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ORIGINAL ARTICLE
Cardiac Rehabilitation

Efficacy of Inspiratory Muscle Training in Patients With Acute Decompensated Heart Failure

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Background: Inspiratory muscle training (IMT) is supported for outpatients with stable chronic heart failure, but its efficacy in hospitalized patients with acute decompensated heart failure (ADHF) remains unclear. The aim of the present study was to clarify IMT efficacy and safety in hospitalized ADHF patients.

Methods and Results: Patients with inspiratory muscle weakness who underwent cardiac rehabilitation (CR) were analyzed. The control group was historical control data of patients admitted to the same facility. IMT was performed at 30% maximal inspiratory mouth pressure (15 reps/set, 2 sets/day, 5 times/week) with usual CR. Associations between IMT and changes in the 2-min walking distance (2MWD) were assessed using a linear mixed model. In total, 31 and 29 patients in the IMT and control groups (median age 83 [71–88] vs. 86 [77–88] years), respectively, were analyzed. After adjustment for covariates and propensity scores, calculated on the basis of heart-failure severity, frailty, physical function, nutritional status, and inspiratory muscle strength, the 2MWD was significantly higher in the IMT group than in the control group ($F=4.697$; $P=0.035$; Δ2MWD; +31.9 vs. +16.3 m). Among 348 IMT sessions, no adverse cardiovascular events or absolute termination criteria were identified. Eleven (3.2%) IMT sessions met relative termination criteria.

Conclusions: Adding IMT to usual CR improves the 2MWD, can be safely performed in hospitalized patients with ADHF, and may represent a novel CR approach in patients with ADHF.

Key Words: Acute decompensated heart failure; Cardiac rehabilitation; Exercise tolerance; Respiratory muscle training

The incidence of inspiratory muscle weakness (IMW) is approximately 70%[1] among hospitalized patients with acute decompensated heart failure (ADHF). Inspiratory muscle strength is related to exercise tolerance, which is a prognostic factor. Accordingly, inspiratory muscle training (IMT) for IMW is an additional therapy for cardiac rehabilitation (CR) in outpatients with stable chronic heart failure (CHF).[2] IMT is effective in improving exercise tolerance, as measured using the peak maximal oxygen consumption and 6-min walking distance (6MWD), in outpatients with CHF.[3] The mechanism by which IMT improves exercise tolerance has not yet been fully elucidated; however, it may correct ventilation-perfusion mismatch by improving the endurance of respiratory muscles,[4] and it may reduce lower-limb fatigue during exercise by attenuating the metabolic reflex of respiratory muscles.[5] Regarding the safety of IMT, Ramos et al.[6] revealed that low-intensity IMT did not induce serious hemodynamic changes or relevant clinical abnormalities in an older population, including outpatients with myocardial infarction and/or CHF in stable condition. Thus, accumulating evidence supports IMT for outpatients with stable CHF. In contrast, evidence regarding the efficacy and safety of IMT in hospitalized patients with ADHF is lacking[2] despite the high incidence of IMW.[1]

Knowledge of the efficacy and safety of IMT in hospitalized patients with ADHF is essential for the implementation of specific CR interventions to improve and accelerate recovery. Therefore, the present study aimed to clarify the efficacy and safety of IMT in hospitalized patients with ADHF. Based on the findings of previous studies, we hypothesized that IMT could be safely and effectively performed in hospitalized patients with ADHF if the clinical conditions and risks are appropriately controlled.

Methods

Study Design and Participants

This single-center, prospective, observational study was

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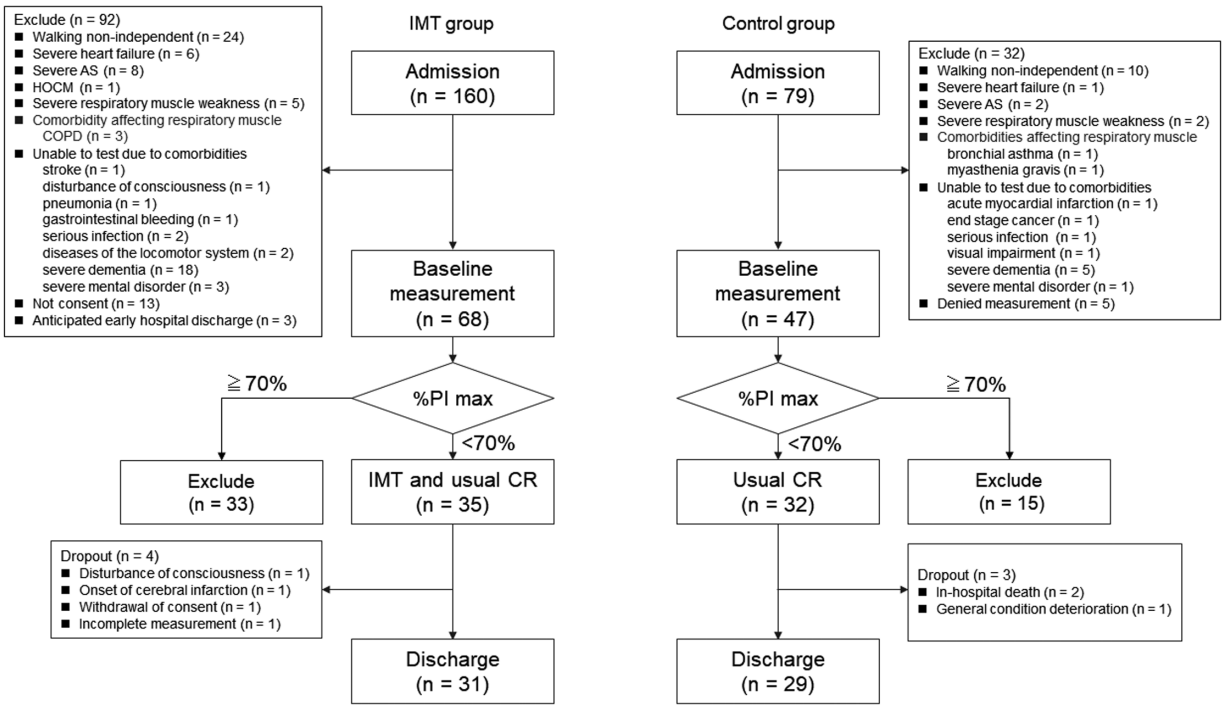

