical function measured on POD7 were compared between the NMES group and the control group using Student's *t*-test and the Mann-Whitney U test, as appropriate. All outcomes were assessed by intention-to-treat analysis. All statistical analysis was performed using SPSS version 22 (SPSS, Chicago, IL).

Sample size calculation

Although we reported the favorable effects of NMES on the decline in knee extensor and grip strength after cardiac surgery[7], the results of that study may lead to overestimation of the effects of NMES because the study was conducted as a nonrandomized, controlled trial with an unblinded tester design. Therefore, sample size was not calculated, but the aim was to enroll as many patients as the previous study (60 patients per group) to confirm the effects of NMES and to serve as reference data for sample size calculations for future studies.

We performed a post hoc power calculation after completing the present trial. The sample size was calculated to detect a difference in KEIS on POD7 (alpha=0.05, power=0.8).

Results

Study participants

The CONSORT diagram presenting patient flow through the study is presented in Figure 1. Of the 498 patients who underwent cardiovascular surgery during the study period, 360 were excluded according to the exclusion criteria. As a result, 138 patients were enrolled in this study and underwent randomization: 68 were allocated to receive NMES plus the standard postoperative rehabilitation program, and 70 controls received only the standard rehabilitation program after surgery. After randomization, 19 patients dropped out for the following reasons: cancellation of operation (NMES, n=3; control, n=2); chose to decline after the operation (NMES, n=3; control, n=4); postoperative delirium (NMES, n=1; control, n=4); and postoperative hemodialysis (control, n=1). The reasons for declining were: refusal of 24-h urine collection (NMES, n=1; control, n=2); anxiety about the operation (NMES, n=1; control, n=1); and complaint of muscle discomfort induced by NMES (NMES, n=1). Finally, 119 patients (NMES group, n=60; Control group, n=59) were enrolled in the analysis after excluding patients lost to follow-up. The baseline characteristics of the study participants are shown in Table 1. All 119 participants were analyzed according to intention-to-treat analysis. The 60 subjects who were assigned to the NMES group received the NMES intervention as scheduled (number of sessions: 3 sessions before surgery and 5 sessions after surgery; duration for each muscle: 30-second intervals repeated for 30 minutes of a session).

Effects of NMES on primary and secondary outcomes

A comparison of the mean concentrations of 3-MH/Cre over 6 days after surgery is presented in Figure 2. There was no significant difference in the mean 3-MH/Cre after surgery between the NMES and control groups (225.3 [204.0-248.3] μmol/g vs 227.3 [206.3-259.9] μmol/g, p=0.531). Physical function measures on POD7 are shown in Figure 3, and there were no differences between NMES and control (KEIS: 0.44±0.13 kgf/kg vs 0.41±0.12 kgf/kg, p=0.149; usual walking speed: 1.04±0.24 m/sec vs 0.99±0.23 m/sec, p=0.294; grip strength: 29.1±10.5 kg vs 26.9±8.7 kg, p=0.213). A post hoc power calculation showed that 274 patients per group were calculated as the sample size needed to detect a difference in KEIS on POD7.

Discussion

The present randomized controlled trial was strictly designed to reduce potential biases using blinded outcome assessment of physical function and statistical analysis. However, contrary to our expectation, NMES did not provide any positive effects on study outcomes.

NMES did not show significant effects on 3-MH and KEIS, as primary outcomes of this study, in the total patient population. Iwatsu and colleagues demonstrated that the value of urinary 3-MH/Cre peaked significantly earlier in the NMES group than in the non-NMES group[7]. In contrast, there was no difference in convergence of the 3-MH increase after surgery between the groups in the present study, suggesting that muscle proteolysis was not attenuated when analyzed in overall patients. Contrary to our expectations, postoperative KEIS likewise did not differ significantly between the NMES and control groups. In this

study, examiners who performed KEIS measurements were blinded to patient allocation. Favorable intra- and interclass correlation coefficients >0.9 were also provided prior to starting measurements. Therefore, compared to a prior nonrandomized trial[7], the present randomized controlled trial is likely to provide more valid data regarding the effect of NMES on KEIS.

