Neuromuscular electrical stimulation is feasible in patients with acute heart failure

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Abstract

Aims In acute heart failure (AHF), immobilization is caused by unstable haemodynamics and dyspnoea, leading to protein wasting. Neuromuscular electrical stimulation (NMES) has been reported to preserve muscle mass and improve functional outcomes in chronic disease. NMES may be effective against protein wasting frequently manifested in patients with AHF; however, whether NMES can be implemented safely without any adverse effect on haemodynamics has remained unknown. This study aimed to examine the feasibility of NMES in patients with AHF.

Methods and results Patients with AHF were randomly assigned to the NMES or control group. The intensity of the NMES group was set at 10–20% maximal voluntary contraction level, whereas the control group was limited at a visible or palpable level of muscle contraction. The sessions were performed 5 days per week since the day after admission. Before the study implementation, we set the feasibility criteria with following items: (i) change in systolic blood pressure (BP) > ±20 mmHg during the first session; (ii) increase in heart rate (HR) > ±20 b.p.m. during the first session; (iii) development of sustained ventricular arrhythmia, atrial fibrillation (AF), and paroxysmal supraventricular tachycardia during all sessions; (iv) incidence of new-onset AF during the hospitalization period < 40%; and (v) completion of the planned sessions by >70% of patients. The criteria of feasibility were set as follows; the percentage to fill one of (i)–(iii) was <20% of the total subjects, and both (iv) and (v) were satisfied. A total of 73 patients (median age 72 years, 51 men) who completed the first session were analysed (NMES group, n = 34; control group, n = 39). Systolic BP and HR variations were not significantly different between two groups (systolic BP, P = 0.958; HR, P = 0.665). Changes in BP > ±20 mmHg or HR > ±20 b.p.m. were observed in three cases in the NMES group (8.8%) and five in the control group (12.8%). New-onset arrhythmia was not observed during all sessions in both groups. During hospitalization, one patient newly developed AF in the NMES group (2.9%), and one developed AF (2.6%) and two lethal ventricular arrhythmia in the control group. Thirty-one patients in the NMES group (91%) and 33 patients in the control group (84%) completed the planned sessions during hospitalization. This study fulfilled the preset feasibility criteria.

Conclusions NMES is feasible in patients with AHF from immediately after admission.

Keywords Neuromuscular electrical stimulation; Acute heart failure; Skeletal muscle; Rehabilitation

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Introduction

Patients with heart failure (HF) are inclined to protein catabolism because inflammatory cytokines are elevated and IGF-1 is decreased.1 Consequently, muscle mass and strength progressively decrease, and reduction in exercise tolerability progresses.2-4 In patients with HF, declining exercise capacity not only leads to poor quality of life but also is a strong prognostic factor.2,5 Patients with HF experience frequent hospitalizations due to exacerbation of HF, and physical function declines progressively especially during this period.6 In the management of patients with acute HF (AHF), immobilization
is caused by deterioration of haemodynamics and dyspnoea, which drives further protein wasting. Early ambulation may prevent protein catabolism; however, in patients with AHF, no other proactive precaution against muscle wasting was established.

Neuromuscular electrical stimulation (NMES) has been reported to preserve muscle mass in critically ill patients and patients with chronic HF. Treatment with NMES also provides a similar gain in functional outcomes without adverse events when compared with conventional aerobic exercise training in chronic HF. As NMES can induce muscle contraction without a patient’s volitional effort, it will be applicable in patients with AHF who have exercise difficulty due to instability of haemodynamics or respiratory status. Even in the acute phase of AHF, NMES is likely to work preventively on protein catabolism, which may contribute to functional decline prevention and in turn improve long-term prognosis. Despite the establishment of safety of NMES in patients in the intensive care unit and clinically stable patients with chronic HF, it has not been examined in the acute phase of patients with AHF. The feasibility and safety of NMES in AHF should be examined because, in the early phase of hospitalization, patients with AHF often manifest circulatory and/or respiratory instability that may worsen with NMES. Therefore, the purpose of this study was to examine the feasibility of NMES in patients with AHF immediately after admission.