Figure 1. Flowchart of patient selection in the present study. AS, aortic stenosis; COPD, chronic obstructive pulmonary disease; CR, cardiac rehabilitation; HOCM, hypertrophic obstructive cardiomyopathy; IMT, inspiratory muscle training; PI_{max}, maximal inspiratory mouth pressure.

designed to determine the feasibility, efficacy, and safety of implementing an IMT program for patients with ADHF. During the study period, eligible patients who were admitted from April 2023 to February 2024 were assigned to the IMT group using the usual CR program with the addition of IMT, and those who were admitted from November 2022 to March 2023 were allocated to the control group receiving only the usual CR. The present study was conducted in accordance with the Declaration of Helsinki (2013 revised version) and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects (2022 revised version). The study protocol was approved by the Ethics Committee of Sendai Medical Center (Approval no. 23-103) and the Ethics Committee of Hirosaki University Graduate School of Medicine (Approval no. T2023-028). Verbal and written informed consent was obtained from all participants in the intervention group. The research protocol was published on National Hospital Organization Sendai Medical Center website (https://nsmc.hosp.go.jp/Idea/rinri/jinsoku23-103.pdf); thus, each ethics committee waived the need for informed consent from patients in the control group. Patients in the control group could refuse to participate and withdraw at any time via the institution's website. If patients in the control group or their families refused to participate, then they were excluded from the study.

The study flowchart is presented in **Figure 1**. First, after CR was prescribed by a physician, patients were selected according to the inclusion and exclusion criteria, and baseline inspiratory muscle strength and outcomes were measured prior to CR commencement. Subsequently, patients with IMW who underwent IMT in addition to usual CR were enrolled in the present study. Outcomes were measured at discharge.

The inclusion criteria were as follows: (1) patients with a diagnosis of ADHF based on the Japanese Circulation Society (JCS) guidelines[7] who were admitted to the acute care hospital of Sendai Medical Center between November 2022 and February 2024; (2) those prescribed CR by a physician; and (3) those deemed to have IMW. The exclusion criteria were as follows: (1) inability to walk independently before admission; (2) severe heart failure requiring intensive care, including circulatory support, ventilator use, non-invasive positive-pressure ventilation, hemodialysis, and intra-aortic balloon pumping; (3) severe aortic valve stenosis; (4) obstructive hypertrophic cardiomyopathy; (5) poorly controlled arrhythmia causing hemodynamic abnormalities; (6) inability to measure inspiratory muscle strength because of severe respiratory muscle weakness or the presence of a respiratory or neuromuscular disease that could affect respiratory muscle strength (e.g., chronic obstructive pulmonary disease [COPD] and myasthenia gravis); (7) impairment due to stroke, injury, or other medical conditions that could preclude participation in the measurement; (8) no consent; and (9) anticipated hospital discharge prior to the completion of baseline study measurements.

Evaluation of Respiratory Muscle Strength

Muscle strength was measured using a spirometer (Autospiro AS-507, Minato Medical Science, Osaka, Japan) and pressure transducer (Autospiro AAM-377, Minato Medical Science, Osaka, Japan). Maximal inspiratory mouth pressure (PI_{max}) and maximal expiratory mouth pressure (PE_{max}),

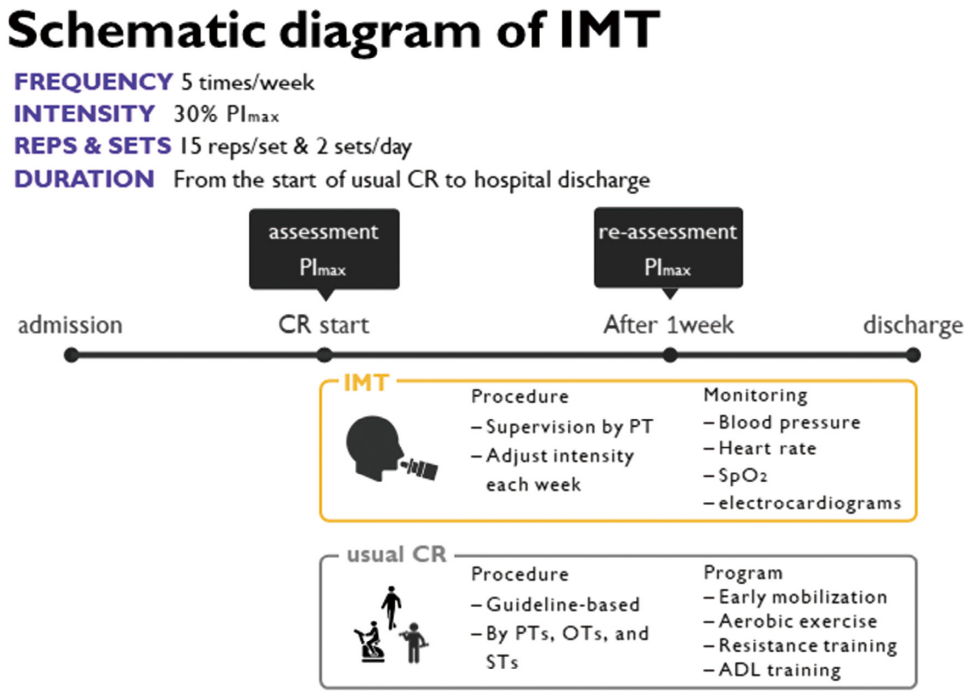

Figure 2. Schematic diagram of IMT. ADL, activities of daily living; CR, cardiac rehabilitation; IMT, inspiratory muscle training; OT, occupational therapist; PI_{max}, maximal inspiratory mouth pressure; PT, physiotherapist; ST, speech-language-hearing therapists; SpO_2, percutaneous arterial oxygen saturation.

which are indicators of inspiratory and expiratory muscle strength, respectively, were assessed. Measurements were performed according to the American Thoracic Society (ATS)/European Respiratory Society statement.[8] Subsequently, the percentages of PI_{max} (%PI_{max}) and PE_{max} (%PE_{max}) were calculated based on the values estimated using age, sex, height, and weight.[9] IMW was defined as %PI_{max} <70%.[10]

IMT

A schematic diagram of IMT is shown in **Figure 2**. IMT was performed using Threshold IMT (Philips Respironics, Inc., Murrysville, PA, USA); it was initiated at the same time as CR and was performed at 30% PI_{max} (15 reps/set, 2 sets/day, 5 times/week) in accordance with previous studies.[3,6] A 1-min break was provided between the sets. The IMT intensity was adjusted weekly and continued until discharge. The participants were instructed as follows: (1) tightly cover the mouthpiece with their lips; (2) do not remove the mouthpiece from their mouths; and (3) inhale as forcefully as possible. IMT was performed under the supervision of a physiotherapist; additionally, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), percutaneous arterial oxygen saturation (SpO_2), and electrocardiograms were monitored to ensure safety.