The negative results may be explained by postoperative physical activity other than early mobilization after surgery that was not controlled in this study. Preoperative physical activity has reported to be independently associated with reduced prolonged length of stay in intensive care unit[13]. Additionally, the amount of postoperative physical activity negatively correlates with the length of hospital stay[14]. Some patients could be active in the postoperative phase, while others may not be, even though they were asked to expand their physical activities on the ward in this study. Physical activity can confound the results, although the subjects were randomly allocated. Dose-response is another issue to be considered. A meta-analysis showed a positive correlation between the volume of functional electrical stimulation and improvement in peak oxygen consumption in patients with heart failure[15]. Another recent meta-analysis in patients with heart failure also reported significant improvement in peak oxygen consumption and 6-min walk distance for studies with ≥30 h of total NMES intervention compared with <30 h[16]. The effects of NMES may thus depend on the "dose" of the intervention, and the dose-effect relationship will be an issue to explore for effective NMES in patients undergoing cardiovascular surgery.

Additionally, the clinical indication for NMES is another issue to be examined. Using the present results, 274 patients per group were calculated as the sample size needed

386 to detect a difference in KEIS between the groups (alpha=0.05, power=0.8), which was a
387 larger number than was expected. Based on this, it would take three to four-fold recruitment
388 period that was needed in the present study and it seems not feasible. However, when
389 focusing on particular patients, a possible indication for NMES may be identified that
390 results in reduced sample size. The surgical stress of cardiopulmonary bypass is known as a
391 factor that accelerates postoperative muscle proteolysis[8]. Preoperative diabetes may also
392 increase muscle proteolysis after surgery, because perioperative hyperglycemia causes
393 elevated inflammatory responses[17]. Frail patients are also known to be at risk for marked
394 functional declines after surgery[1,18], probably due to an increased chronic inflammatory
395 state[19] that may be further exacerbated by cardiac surgery. NMES is expected to attenuate
396 postoperative muscle proteolysis and subsequent functional declines in patients with these
397 factors. As reported previously[6], there were also no harmful effects, such as marked
398 increase in systolic blood pressure, heart rate, or pacemaker malfunction, except in one
399 patient who dropped out due to muscle soreness, in the present study. This low rate of
400 adverse events related to NMES may contribute to the development of a new perioperative
401 management strategy in a particular patient population. Considering these points, we have
402 launched a new randomized controlled trial focusing on elderly patients with diabetes
403 mellitus based on the sample size calculation using a subgroup analysis of the present data
404 (Trial no. UMIN000029940).

405 Japan is becoming a super-aged society and the populations ≥65 and ≥75 years old
406 accounted for 27.6% and 13.7%, respectively, in 2017[20]. This aged population, together
407 with advances in surgical techniques and perioperative management, has led to the

extension of surgical indications for geriatric patients. According to the latest national data reported by the Japanese Association for Thoracic Surgery, the prevalence of patients ≥70 years old undergoing thoracic surgery was 53.4% in 2014, of whom 22.5% were octogenarian patients[21]. As the number of elderly patients increases, low physical function is expected to grow rapidly along with associated declines in short- and medium-term clinical outcomes and quality of life after cardiac surgery[22-24]. The effects of NMES on perioperative management of such high-risk patients should be studied in the future.

This study has several limitations that merit discussion. The effect of urine collection immediately after surgery on 3-MH/Cre estimation may need to be discussed. Because postoperative 3-MH excretion increases within 24 hours and peaks at 72 hours, we need to collect all the 3-MH that spills over from skeletal muscle. However, sampling urine immediately after surgery may affect the accuracy of 3-MH estimation because of the effects of various factors induced by the operation on urine flow. Another limitation was that we calculated the mean concentration of 3-MH/Cre over six days after surgery. Iwatsu and colleagues demonstrated that the urinary 3-MH/Cre peaked earlier in the NMES group[7]; if a similar benefit occurred in this trial, it may not have been detected. Nevertheless, the results of the present study provide fundamental findings contributing to the step-by-step advance toward clinical application of NMES to perioperative patient care.

In conclusion, the data of this pilot study did not show clear beneficial effects of NMES in patients who underwent cardiovascular surgery. Further trials need to be performed to explore indications for NMES based on patients' characteristics and to examine the dose-response relationship.