Methods

Study population

This was a randomized tester-blinded trial to examine the feasibility of NMES during the acute phase of AHF. Patients who were admitted to Nagoya Ekisaikai Hospital due to AHF and had ambulatory ability before admission between October 2013 and July 2015 were consecutively enrolled in the study. Patients were eligible for inclusion if they met the modified Framingham criteria. The exclusion criteria were as follows: peripheral arterial disease (Fontaine classification III), dialysis, psychiatric disease, neuromuscular disease, and dementia. Patients were also excluded if they had the following: (i) New York Heart Association functional class I or II, (ii) acute coronary syndrome, (iii) intra-aortic balloon pump or extracorporeal membrane oxygenation, (iv) systolic blood pressure (BP) < 80 mmHg even with inotropic or vasopressor support, (v) intubation, (vi) agitation requiring sedation physically or by medication, and (vii) severe ventricular arrhythmia.

Written informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the human (ethics) subjects committee of Ekisaikai Hospital (approval number 2013-024).

Neuromuscular electrical stimulation

Patients were randomly assigned to either the NMES or control group, using stratified randomization by sex and left ventricular ejection fraction (LVEF) (LVEF ≥ 40% vs LVEF < 40%) with a random number table upon admission by one independent person. In this study, whether NMES can be feasible or safely implemented in patients with AHF was investigated by showing that the preset feasibility criteria can be fulfilled and that there are no differences in haemodynamics and adverse effect between the NMES and control groups.

Patients received NMES on the bilateral quadriceps femoris and triceps surae, and the sessions were conducted during the entire hospitalization period 5 days per week, from Monday to Friday in both groups. The first session was performed on the day after admission.

In this study, we adopted the same NMES protocol described elsewhere. We applied NMES with a variable-frequency train that began with high-frequency bursts (200 Hz), followed by low-frequency stimulation (20 Hz). The stimulation consists of a direct electrical current for 0.4 s, followed by a pause lasting 0.6 s. Pulse groups consisting of 10 impulse trains were delivered at 30 s intervals during the session. As for intensity of stimulation, 10% of maximal voluntary contraction (MVC) was prescribed for the first and second pulse groups and 20% MVC for the third pulse group by setting electrical current adjust system, and repetitions of 10–20% MVC stimulation were prescribed throughout the session. Based on our previous study (unpublished data), the current intensity of 10% MVC on the quadriceps was determined at the level of heel lifting from a pillow placed under the knee in hook lying, and 20% MVC was determined at the level of lower leg lifting. The current intensities for the triceps surae were set at the same levels as those for the quadriceps. The duration of the session was set at 30 min and extended to 60 min on the basis of on the patient’s tolerance. We have previously confirmed that the described protocol is acceptable and can be safely performed without causing an abnormal cardiovascular response and neuromuscular fatigue in community-dwelling older adults (n = 20; mean age ± SD, 74 ± 5.8 years; Sampei and Yamada, unpublished data, 2011). The control group was exposed to the same regimen of NMES with the intensity of stimulation set at a visible or palpable level of muscle contractions as judged objectively and subjectively. The surface electrodes (62 × 62 mm) were placed bilaterally on the vastus lateralis, vastus medialis, and triceps surae, and the detailed position of the electrodes was described elsewhere.

During the session, electrocardiogram was continuously monitored to detect arrhythmias. BP and heart rate (HR)
were measured before and 10, 20, and 30 min after the session started, and we reported BP and HR 30 min after the session started as time when session was completed enough. The intracardiac electrocardiogram was monitored in all patients with implantable cardioverter defibrillator or in those with pacemaker during the first session. Pain in the lower limb was also assessed on a visual analogue scale ranging from 0 to 10 cm during the NMES session.