Usual CR

All participants from both the IMT and control groups received comprehensive multidisciplinary CR intervention, from physicians, nurses, physiotherapists, occupational therapists, speech-language therapists, pharmacists, and social workers, as needed. Patients in the IMT and control groups underwent acute and early convalescent CR during hospitalization. CR was initiated when the patients' hemodynamics became stable and the attending physician deemed it was possible. CR was performed according to the JCS/Japanese Association of Cardiac Rehabilitation guidelines.[11] Early bed mobilization (getting out of bed, sitting, standing, and walking) was performed during the acute phase, whereas exercise therapy (low-intensity resistance training, aerobic exercise, and activity of daily living [ADL] exercises) was performed during the early recovery phase. Exercise therapy was performed under the supervision of a physical therapist. Exercises were prescribed during the acute and early recovery phases based on the JCS/Japanese Association of Cardiac Rehabilitation guidelines[11] and were tailored to individual goals.

Primary and Secondary Endpoints

The primary endpoint was the effectiveness of IMT, as assessed using the 2-min walking distance (2MWD), which was measured using the 2-min walking test (2MWT). The 2MWT can be performed easily, quickly, and with low risk even in acute patients, and test-retest, inter-reliability, and intrareliability of the 2MWT have been reported in frail, older adults living in long-term care[12] and patients with moderate-to-severe COPD.[13] The baseline 2MWT was performed within 2 days, including the date of CR initiation, and the 2MWT at discharge was performed within 2 days before the date of discharge after confirming the absence of any absolute or relative termination criteria in the JCS/Japanese Association of Cardiac Rehabilitation guidelines.[11] The 2MWT, which was conducted with modifications of the ATS guidelines[14] for the 6-min walking test

(6MWT), was performed over a 30-m out-and-back course. The participants were instructed to walk as fast as possible until they were asked to stop; they stopped walking after 2 min, and the distance covered was then recorded. The instructions were provided to patients according to the ATS guidelines.[14] The 2MWD was evaluated by a physiotherapist.

Dyspnea and leg fatigue were assessed using the visual analog scale (VAS) before and after the 2MWT.[15] The VAS is a 100-mm long straight line; the left end indicates no feeling of lower-limb fatigue or dyspnea (0 mm), whereas the right end denotes the maximum possible feeling of lower-limb fatigue or dyspnea (100 mm). Before and after the 2MWT, participants were instructed to linearly and subjectively assess for lower-limb fatigue and dyspnea, which were quantified by measuring the length (mm) from the left end of the VAS.

The secondary endpoint was the safety of IMT, which was defined as: (1) the presence of cardiovascular adverse events;[16] and (2) the appearance of absolute or relative termination criteria during exercise,[11] as well as findings suggestive of excessive exercise[17] based on the Japanese guidelines (**Supplementary Table 1**).

Data Extraction

The following data were collected from electronic medical records: (1) basic characteristics (age, sex, height, weight, body mass index, etiology of heart failure, comorbidities, and medications taken at the time of CR commencement); (2) clinical and laboratory findings at admission (New York Heart Association [NYHA] classification, clinical scenario, Nohria-Stevenson classification, left ventricular ejection fraction, and blood chemistry data [N-terminal pro-B-type natriuretic peptide [NT-proBNP] levels and NYHA classification stage were also collected at the time of discharge]); (3) Mini-Mental State Examination (MMSE)[18] and Controlling Nutritional Status (CONUT)[19] scores as indices of cognitive function and nutritional status, respectively; (4) physical frailty and sarcopenia, as evaluated using the revised Japanese version of the Cardiovascular Health Study criteria[20] and 2019 Asian Working Group for Sarcopenia criteria[21] (in the present study, the amount of skeletal muscles was measured through bioelectrical impedance analysis); and (5) CR status and length of hospital stay.

Measurement of Other Clinical Data

ADL was evaluated using the Barthel index,[22] with scores ranging from 0 (fully dependent) to 100 (fully independent). Quality of life was assessed using the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L),[23] which consists of 5-dimension questions regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the EQ-5D-5L, the health condition for each item is selected from 5 levels, and the EQ-5D-5L scores range from −0.0246 to 0.9384, with higher values indicating higher quality of life. Physical function was evaluated using the Short Physical Performance Battery (SPPB),[24] gait speed, and handgrip strength.[21] These measurements were performed by a physiotherapist and/or occupational therapist.

Sample Size Calculation

The sample size was calculated using G*Power (version 3.1.9.7; Heinrich Heine University, Düsseldorf, Germany). The G*Power settings were as follows: an F-test (repeated-measures between-factors analysis of variance) was performed, with an effect size (f) of 0.4 [large], α error of 0.05, power of 0.8, group and measurement number of 2, and repeated measures correlation of 0.5. The required sample size was determined to be 20 patients in each group. An effect size (f) of 0.4 meant η^2=0.14. Furthermore, when the effect size (f) was set to 0.25 (medium)[25] and the other settings were unchanged, the required sample size was 49 participants per group. However, as previous studies have not examined the effect size of IMT in patients with acute heart failure, the required sample sizes for each group were therefore determined to be ≥20 and ≤49 on the basis of the aforementioned calculations.

Statistical Analyses

Continuous variables are expressed as means±SD or medians (interquartile ranges), whereas qualitative variables are expressed as the number of participants (%). Baseline and clinical data were compared between the 2 groups using the unpaired Student t-test, Mann-Whitney U test, chi-squared test, and Fisher exact test. Clinical data at admission and discharge were compared using the paired Student t-test and Wilcoxon signed-rank test. Additionally, effect size (r) was used for within-group and between-group comparisons of clinical data, including the 2MWD. The effect size (r) was considered small, medium, and large at values of 0.10, 0.30, and 0.50,[25] respectively.

To analyze IMT safety, changes in blood pressure, HR, and SpO_2 were compared before and after IMT implementation using the Shaffer multiple comparison test. Descriptive statistics were also calculated for the number of serious cardiovascular events, hemodynamic changes during exercise, and exacerbation of heart failure due to IMT.