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Figure legends

Central Picture. Comparisons of primary outcomes between the intervention and control groups.

Figure 1. CONSORT diagram presenting participant flow through the study.
NMES, neuromuscular electrical stimulation.

Figure 2. Comparison of mean concentration of 3-methylhistidine/creatinine over six days after surgery between the intervention and control groups. The upper and lower borders of the box represent the upper and lower quartiles. The middle horizontal line represents the median. The upper and lower whiskers represent the maximum and minimum values of non-outliers. Extra dots represent outliers.

Figure 3. Comparisons of indicators of physical function at seven days after surgery between the intervention and control groups. The upper and lower borders of the box represent the upper and lower quartiles. The middle horizontal line represents the median. The upper and lower whiskers represent the maximum and minimum values of non-outliers. Extra dots represent outliers.

Video legends

Video 1. Neuromuscular electrical stimulation after surgery.
Ten pulse trains (10 seconds) are delivered to each muscle with 30-second intervals and

repeated for 30 minutes of a session. The intensities of neuromuscular electrical stimulation were set at 10 and 20 % of maximal voluntary contraction, which was estimated by the degree of elevation of the stimulated leg (full knee extension approximately equals 20% of maximal voluntary contraction). Repetitions of 10%-10%-20% maximal voluntary contraction were set throughout the session. In this video, ten times of 10% maximal voluntary contraction are demonstrated followed by ten times of 20% maximal voluntary contraction for knee extensor muscles. When applied, the patients' ankle is fixed by putting a 5-kg sandbag on the ankle.

584 **Tables**

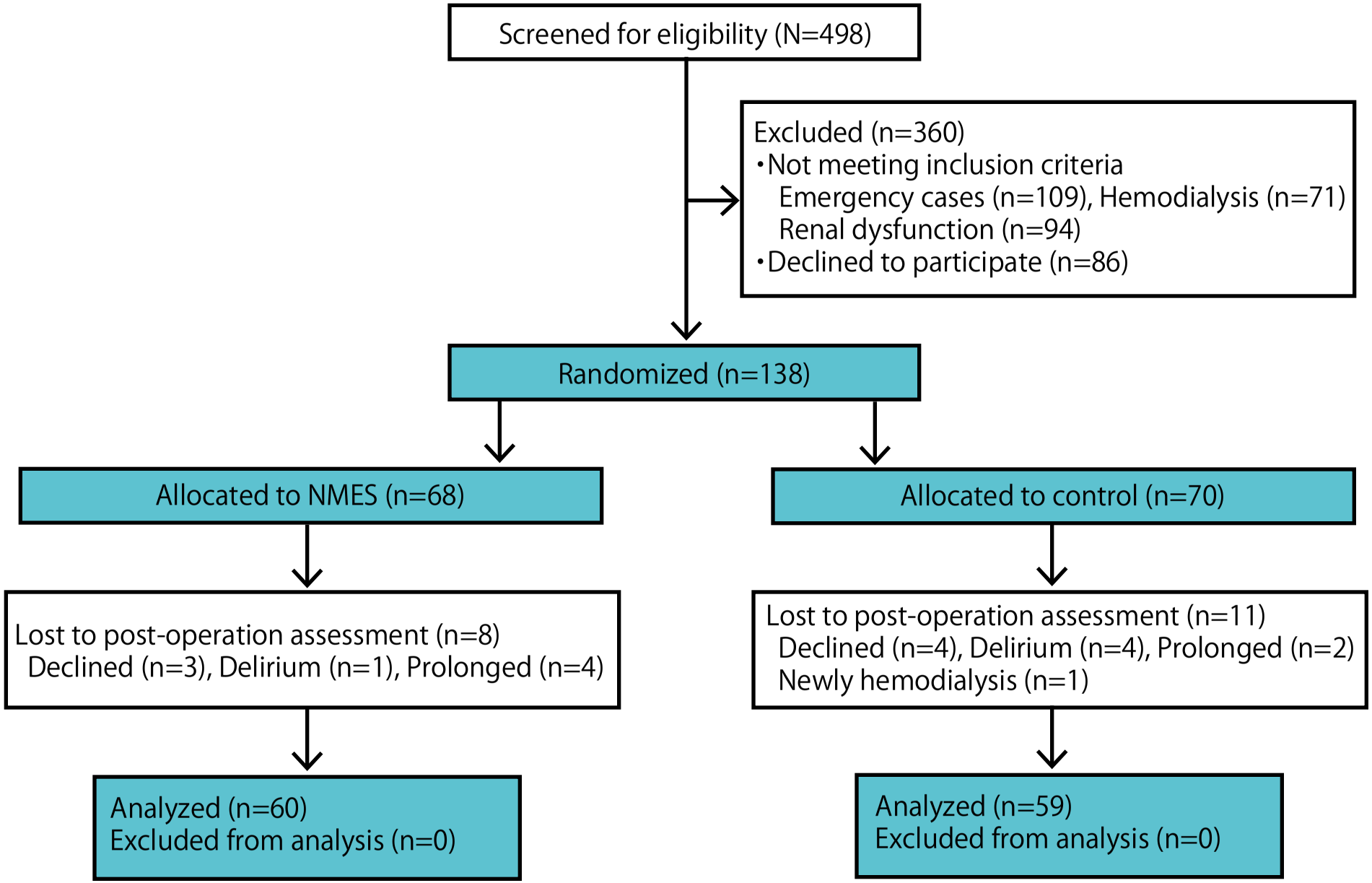
585 **Table 1.** Characteristics of the study participants