Feasibility outcomes

Before the study implementation, we set the feasibility criteria as follows: (i) change in systolic BP > ±20 mmHg during the first session; (ii) increase in HR > + 20 b.p.m. during the first session; (iii) development of sustained ventricular arrhythmia, atrial fibrillation (AF), and paroxysmal supraventricular tachycardia during all sessions; (iv) incidence of new-onset AF during the hospitalization period < 40%; and (v) completion of the planned sessions by >70% of patients. Acceptable ranges of change in systolic BP and HR were determined on the basis of clinical expert opinion. If the percentage to fill one of (i)–(iii) was under 20% of the total subjects and both (iv) and (v) was satisfied, we defined the feasibility of NMES as high.

Echocardiography

All patients and examiners of echocardiography were masked to the treatment assignment. Echocardiography was performed with Vivid Q (GE Healthcare, Horten, Norway) just before and after the first session to examine the adverse haemodynamic effect induced by NMES. Left ventricular end-diastolic dimension (LVDD) and left atrial dimension (LAD) were measured from standard M-mode, and LVEF was calculated with the biplane Simpson method. The tissue Doppler images of the mitral annulus movement were recorded in the apical four-chamber view. Peak early transmitral velocity (E) was obtained from the transmitral flow, and peak early diastolic mitral annular velocity (E′) was also measured with pulsed-wave Doppler. E/E′ was calculated to estimate the left ventricular filling pressure. Inferior vena cava diameter was also measured, and right atrial pressure (RAP) was estimated according to Guidelines for the Echocardiographic Assessment of the Right Heart in Adults, as follows:17 inferior vena cava diameter ≤ 2.1 cm that collapses >50% with a sniff, RAP of 3 mmHg; inferior vena cava diameter > 2.1 cm that collapses <50% with a sniff, RAP of 15 mmHg; and indeterminate cases in which the inferior vena cava diameter and collapse do not fit this paradigm, RAP of 8 mmHg. The peak velocity (in m/s) of the tricuspid valve regurgitant jet (V) was recorded from the apical four-chamber window, and tricuspid regurgitation peak gradient (TRPG) was calculated by the Bernoulli equation: TRPG = 4(V)2.17

Laboratory examination

Haemoglobin, serum creatinine, serum albumin, and Brain natriuretic peptide levels were also measured within 24 h of hospitalization.

Statistical analysis

According to the estimated BP variability from a previous study,18 a total sample size of 30 participants in each group would provide 90% power to detect BP difference of >20 mmHg between the baseline BP and BP at 10, 20, and 30 min after the session started, using one-way repeated-measures analysis of variance test with 0.05 level of significance. Continuous variables were expressed as means ± standard deviations or medians with lower and upper quartiles as appropriate. Continuous variables were compared by t-test or Mann–Whitney test as appropriate. Categorical variables were expressed as counts (percentage) compared by χ2 or Fisher exact test. The changes in BP and HR during the first session were evaluated using one-way repeated-measures analysis of variance over time and compared using two-way repeated-measures analysis of variance between the NMES and control groups. Echocardiographic parameters before and after the first session were compared by paired t-test. The primary outcome was the fulfilment of the feasibility criteria. In the haemodynamic change during the session, adverse events were also assessed as a secondary outcome.

All statistical analyses were performed using PASW Statistics 18 (SAS Institute, Cary, NC, USA), and a P value < 0.05 was considered statistically significant.

Results

Patient characteristics

The patient flow chart is depicted in Figure 1. Among 372 subjects who were admitted for AHF in Nagoya Ekisaikai Hospital, 78 were allocated. Of these, four patients in the NMES group and one patient in the control group did not receive any sessions and were excluded from the analysis; one patient in each group withdrew the informed consent; of the other three patients in the NMES group, one patient showed agitation, one patient was intubated before the first session, and another patient was misdiagnosed with HF. As a result, a total of 73 patients who finished the first session were analysed.
The baseline characteristics of the NMES (n = 34) and control (n = 39) groups are presented in Table 1. The median value of age, duration of hospitalization, and mean LVEF in all subjects were 72 years, 18 days, and 40.4%, respectively. All parameters were not significantly different between the two groups except the prevalence of patients on beta-blocker