To analyze the effectiveness of IMT, a linear mixed model was used to test for group×time interactions to determine whether changes in the 2MWD over time differed between the groups. The model included terms for the group (control and IMT) and time (start of CR [baseline] and hospital discharge [discharge]). Propensity scores were used to adjust for covariates in the linear mixed model because the sample size was not necessary to adjust for all covariates. From a clinical perspective, we adjusted for age, sex, height, weight, smoking history, NYHA classification, left ventricular ejection fraction, ΔNT-proBNP (calculated by subtracting NT-proBNP at baseline from NT-proBNP at discharge), hemoglobin level, CONUT score, physical frailty, PI_{max}, SPPB score, and gait speed at baseline. Additionally, as a post-hoc test, the effect size of the main effect and interaction was calculated. However, to date, no effect size calculations or standard values were reported for the linear mixed model. Hence, the present study used the effect size (η^2), which was calculated from the sum of squares by the split-plot analysis of variance. It was considered small, medium, and large at values of 0.01, 0.06, and 0.14,[25] respectively. All analyses were performed using R (version 4.3.0, CRAN), with statistical significance set at a two-tailed P value of <0.05.

Results

Research Participants

A total of 31 and 29 participants in the IMT and control groups, respectively, was analyzed (**Figure 1**). The baseline characteristics of the study participants are presented in **Table 1**.

Table 1. Baseline Characteristics

	Overall (n=60)	IMT (n=31)	Control (n=29)	P value
Basic characteristics				
Age (years)	85.0 [73.8–88.0]	83.0 [71.0–87.5]	86.0 [77.0–88.0]	0.283
Sex (male)	28 (46.7)	13 (41.9)	15 (51.7)	0.448
Height (cm)	154.9±10.2	155.1±10.8	154.6±9.6	0.848†
Weight (kg)	55.7 [47.9–62.2]	57.8 [49.7–65.0]	52.2 [44.5–61.2]	0.186
BMI (kg/m^2)	23.5±4.4	24.2±4.4	22.8±4.3	0.233†
Smoking history				0.204‡
None	43 (71.7)	20 (64.5)	23 (79.3)	
Past	13 (21.7)	9 (29.0)	4 (13.8)	
Current	4 (6.7)	2 (6.5)	2 (6.9)	
Heart failure etiology				
IHD	15 (25.0)	9 (29.0)	6 (20.7)	0.456
Cardiomyopathy	6 (10.0)	3 (9.7)	3 (10.3)	1.000‡
VHD	9 (15.0)	3 (9.7)	6 (20.7)	0.292‡
HHD	8 (13.3)	4 (12.9)	4 (13.8)	1.000‡
CHD	1 (1.7)	0 (0.0)	1 (3.4)	0.483‡
Arrythmia	19 (31.7)	10 (32.3)	9 (31.0)	0.919
Comorbidity				
Diabetes	20 (33.3)	15 (48.4)	5 (17.2)	0.011
Stroke	19 (31.7)	11 (35.5)	8 (27.6)	0.511
Dementia	3 (5.0)	2 (6.5)	1 (3.4)	1.000‡
CKD	13 (21.7)	7 (22.6)	6 (20.7)	0.859
Medication				
ACEi	3 (5.0)	1 (3.2)	2 (6.9)	0.606‡
ARB	13 (21.7)	7 (22.6)	6 (20.7)	0.859
ARNI	15 (25.0)	11 (35.5)	4 (13.8)	0.053
β-blocker	26 (43.3)	15 (48.4)	11 (37.9)	0.414
MRA	14 (23.3)	9 (29.0)	5 (17.2)	0.281
SGLT2i	22 (36.7)	11 (35.5)	11 (37.9)	0.844
Nitrate	10 (16.7)	3 (9.7)	7 (24.1)	0.175‡
Diuretics	59 (98.3)	31 (100.0)	28 (96.6)	0.483‡
Positive intravenous inotropic drug	9 (15.0)	3 (9.7)	6 (20.7)	0.292‡
Clinical and laboratory findings				
NYHA III, IV				
At start of CR	53 (88.3)	29 (93.5)	24 (82.8)	0.247‡
At discharge	4 (6.7)	2 (6.5)	2 (6.9)	1.000‡
Clinical scenario				0.685‡
1	34 (56.7)	18 (58.1)	16 (55.2)	
2	21 (35.0)	10 (32.3)	11 (37.9)	
3	4 (6.7)	3 (9.7)	1 (3.4)	
4	0 (0.0)	0 (0.0)	0 (0.0)	
5	1 (1.7)	0 (0.0)	1 (3.4)	
Nohria-Stevenson classification				0.622‡
Warm and wet	41 (68.3)	21 (67.7)	20 (69.0)	
Cold and wet	17 (28.3)	8 (25.6)	9 (31.0)	
Cold and dry	2 (3.3)	2 (6.5)	0 (0.0)	
LVEF (%)	49.6±21.3	48.7±20.9	50.6±22.0	0.746†
HFpEF	31 (51.7)	14 (45.2)	17 (58.6)	0.505‡
HFmrEF	7 (11.7)	5 (16.1)	2 (6.9)	
HFrEF	22 (36.7)	12 (38.7)	10 (34.5)	

(**Table 1** continued the next page.)