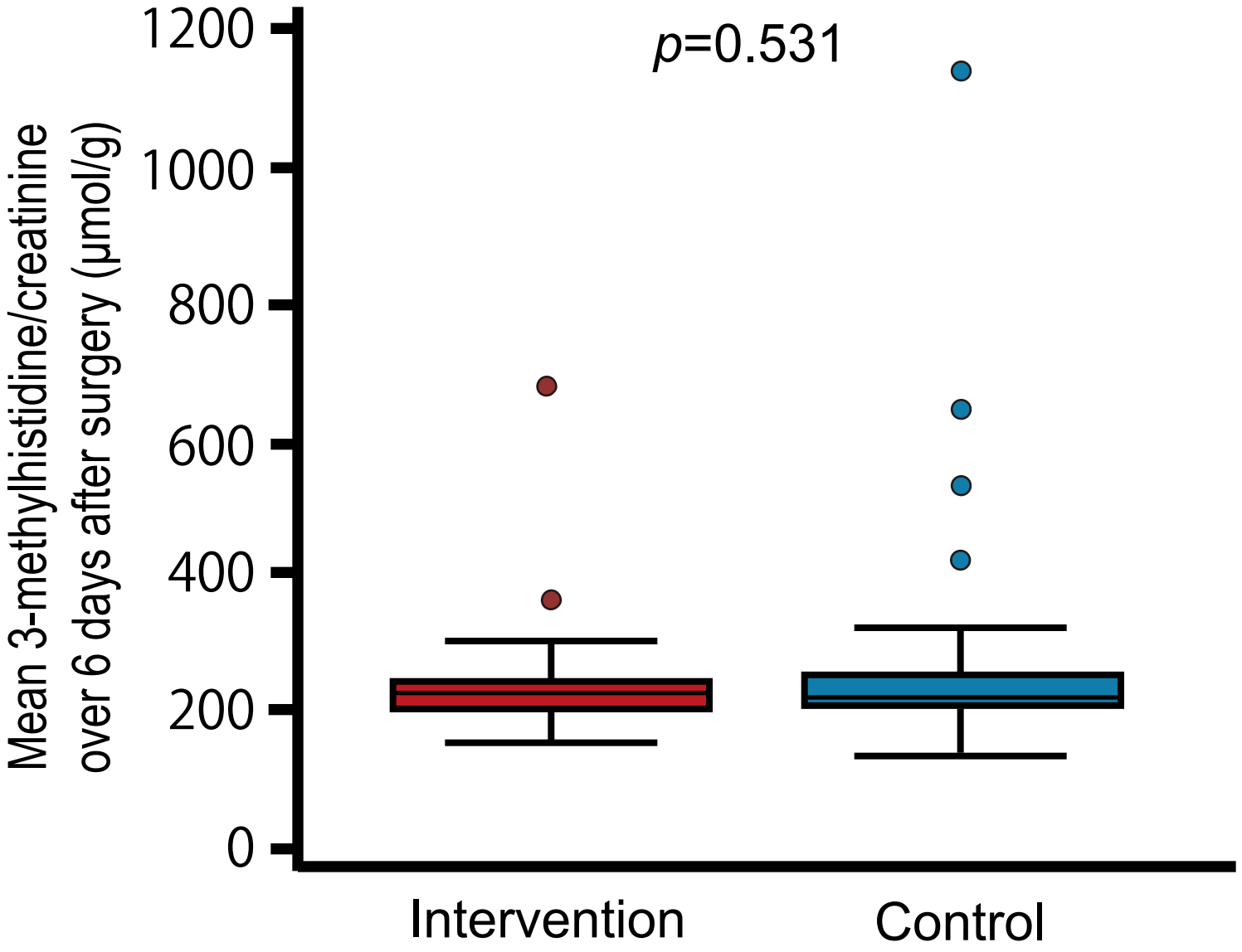
		NMES (n=60)	Control (n=59)
Age	yo	67 [55-74]	70 [61-77]
Men	n (%)	39 (66.1)	37 (61.7)
Body mass index	kg/m2	22.5 [20.4-24.8]	22.3 [20.4-24.9]
Comorbidities			
Hypertension	n(%)	28(46.7)	26(44.1)
Diabetes	n (%)	16 (27.1)	15 (25.0)
Dyslipidemia	n (%)	37 (61.7)	33(55.9)
Serous Creatinine		0.89±0.23	0.89±2.1
Hematocrit	%	41.4±3.9	40.4±4.7
Preoperative echocardiogram			
LV diameter in diastole	mm	49.5±9.1	50.6±9.4
LV diameter in systole	mm	32 [27-41]	33 [29-38]
LV Ejection Fraction	%	62 [49-68]	61 [52-66]
Pre-operative medications			
ACE/ARB	n (%)	31(51.7)	24(40.7)
Beta blocker	n (%)	20(33.3)	22(37.3)
Calcium blocker	n (%)	13(21.7)	12(20.3)
Diuretics	n (%)	23(38.3)	20(33.9)
Statin	n (%)	29(48.3)	18(31.0)
Operation time	min	212 [166-261]	194 [168-239]
Cardiopulmonary bypass	n (%)	47 (79.7)	45 (75.0)
Cardiopulmonary bypass time	min	108 [85-178]	109 [81-159]
Aortic cross-clamp time	min	94.6 ± 57.8	84.4 ± 37.7