Table 1 Patient characteristics

|                         | NMES (n = 34) | Controls (n = 39) | P value |
|-------------------------|--------------|------------------|--------|
| Age (years)             | 75 (62–80)   | 70 (63–79)       | 0.650  |
| Male, n (%)             | 25 (73.5)    | 26 (66.7)        | 0.524  |
| Body mass index (kg/m²) | 23.6 (20.4–23.8) | 23.5 (20.3–26.4) | 0.757  |
| NYHA functional class II/IV | 17/17       | 16/23            | 0.486  |
| Ischaemic aetiology of HF (%) | 12 (35.3) | 11 (28.2)        | 0.515  |
| Atrial fibrillation (%) | 16 (47.1)    | 16 (41.0)        | 0.604  |
| Prior history of HF hospitalization | 9 (26.5) | 10 (25.6)       | 0.936  |
| Medication, n (%)       |              |                  |        |
| Beta-blocker            | 18 (52.9)    | 6 (15.4)         | 0.001  |
| ACE inhibitor or ARB    | 15 (44.1)    | 11 (28.2)        | 0.157  |
| Aldosterone blocker     | 7 (20.6)     | 6 (15.8)         | 0.597  |
| Diuretic                | 9 (26.5)     | 9 (23.1)         | 0.737  |
| Laboratory data         |              |                  |        |
| Haemoglobin (g/dL)      | 12.5 ± 2.3   | 11.9 ± 2.8       | 0.361  |
| Blood urea nitrogen (mg/dL) | 18.6 (13.2–22.4) | 17.2 (11.5–24.7) | 0.969  |
| Creatinine (mg/dL)      | 0.96 (0.81–1.90) | 1.03 (0.76–1.53) | 0.317  |
| Na (mEq/L)              | 142 (140–144) | 141 (140–144)    | 0.300  |
| Albumin (g/dL)          | 3.3 (3.1–3.6) | 3.2 (2.9–3.4)    | 0.113  |
| Brain natriuretic peptide (pg/mL) | 656 (335–1370) | 473 (286–1096) | 0.177  |
| C-reactive protein (mg/dL) | 0.66 (0.33–1.84) | 1.53 (0.46–3.15) | 0.025  |
| Systolic BP (mmHg)      | 155 ± 40     | 167 ± 43         | 0.220  |
| Implantable cardioverter defibrillator (%) | 1 (2.9) | 1 (2.6) | 1.000 |
| Cardiac resynchronization therapy (%) | 2 (5.9) | 0 (0) | 0.123 |
| Pacemaker (%)           | 1 (2.9)      | 1 (2.6)          | 1.000  |
| Diastolic BP (mmHg)     | 100 ± 30     | 100 ± 27         | 0.958  |
| HR (b.p.m.)             | 109 (80–140) | 106 (86–148)     | 0.510  |
| LVEF (%)                | 37.5 ± 15.3  | 42.9 ± 20.3      | 0.205  |
| Hospitalization periods (days) | 20 (16–26) | 18 (16–22)       | 0.431  |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; NMES, neuromuscular electrical stimulation; NYHA, New York Heart Association.

Data are presented as means ± standard deviations, medians (with lower and upper quartiles), or numbers (with percentages), where appropriate.
Feasibility of NMES in acute heart failure

upon admission and C-reactive protein level. The device used by one of the patients who received cardiac resynchronization therapy in the NMES group was cardiac resynchronization therapy with defibrillation. In the first session, nine cases in each group received a 60 min session, and the remaining a 30 min session. Electrical current value of 10% and 20% MVC were 28 (24–37) mA and 48 (39–61) mA in the NMES group, and 26 (21–33) mA and 31 (25–37) mA in the control group (10% MVC, \( P = 0.214; 20\% \) MVC, \( P < 0.001 \)). Intravenous medications that may affect haemodynamics during the first session are shown in Table 2. The prevalence of each medication use was not significantly different between both groups. The number of sessions that was adjusted to intensity decrease was nine of 343 sessions in the NMES group and three of 382 sessions in the control group.