	Overall (n=60)	IMT (n=31)	Control (n=29)	P value
Clinical and laboratory findings				
NT-proBNP (pg/dL)				
At start of CR	4,717.5 [1,943.8–7,744.0]	4,236.0 [1,886.5–7,016.0]	4,799.0 [3,004.0–7,906.0]	0.528
At discharge	1,371.5 [710.0–2,483.5]	1,267.0 [569.5–2,526.0]	1,507.0 [914.0–2,032.0]	0.547
Amount of change	−3,450.0±3,753.8	−2,774.9±2,792.0	−4,268.8±4,488.4	0.310
Hemoglobin (mg/dL)	12.1±2.9	11.9±2.2	12.5±3.4	0.420†
eGFR (mL/min/1.73 m^2)	44.7 [31.2–55.2]	46.4 [31.2–58.2]	44.1 [31.3–52.4]	0.716
Creatinine (mg/dL)	1.1 [0.8–1.4]	1.0 [0.8–1.4]	1.2 [0.8–1.6]	0.429
CRP (mg/dL)	0.3 [0.1–1.0]	0.2 [0.1–1.1]	0.3 [0.2–0.6]	0.814
CIED				0.070‡
Nothing	50 (83.3)	23 (74.2)	27 (93.1)	
ICD	1 (1.7)	0 (0.0)	1 (3.4)	
Pacemaker	6 (10.0)	5 (16.1)	1 (3.4)	
CRT-D	2 (3.3)	2 (6.5)	0 (0.0)	
CRT-P	1 (1.7)	1 (3.2)	0 (0.0)	
Physical frailty	44 (73.3)	22 (71.0)	22 (75.9)	0.668
Sarcopenia*	27 (54.0)	10 (43.5)	17 (63.0)	0.168
Low muscle quantity	28 (56.0)	10 (43.5)	18 (66.7)	0.100
SMI (kg/m^2)	6.1 [5.4–7.3]	6.5 [5.5–7.4]	5.9 [5.2–6.9]	0.329
Low muscle strength	40 (80.0)	18 (78.3)	22 (81.5)	1.000‡
Handgrip strength (kg)	17.0 [14.0–21.9]	16.6 [13.9–20.9]	17.9 [14.8–23.8]	0.465
Low physical performance	45 (90.0)	20 (87.0)	25 (92.6)	0.651‡
SPPB (score)	6.9±3.5	7.2±3.3	6.5±3.6	0.475†
Gait speed (m/s)	0.6±0.3	0.6±0.2	0.6±0.3	0.837†
5-times chair stand (s)§	11.9 [9.3–15.3]	9.8 [8.6–13.2]	12.9 [11.1–15.8]	0.115
Cognitive function				
MMSE (score)	26.0 [22.0–28.3]	26.0 [24.5–28.5]	24.0 [21.0–28.0]	0.105
Nutritional status				
CONUT (score)	3.0 [1.0–5.0]	3.0 [1.0–4.0]	3.0 [2.0–5.0]	0.483
Length of hospital stay (days)	17.5 [14.0–24.0]	18.0 [14.0–24.0]	17.0 [14.0–24.0]	0.950
Usual cardiac rehabilitation				
Commencement (days)	2.5 [2.0–4.0]	2.0 [2.0–4.0]	3.0 [2.0–5.0]	0.293
No. sessions (times)	11.5 [8.8–15.0]	12.0 [9.0–17.0]	11.0 [8.0–15.0]	0.619
Total time during hospitalization (min)	890.0 [695.5–1,145.0]	920.0 [700.0–1,200.0]	840.0 [700.0–1,060.0]	0.391
Physical therapy intervention	60 (100.0)	31 (100.0)	29 (100.0)	1.000
Total time (min)	680.0 [555.0–875.0]	700.0 [540.0–940.0]	660.0 [580.0–840.0]	0.604
Occupational therapy intervention	59 (98.3)	31 (100.0)	28 (96.6)	0.483‡
Total intervention time‖ (min)	160.0 [140.0–220.0]	160.0 [140.0–230.0]	170.0 [140.0–220.0]	0.889
Swallowing therapy intervention	3 (5.0)	3 (9.7)	0 (0.0)	0.238‡
Total intervention time‖ (min)	240.0 [165.0–240.0]	240.0 [165.0–240.0]	–	–
IMT				
Commencement (days)	–	4.0 [3.0–5.5]	–	
No. sessions (times)	–	9.0 [5.5–11.5]	–	
IMT intensity (cmH_2O)				
At start	–	8.4 [7.0–10.7]	–	
At discharge	–	11.0 [8.1–14.4]	–	

Data are presented as average±SD, median [interquartile range], or n (%). *Sarcopenia could not be determined in 8 patients in the IMT group and 2 patients in the control group because of contraindications to bioelectrical impedance analysis measurement due to CIEDs. †Unpaired t-test. ‡Fisher's exact test. §20 patients (12 patients in the IMT group and 8 patients in the control group) were excluded due to the inability to stand independently. ‖Calculations based on patients who underwent intervention. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CIED, cardiovascular implantable electronic device; CHD, congenital heart disease; CKD, chronic kidney disease; CONUT, controlling nutritional status; CR, cardiac rehabilitation; CRP, C-reactive protein; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHD, hypertensive heart disease; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; IMT, inspiratory muscle training; LVEF, left ventricular ejection fraction; MMSE, mini-mental state examination; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SMI, skeletal muscle mass index; SPPB, short physical performance battery; VHD, valvular heart disease.

Table 2. Clinical Data at Baseline and Hospital Discharge in the IMT and Control Groups

	IMT (n=31)					Control (n=29)					Baseline comparison (IMT vs. control)	
	Baseline	Discharge	Change	P value*	ES (r)*	Baseline	Discharge	Change	P value*	ES (r)*	P value	ES (r)
2MWD (m)	72.5±31.6	104.2±36.7	+31.7±23.2	<0.001	0.812	76.2±41.6	92.5±41.3	+16.3±25.1	0.002	0.509	0.696	0.051
Dyspnea (mm)†	+25.1±28.2	+22.1±27.3	−3.0±38.4	0.817‡	0.043	+24.7±23.6	+21.2±33.2	−3.5±31.1	0.212‡	0.235	0.699‡	0.050
Lower-limb fatigue (mm)†	+26.9±24.0	+15.3±21.5	−11.6±26.2	0.020	0.411	+20.8±23.1	+25.4±29.8	+4.7±24.9	0.321‡	0.187	0.255‡	0.147
PI_{max} (cmH_2O)	29.1±10.4	41.1±15.1	+12.0±12.5	<0.001	0.699	26.4±10.2	31.6±17.5	+5.1±12.6	0.037	0.383	0.320	0.305
%PI_{max} (%)	53.3±9.2	81.0±31.2	+27.7±29.9	<0.001‡	0.781	49.1±11.9	60.9±28.8	+11.8±26.1	0.025‡	0.412	0.183‡	0.172
PE_{max} (cmH_2O)	48.2±14.3	54.5±22.0	+6.3±15.0	0.055†	0.345	41.7±14.2	43.4±13.2	+1.7±10.5	0.400	0.159	0.085	0.224
%PE_{max} (%)	63.2±17.1	76.1±25.6	+13.0±21.0	0.002	0.532	54.5±16.4	60.3±21.1	+5.9±16.6	0.069	0.337	0.050	0.255
BI (score)	63.5±25.5	96.5±6.5	+32.9±23.4	<0.001‡	0.801	62.4±24.9	92.8±11.5	+30.3±22.6	<0.001‡	0.796	0.862	0.023
EQ-5D-5L (score)	0.611±0.241	0.786±0.178	+0.175±0.230	<0.001‡	0.644	0.650±0.254	0.800±0.147	+0.150±0.186	<0.001‡	0.679	0.496‡	0.088
SPPB (score)	7.2±3.3	8.7±2.9	+1.5±2.1	<0.001‡	0.617	6.5±3.6	8.4±3.4	+1.9±1.4	<0.001‡	0.763	0.475	0.094
Gait speed (m/s)	0.6±0.2	0.8±0.2	+0.2±0.2	<0.001	0.661	0.6±0.3	0.8±0.3	+0.1±0.2	0.006	0.494	0.837	0.027
Hand grip strength (kg)	18.3±6.8	18.8±7.7	+0.5±2.7	0.230‡	0.218	19.3±6.5	19.2±7.8	−0.2±3.0	0.775	0.055	0.465‡	0.095