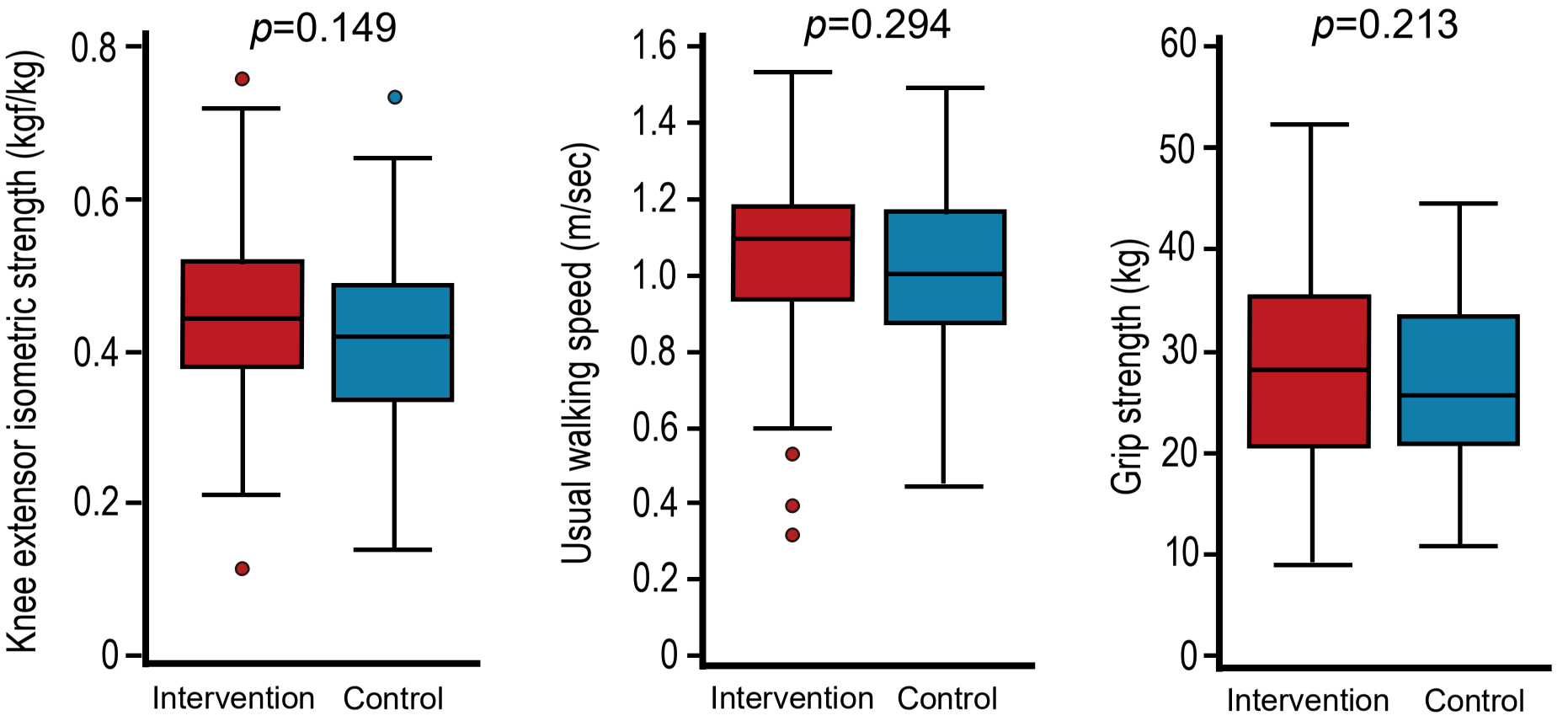
Operative procedure			
Coronary artery bypass grafting	n (%)	19 (32.2)	22 (36.7)
Valvular	n (%)	44 (74.6)	44 (73.3)
Thoracic Aorta	n (%)	4 (6.8)	2 (3.3)
3-MH/Cre	μmol/g	182.8 [160.1-202.9]	192.9 [171.9-209.3]
KEIS	%body weight	0.50 ± 0.14	0.45 ± 0.14
Grip strength	kg	32.4 ± 10.9	30.0 ± 8.2
Walking speed	m/sec	1.19 ± 0.23	1.15 ± 0.23