Feasibility outcomes of neuromuscular electrical stimulation

Systolic BP during the session increased >20 mmHg compared to baseline in one patient in the NMES group and three patients in the control group, and systolic BP decreased >20 mmHg in two patients in the NMES group during the first session. HR increase of >20 b.p.m. was observed in two patients in the control group during the first session. New-onset arrhythmia did not occur during all sessions in both groups. AF newly developed in one patient in each group during hospitalization. Three patients in the NMES group dropped out from the planned sessions because of cardiac surgery, cerebral infarction, and elevation of creatine kinase. Six patients in the control group dropped out because of ventricular fibrillation, elevation of creatine kinase, treatment of malignancy that was newly diagnosed during hospitalization, agitation, and refusal (two patients). Thus, the completion rate of the planned sessions until discharge was 91% in the NMES group and 84% in the control group. Above these, we concluded that the feasibility of NMES in patients with AHF was high on the basis of the criteria previously described.

### Haemodynamic change during the session

During the first session, BP and HR did not change significantly over time in both groups (Table 3). In addition, BP and HR variations were not significantly different between the two groups (systolic BP, \( P = 0.958; \) diastolic BP, \( P = 0.201; \) HR, \( P = 0.665 \)). Furthermore, there was no difference in BP and HR variations between the two groups even if limited in patients with use of vasodilators (systolic BP, \( P = 0.204; \) diastolic BP, \( P = 0.270; \) HR, \( P = 0.514 \)) or inotropes (systolic BP, \( P = 0.514; \) diastolic BP, \( P = 0.601; \) HR, \( P = 0.715 \)). In echocardiographic parameters, LVEF, LVDD, LAD, TRPG, and RAP did not exhibit significant change before and after the first session except for LVDD in the control group (Table 4).

### Adverse effects

During hospitalization due to AHF, cerebral infarction developed in two patients in the NMES group and one in the control group. Lethal ventricular arrhythmia was documented in two patients in the control group. Two patients showed worsening of HF requiring endotracheal intubation >24 h after admission, and one patient in the control group died during hospitalization. HF symptom including dyspnoea and fatigue did not change just before and after and during sessions in all cases. No patients showed electromagnetic interference during the first session. Visual analogue scale was 4 cm (1–6 cm) in the NMES group and 3 cm (1–5 cm) in the control group, and there was no significant difference between the two groups (\( P = 0.518 \)).

### Table 2 Intravenous medication during first neuromuscular electrical stimulation session

| Medication     | NMES (n = 34) | Controls (n = 39) | \( P \) value |
|----------------|---------------|------------------|---------------|
| Dobutamine     | 7 (20.6)      | 5 (12.8)         | 0.372         |
| Milrinone      | 1 (2.9)       | 0 (0)            | 0.466         |
| Nicardipine    | 1 (2.9)       | 2 (5.1)          | 0.639         |
| Diltiazem      | 5 (14.7)      | 5 (12.8)         | 0.815         |
| Landiolol      | 1 (2.9)       | 4 (10.3)         | 0.217         |
| Nicorandil     | 0 (0)         | 1 (2.6)          | 0.347         |
| Nitrate        | 9 (26.5)      | 11 (28.2)        | 0.868         |

NMES, neuromuscular electrical stimulation.

Data are presented as numbers (with percentages).