Data are presented as average±SD. *vs. baseline. †Calculated by subtracting the VAS before the 2MWT from the VAS after the 2MWT. ‡Wilcoxon signed-rank test or Mann-Whitney U test. BI, Barthel index; EQ-5D-5L, EuroQol 5-dimensional 5-level; ES, effect size; IMT, inspiratory muscle training; PE_{max}, maximum expiratory mouth pressure; PI_{max}, maximum inspiratory mouth pressure; SPPB, short physical performance battery; VAS, visual analog scale; 2MWD, 2-min walk distance.

Efficacy of IMT

The comparison of baseline clinical data indicated that none of the variables was significantly different between the groups, with a small effect size (r). The 2MWD, gait speed, PI_{max}, %PI_{max}, Barthel index score, EQ-5D-5L score, and SPPB score significantly improved; in contrast, no significant improvement in dyspnea was observed after the 2MWT and handgrip strength measurements in both groups. Lower-limb fatigue after the 2MWT measurement and %PE_{max} significantly improved only in the IMT group (**Table 2**).

The comparison of effect size (r) before and after the intervention revealed that the 2MWD, lower-limb fatigue after 2MWT measurement, gait speed, PI_{max}, %PI_{max}, PE_{max}, and %PE_{max} in the IMT group were greater than those in the control group.

The linear mixed model findings are presented in **Table 3**. The crude model showed that changes in the 2MWD over time differed between the groups: the 2MWD increased significantly in the IMT group compared with that in the control group (F=6.119; P=0.016). In the adjusted model, in addition to age, sex, ΔNT-proBNP, and the propensity scores calculated using the prediction model consisting of height, weight, smoking history, NYHA classification, left ventricular ejection fraction, hemoglobin level, CONUT score, physical frailty, PI_{max}, SPPB score, and gait speed at baseline were adjusted. The propensity score C-statistics for adjusted models 1 and 2 were 0.750 (95% confidence interval 0.626–0.873) and 0.759 (0.638–0.800), respectively. The adjusted model 2 revealed that the 2MWD increased significantly in the IMT group compared with that in the control group (adjusted model 2: F=4.697; P=0.035; **Table 3**). Changes in the 2MWD (Δ2MWD; calculated by subtracting the 2MWD at baseline from the 2MWD at hospital discharge) were +31.9 and +16.3 in the IMT and control groups, respectively.

Table 4 shows the effect size (η^2) determined from the sum of squares calculated by the split-plot analysis of variance. Effect size (η^2) indicated that the changes in the 2MWD, PI_{max}, and %PI_{max} were medium, whereas the changes in lower-limb fatigue after the 2MWT measurement were large.

Table 3. Intergroup Comparisons Between the IMT and Non-IMT Groups at Baseline and Hospital Discharge: Linear Mixed Model Analysis

	Crude model				Adjusted model 1*	
	Amount of change (95% CI)		Interaction Group×Time		Amount of change (95% CI)	
	IMT (n=31)	Control (n=29)	F	P value	IMT (n=31)	Control (n=29)
2MWD (m)	+31.7 (23.1, 40.4)	+16.3 (7.3, 25.3)	6.119	0.016	+31.7 (22.3, 41.0)	+16.5 (6.9, 26.2)
Dyspnea (mm)	−3.0 (−15.6, 9.6)	−3.5 (−16.5, 9.5)	0.003	0.958	−3.6 (−17.4, 10.1)	−2.4 (−16.5, 11.8)
Lower-limb fatigue (mm)	−11.6 (−20.8, −2.4)	+4.7 (−4.9, 14.2)	6.066	0.017	−8.7 (−18.3, 1.1)	+2.6 (−7.4, 12.6)
BI (score)	+32.9 (24.6, 41.2)	+30.3 (21.8, 38.9)	0.185	0.669	+32.1 (23.3, 40.8)	+31.4 (22.4, 40.4)
EQ-5D-5L (score)	+0.18 (0.10, 0.25)	+0.15 (0.07, 0.23)	0.209	0.649	+0.16 (0.07, 0.24)	+0.17 (0.09, 0.26)
PI_{max} (cmH_2O)	+12.0 (7.5, 16.5)	+5.1 (0.5, 9.8)	4.525	0.038	+12.8 (7.8, 17.7)	+4.3 (−0.9, 9.4)
%PI_{max} (%)	+27.7 (17.5, 37.8)	+11.8 (1.3, 22.3)	4.759	0.033	+29.3 (18.5, 40.1)	+9.6 (−1.6, 20.7)
PE_{max} (cmH_2O)	+6.3 (1.6, 11.0)	+1.7 (−3.2, 6.5)	1.896	0.174	+7.2 (2.0, 12.4)	+0.7 (−4.6, 6.1)
%PE_{max} (%)	+13.0 (6.1, 19.8)	+5.9 (−1.2, 12.9)	2.099	0.153	+14.4 (6.8, 21.9)	+4.3 (−3.5, 12.1)
SPPB (score)	+1.6 (0.9, 2.2)	+1.9 (1.2, 2.5)	0.467	0.497	+1.4 (0.7, 2.2)	+2.0 (1.2, 2.7)
Gait speed (m/s)	+0.2 (0.1, 0.3)	+0.1 (0.1, 0.2)	1.332	0.253	+0.2 (0.1, 0.3)	+0.1 (0.0, 0.2)
Hand grip strength (kg)	+0.5 (−0.5, 1.5)	−0.2 (−1.2, 0.9)	0.840	0.363	+0.4 (−0.7, 1.5)	+0.1 (−1.1, 1.1)