Continuous variables are shown by mean±standard deviation or median [interquartile range]

LV, left ventricle; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; 3-MH, 3-methylhistidine; Cre, creatinine; KEIS, knee extensor isometric strength; NMES, neuromuscular electrical stimulation


Screened for eligibility (N=498)
Excluded (n=360)
・Not meeting inclusion criteria
Emergency cases (n=109), Hemodialysis (n=71)
Renal dysfunction (n=94)
・Declined to participate (n=86)
Randomized (n=138)
Allocated to NMES (n=68)
Allocated to control (n=70)
Lost to post-operation assessment (n=8)
Declined (n=3), Delirium (n=1), Prolonged (n=4)
Lost to post-operation assessment (n=11)
Declined (n=4), Delirium (n=4), Prolonged (n=2)
Newly hemodialysis (n=1)
Analyzed (n=60)
Excluded from analysis (n=0)
Analyzed (n=59)
Excluded from analysis (n=0)


p=0.531
Mean 3-methylhistidine/creatinine over 6 days after surgery (μmol/g)
1200
1000
800
600
400
200
0
Intervention
Control


p=0.149
Knee extensor isometric strength (kgf/kg)
0.8
0.6
0.4
0.2
0
Intervention
Control
p=0.294
Usual walking speed (m/sec)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
Intervention
Control
p=0.213
Grip strength (kg)
60
50
40
30
20
10
0
Intervention
Control