### Table 3 Cardiovascular response during first neuromuscular electrical stimulation session

|                  | Rest       | 10 min     | 20 min     | 30 min     | \( P \) value |
|------------------|------------|------------|------------|------------|---------------|
| **NMES**         |            |            |            |            |               |
| Systolic BP (mmHg)| 117.6 ± 17.1| 119.6 ± 21.6| 119.1 ± 20.5| 114.5 ± 26.6| 0.385         |
| Diastolic BP (mmHg)| 69.3 ± 9.5 | 68.4 ± 11.4 | 71.0 ± 10.8 | 70.3 ± 10.8 | 0.065         |
| HR (b.p.m.)      | 83.3 ± 20.0| 83.0 ± 20.2 | 82.0 ± 19.8 | 82.5 ± 21.2 | 0.713         |
| **Controls**     |            |            |            |            |               |
| Systolic BP (mmHg)| 118.6 ± 16.6| 120.3 ± 18.5| 120.1 ± 18.3| 117.7 ± 25.3| 0.355         |
| Diastolic BP (mmHg)| 70.4 ± 16.0| 70.5 ± 16.3 | 70.3 ± 15.6 | 69.7 ± 15.7 | 0.829         |
| HR (b.p.m.)      | 88.0 ± 17.3| 90.1 ± 23.0 | 88.2 ± 18.0 | 88.7 ± 22.2 | 0.627         |

BP, blood pressure; HR, heart rate; NMES, neuromuscular electrical stimulation.

Data are presented as means ± standard deviations.

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Table 4 Echocardiographic parameters before and after first neuromuscular electrical stimulation session

|                  | Before NMES session | After NMES session | P value |
|------------------|---------------------|--------------------|---------|
| NMES             |                     |                    |         |
| LVEF (%)         | 41.7 ± 17.3         | 43.5 ± 17.1        | 0.171   |
| LVDd (mm)        | 52.5 ± 10.0         | 52.4 ± 11.2        | 0.631   |
| LAD (mm)         | 42.2 ± 6.3          | 41.5 ± 6.6         | 0.159   |
| E/E'             | 24.9 ± 14.9         | 25.8 ± 15.6        | 0.502   |
| TRPG (mmHg)      | 27.4 ± 6.5          | 29.0 ± 9.1         | 0.108   |
| RAP (mmHg)       | 8.0 ± 3.7           | 8.0 ± 3.7          | 1.000   |
| Controls         |                     |                    |         |
| LVEF (%)         | 45.5 ± 18.6         | 44.6 ± 18.7        | 0.481   |
| LVDd (mm)        | 51.9 ± 9.6          | 53.1 ± 9.1         | 0.017   |
| LAD (mm)         | 40.5 ± 6.7          | 40.6 ± 6.4         | 0.990   |
| E/E'             | 21.2 ± 7.4          | 19.8 ± 8.5         | 0.256   |
| TRPG (mmHg)      | 26.8 ± 13.0         | 26.9 ± 13.0        | 0.964   |
| RAP (mmHg)       | 7.3 ± 4.4           | 6.8 ± 3.4          | 0.340   |

\( E/E' \): ratio of early transmitral flow velocity to early diastolic mitral annular velocity; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NMES, neuromuscular electrical stimulation; RAP, right atrial pressure; TRPG, tricuspid regurgitation pressure gradient.

Data are presented as means ± standard deviations, medians (with lower and upper quartiles).

Discussion

The findings of our study reveal that NMES is safely implemented in AHF immediately after admission. NMES has been reported to be performed safely limitedly in patients in the intensive care unit or clinically stable patients with chronic HF.\(^{10,11,14}\) The present findings demonstrated that NMES can be feasible even in patients with AHF under unstable circulatory dynamics or respiratory conditions. Our results provide evidence on the feasibility of NMES to clinically unstable patients to preserve skeletal muscle function.

Patients with AHF show various BP and HR responses that reflect haemodynamic abnormalities and are both causes and results of AHF. Therefore, BP and HR stabilization is the cornerstone in the management of patients with AHF, and it should be ensured that NMES does not affect these fluctuations. In addition, the agents for AHF treatment such as vasodilators and inotropes also dramatically change these parameters.\(^{19}\) Indeed, in this study, 29 (40%) of the patients were receiving vasodilators such as calcium channel blocker or nitrate, and 13 (18%) of the patients were on inotropic agents such as dobutamine or milrinone during the first session. The fact that BP and HR variations were not significantly different between the two groups in patients with the use of vasodilators or inotropes suggests that NMES does not interfere with BP and HR drug management in patients with AHF. In addition, the absence of a difference in visual analogue scale between the NMES and control groups indicates that pain caused by NMES has no effect on haemodynamics.\(^{20}\)