	Adjusted model 1*		Adjusted model 2†			
	Interaction Group×Time		Amount of change (95% CI)		Interaction Group×Time	
	F	P value	IMT (n=31)	Control (n=29)	F	P value
2MWD (m)	4.505	0.038	+31.9 (22.5, 41.2)	+16.3 (6.7, 26.0)	4.697	0.035
Dyspnea (mm)	0.015	0.904	−4.0 (−17.7, 9.8)	−2.0 (−16.2, 12.2)	0.034	0.855
Lower-limb fatigue (mm)	2.289	0.136	−8.3 (−18.0, 1.4)	+2.2 (−12.2, 7.8)	2.021	0.161
BI (score)	0.010	0.921	+32.2 (23.4, 40.9)	+31.3 (22.2, 40.3)	0.018	0.895
EQ-5D-5L (score)	0.056	0.814	+0.15 (0.07, 0.24)	+0.17 (0.09, 0.26)	0.086	0.771
PI_{max} (cmH_2O)	5.075	0.028	–	–	–	–
%PI_{max} (%)	5.706	0.020	–	–	–	–
PE_{max} (cmH_2O)	2.624	0.111	–	–	–	–
%PE_{max} (%)	3.055	0.086	–	–	–	–
SPPB (score)	0.917	0.342	–	–	–	–
Gait speed (m/s)	0.438	0.511	–	–	–	–
Hand grip strength (kg)	0.221	0.640	–	–	–	–

*Adjusted for age, sex, ΔNT-proBNP, and PS-1. †Adjusted for age, sex, ΔNT-proBNP, and PS-2. PS-1: calculated by height, weight, smoking history, NYHA functional class, EF, hemoglobin, CONUT, physical frailty, and PI_{max} at baseline (c-statistic 0.750; 95% CI 0.626–0.873). PS-2: calculated using PS-1 variables, SPPB, and gait speed at baseline (c-statistic 0.759; 95% CI 0.638–0.800). CI, confidence interval; PS, propensity score. Other abbreviations and missing data as described in Table 2.

Table 4. Effect Size (η^2) of Comparison Group, Time, and Interaction*

	Group			Time			Interaction		
	F	P value	η^2	F	P value	η^2	F	P value	η^2
2MWD (m)	0.185	0.669	0.024	59.332	<0.001	0.884	6.119	0.016	0.091
Dyspnea (mm)	0.014	0.906	0.041	0.523	0.472	0.953	0.003	0.958	0.005
Lower-limb fatigue (mm)	0.137	0.713	0.050	1.108	0.297	0.147	6.066	0.017	0.804
BI (score)	0.383	0.539	0.006	113.108	<0.001	0.993	0.185	0.669	0.002
EQ-5D-5L (score)	0.317	0.576	0.026	35.892	<0.001	0.969	0.209	0.649	0.006
PI_{max} (cmH_2O)	3.803	0.056	0.305	27.971	<0.001	0.598	4.525	0.038	0.097
%PI_{max} (%)	7.164	0.010	0.247	29.454	<0.001	0.648	4.759	0.033	0.105
PE_{max} (cmH_2O)	5.108	0.028	0.783	5.607	0.021	0.162	1.896	0.174	0.055
%PE_{max} (%)	6.869	0.011	0.597	14.698	<0.001	0.353	2.099	0.153	0.050
SPPB (score)	0.349	0.557	0.075	55.197	<0.001	0.917	0.467	0.497	0.008
Gait speed (m/s)	0.092	0.762	0.013	30.392	<0.001	0.946	1.332	0.253	0.041
Hand grip strength (kg)	0.138	0.712	0.762	0.227	0.636	0.051	0.840	0.363	0.187

*Effect size was calculated from the sum of squares calculated by split-plot analysis of variance excluding 7 patients (4 in the IMT group and 3 in the control group) who dropped out during the follow-up period. Abbreviations as described in Table 2.

Table 5. Safety of Inspiratory Muscle Training: Incidence of the Event

	No. sessions	Incidence
Cardiovascular adverse event	348	0 (0.0)
Absolute termination criteria	348	0 (0.0)
Relative termination criteria	348	11 (3.2)
Worsening of perceived chest or other symptoms	348	0 (0.0)
SpO_2 <90% or 5% decrease at rest		
Overall	348	3 (0.9)
Oxygen therapy (–)	271	3 (1.1)
Oxygen therapy (+)	77	0 (0.0)
New arrhythmia or ST-segment depression	0	0 (0.0)
Blood pressure decreased or increased		
SBP <80 mmHg	348	8 (2.3)
SBP ≥250 mmHg	348	0 (0.0)
DBP ≥115 mmHg	348	0 (0.0)
Appearance of bradycardia ≤40/min*	251	0 (0.0)
Difficulty continuing exercise training	348	0 (0.0)
If patient received a positive intravenous inotropic drug†	21	
HR <50 beats/min or >130 beats/min‡	4	0 (0.0)
HR increased >30 beats/min at rest‡	4	0 (0.0)
SBP <70 mmHg	21	0 (0.0)
SBP decreased >20 mmHg	21	0 (0.0)
Symptoms of excessive exercise loading		
Borg scale >13	348	27 (7.8)
HR increase 30 beats/min from rest (if using β-blocker: >20 beats/min)	348	9 (4.6)

Data are presented as n (%). *97 sessions performed in patients with CIEDs implants were excluded. †21 sessions performed in patients receiving positive intravenous inotropic drug. ‡17 sessions performed on a patient whose HR was completely dependent on her CIEDs were excluded. CIEDs, cardiovascular implantable electronic devices; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; SpO_2, peripheral arterial oxygen saturation.

Safety of IMT

The adverse cardiovascular events, absolute or relative termination criteria, and findings suggestive of excessive exercise during IMT are presented in **Table 5**. Among 348 IMT sessions, there were no cardiovascular adverse events or absolute termination criteria. In contrast, 11 (3.2%) IMT sessions met the relative termination criteria. Decreased SpO_2 occurred in 3 (0.9%) sessions, whereas decreased SBP was detected in 8 (2.3%) sessions. The breakdown of "decrease in SpO_2" occurred without oxygen therapy, and the matching definition was "decrease in SpO_2 of 5% or more at rest". Nevertheless, all patients with relative termination criteria did not require medical treatment. Symptoms of excessive exercise load were observed in 27 (7.8%) sessions for a Borg scale score of >13 and 9 (4.6%) sessions for an increase in HR >20 beats/min from rest among patients taking β-blockers.