Excessive venous return is one of the major concerns for an adverse effect in applying NMES because this may cause an increase in cardiac preload, which worsens HF symptom.\(^{21}\) As elevations of RAP and TRPG were not observed in this study, there was no case with exacerbation of HF requiring intubation after admission in the NMES group. Because our NMES protocol was designed to stimulate both sides of the quadriceps and triceps in each extremity alternately, not concurrently, in order to suppress muscle fatigue, it is considered that the rise in venous return to the heart may be within the range that did not affect haemodynamics.

Although AF and ventricular tachycardia are often observed and sometimes become a life-threatening cause during AHF management,\(^{18,22}\) our result revealed that these arrhythmias were not significantly induced by NMES. NMES may not have adverse effects on autonomic nerves and haemodynamics enough to cause arrhythmia because NMES is known to improve sympathetic nerve activity in patients with AHF in addition to less influence on BP, HR, and venous return.\(^{23}\) As another mechanism that induces arrhythmias, it is also necessary to evaluate whether NMES directly stimulates the heart or interferes with the pacemakers because implantable cardioverter defibrillators and pacemakers were implanted in several patients with AHF.\(^{18}\) As in a previous report,\(^{24,25}\) electromagnetic interference was not observed in intracardiac electrocardiogram in our study, indicating that NMES can be safely used in patients with AHF wearing these devices.

This study satisfied all feasibility criteria, which we set up before the study implementation in order to evaluate whether NMES can be safely applied in patients with AHF. We believe that the clinical application of NMES to patients with AHF does not clinically cause problems in safety except for patients wearing mechanical cardiac support.

We must describe several limitations in this study. First, patients with severe HF symptom, or intubated patients, were excluded from enrolment because of inability to acquire informed consent, suggesting selection bias. However, NMES can be feasible and realized technically even using a ventilator. We speculate that the NMES can be expected to be more effective in clinically severe patients because they have difficulty acquiring early ambulation and require long-term hospitalization. Then, we focused on the feasibility of NMES in patients with AHF, not on endpoint of the skeletal muscle function, because whether NMES can be implemented safely has been a challenge to solve under unstable haemodynamics. Therefore, further study will be necessary to establish the effect on physical function and prognostic effects of NMES in patients with AHF. Nevertheless, we believe that this study provides preliminary data for conducting an intervention study to investigate the effect of skeletal muscle preservation in patients with AHF in the future.
Conclusions

The present findings demonstrate that NMES can be safely implemented in patients with AHF during the early phase of hospitalization. NMES to patients with AHF under mechanical support of haemodynamics or manifesting severe myocardial electrical instability will be the subject of the future study.

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Conflict of interest

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References

1. von Haehling S, Steinbeck L, Doehner W, Springer J, Anker SD. Muscle wasting in heart failure: An overview. Int J Biochem Cell Biol 2013; 45: 2257–2265.
2. Mancini DM, Walter G, Reichek N, Lenkinski R, McCully KK, Mullen JL, Wilson JR. Contribution of skeletal muscle to exercise intolerance and altered muscle metabolism in heart failure. Circulation 1992; 85: 1364–1373.
3. Volderrani M, Clark AL, Ludman PF, Swan JW, Adamopoulos S, Piepoli M, Coats AJ. Predictors of exercise capacity in chronic heart failure. Eur Heart J 1994; 15: 801–809.
4. Harrington D, Anker SD, Chua TP, Webb-Peploe KM, Ponikowski PP, Poole-Wilson PA, Coats AJ. Skeletal muscle function and its relation to exercise tolerance in chronic heart failure. J Am Coll Cardiol 1997; 30: 1758–1764.
5. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991; 83: 778–786.
6. Goodlin SJ. Palliative care in congestive heart failure. J Am Coll Cardiol 2009; 54: 386–396.
7. Schefold JC, Bierbrauer J, Weber-Carstens S. Intensive care unit-acquired weakness (ICUAW) and muscle wasting in critically ill patients with severe sepsis and septic shock. J Cachexia Sarcopenia Muscle 2010; 1: 147–157.
8. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, Ross A, Anderson L, Baker S, Sanchez M, Penley L, Howard A, Dixon L, Leach S, Small R, Hite RD, Haponik E. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med 2008; 36: 2238–2243.
9. Gerovasili V, Stefanidis K, Vitzilaios K, Karatzanos E, Politis P, Koroneos A, Chatzimichail A, Routsi C, Roussos C, Nanas S. Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomized study. Crit Care 2009; 13: R161.
10. Maillefert JF, Eicher JC, Walker P, Dulieu V, Rouzier-Marcet I, Brany F, Cohen M, Brunotte F, Wolf JE, Casillas JM, Didier JP. Effects of low-frequency electrical stimulation of quadriceps and calf muscles in patients with chronic heart failure. J Cardiopulm Rehabil 1998; 18: 277–282.
11. Quitan M, Sochor A, Wiesinger GF, Kollmitzer J, Sturm B, Pacher R, Mayer W. Strength improvement of knee extensor muscles in patients with chronic heart failure by neuromuscular electrical stimulation. Artif Organs 1999; 23: 432–435.
12. Sbruzzi G, Riberio RA, Schaan BD, Signori LL, Silva AM, Irigoyen MC, Plentz RD. Functional electrical stimulation in the treatment of patients with muscle weakness: a meta-analysis of randomized controlled trials. Eur J Cardiovasc Prev Rehabil 2010; 17: 254–260.
13. Smart NA, Dieberg G, Giallauria F. Functional electrical stimulation for chronic heart failure: A meta-analysis. Int J Cardiol 2015; 187: 80–86.
14. Segers J, Hermans G, Bruyninckx F, Meyfroidt G, Langer D, Gosselin R. Feasibility of neuromuscular electrical stimulation in critically ill patients. J Crit Care 2014; 29: 1082–1088.
15. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971; 285: 1441–1446.
16. Iwatsu K, Yamada S, Iida Y, Sampei H, Kobayashi K, Kainuma M, Usui A. Feasibility of neuromuscular electrical stimulation immediately after cardiovascular surgery. Arch Phys Med Rehabil 2015; 96: 63–68.
17. Rudski LG, Lai WW, Afiflalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685–713.
18. Sato N, Kajimoto K, Keida T, Mizuno M, Minami Y, Yumino D, Asai K, Murai K, Munakata R, Aokage T, Sakata Y, Mizuno K, Takano T, TEND Investigators. Clinical features and outcome in
hospitalized heart failure in Japan (from the ATTEND Registry). Circ J 2013; 77: 944–951.

19. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62: e147–e239.

20. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain 1997; 72: 95–97.

21. Kondo T, Yamada S, Asai C, Okumura T, Tanimura D, Murohara T. Skeletal muscle pump function is associated with exercise capacity in patients with heart failure. Circ J 2018; 82: 1033–1040.

22. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–2200.

23. Groehs RV, Antunes-Correa LM, Nobre TS, Alves MJ, Rondon MU, Barreto AC, Negrão CE. Muscle electrical stimulation improves neurovascular control and exercise tolerance in hospitalised advanced heart failure patients. Eur J Prev Cardiol 2016; 23: 1599–1608.

24. Kamiya K, Satoh A, Niwano S, Tanaka S, Miida K, Hamazaki N, Maekawa E, Matsuzawa R, Nozaki K, Masuda T, Ako J. Safety of neuromuscular electrical stimulation in patients implanted with cardioverter defibrillators. J Electrocardiol 2015; 49: 99–101.

25. Cenik F, Schoberwalter D, Keilani M, Maehr B, Wolzt M, Marhold M, Crevenna R. Neuromuscular electrical stimulation of the thighs in cardiac patients with implantable cardioverter defibrillators. Wien Klin Wochenschr 2016; 128: 802–808.