Supplementary Table 2 shows the changes in vital signs with IMT. Except for SBP in patients taking β-blockers, there were no significant changes in SBP and DBP with IMT. HR increased significantly with IMT compared with that at rest, except in patients using positive intravenous inotropic drugs; however, the effect size (r) was very small. No significant change in HR was observed among patients using positive intravenous inotropic drugs; the effect size (r) was moderate. Additionally, the HR during IMT in patients implanted with a cardiovascular-implantable electronic device remained within the HR range set by the device. SpO_2 increased significantly with IMT, except in patients receiving oxygen therapy. The Borg scale score increased significantly after IMT compared with that at rest; the effect size (r) was large.

Discussion

In the present study, IMT could be performed safely in hospitalized patients with ADHF and that the addition of IMT to the usual CR improved the 2MWD, an index of exercise tolerance, as compared with the usual CR alone. The degree of improvement in the 2MWD was greater in the IMT group than that in the control group (+31.9 vs. +16.3 m, respectively). In patients with COPD and older frail adults, the minimal important difference in the 2MWD was 5.5–7.7 m.[12] Previous studies have confirmed the efficacy and safety of IMT[4,5,8] in stable outpatients with CHF; however, to date, its efficacy in hospitalized patients with ADHF remains unclear. Our results suggest that adding IMT to conventional CR to improve exercise tolerance is an effective and safe option for CR in hospitalized patients with ADHF.

The improvement in 2MWD due to IMT in hospitalized patients with ADHF may be attributed to the prevention of disuse-induced IMW during hospitalization. IMW reduces the tidal volume during exercise and induces respiratory muscle fatigue.[26] Rapid and shallow ventilation patterns due to inspiratory muscle fatigue increase the dead-space ventilation ratio[27] and reduce exercise tolerance.[28] Hamazaki et al. reported that decreased PI_{max} in

outpatients with CHF was associated with increased tidal volume and dead-space ventilation ratio during exercise, leading to a ventilation-perfusion mismatch.[10] In addition, the respiratory muscle metaboreflex causes vasoconstriction of active skeletal muscles during exercise,[5] limiting exercise performance by reducing blood flow.[29] In outpatients with CHF, reduced lower-limb blood flow induced by respiratory muscle loading[5] causes lower-limb fatigue.[5] IMT attenuates the respiratory muscle metabolic reflex by suppressing respiratory muscle fatigue, thereby improving lower-limb blood flow.[5] Furthermore, this hypothesis is supported by the fact that IMT was effective in improving the 2MWD in the present study, even though it was implemented for a very short time compared with previous studies.[3] Although the conditions were different, previous studies have found that 6–12 weeks of IMT is necessary to improve exercise tolerance.[3] In other words, it is speculated that the effect of IMT in improving PI_{max} was limited during the present study period. However, preventing disuse-induced IMW with IMT may contribute to prehospitalization inspiratory muscle strength and exercise tolerance when heart failure is compensated. Therefore, IMT should be considered in patients with ADHF to prevent IMW during hospitalization.

In the present study, there was no incidence of cardiovascular adverse events or absolute termination criteria due to IMT, and the incidence of relative contraindications due to decreased SBP and SpO_2 was 2.3% (n=8) and 0.9% (n=3), respectively. The incidence of adverse events due to early mobilization is 0.2%[30] in older patients with acute-phase cardiovascular disease, and the incidence of those due to hemodynamic changes and oxygen desaturation are 3.8% and 1.9%, respectively, in patients in the intensive care unit.[31] Therefore, IMT can be safely performed in hospitalized patients with ADHF if the risks and pathologies are appropriately controlled. Changes in SBP, DBP, and SpO_2 due to IMT implementation did not show significant differences for many items; even if they did, the effect size was very small. The increase in blood pressure and HR due to muscle contraction depends on muscle mass and exercise intensity;[32] thus, it is possible that the IMT for inspiratory muscles, which have a small muscle mass in the whole body, did not significantly change the SBP, DBP, and HR. In contrast, when positive intravenous inotropic drugs were administered, the effect size of the changes in SBP, DBP, and HR due to IMT was moderate. However, according to the raw data, the magnitude of the change did not necessarily indicate a clinically high risk. Appropriate adjustment of exercise load contributes to safe exercise in patients receiving intravenous inotropic drugs;[30] given the insufficient evidence, further research is required. The Borg scale scores increased significantly after IMT, and the effect size was large. Continuous monitoring during IMT may help in preventing overloading because the Borg scale score increases by approximately 3 points.

The effectiveness of the current guideline-based CR for hospitalized patients with ADHF has been reported.[30] Nonetheless, it consists of resistance, aerobic, and ADL training; IMT is not common.[2,11] Therefore, based on the findings of the present study, the addition of IMT for hospitalized patients with ADHF may further improve rehabilitation outcomes.

The present study has some limitations. First, generalizability of the findings must be carefully considered as this was a single-center study. The present study excluded patients who were unable to walk independently, whose PI_{max} could not be measured owing to severe IMW, or whose PI_{max} is normal. Therefore, future studies should investigate whether the same efficacy can be achieved in patients with lower ADL levels, severe IMW, or normal inspiratory muscle strength. Second, there is no certainty that the IMT protocol used was the most effective. Although the efficacy of various protocols has been investigated in CHF, no consensus has yet been reached.[3] As the IMT safety in hospitalized patients with ADHF is unknown, it is necessary to confirm its efficacy and safety at low intensity. Therefore, findings in the present study are important because they show that low-intensity IMT can be performed safely and improve the 2MWD with a moderate effect size. Meanwhile, the optimal IMT protocol for ADHF requires further research. Third, this study uses 2MWD as the primary endpoint. A similar measure is the 6MWD, which is a well known predictor of death and rehospitalization. However, the 6MWT may cause adverse events in patients with ADHF in the early stages of hospitalization;[33] thus, the 2MWT, which is less physically demanding, was used in the present study. While a correlation greater than 0.9 was found between 2MWD and 6MWD,[34,35] there is no consensus on the relationship between 2MWD and peak$\dot{V}O_2$. Moderate correlations between 2MWD and peak$\dot{V}O_2$ have been reported in chronic stroke[34] and stable COPD[35] but not in healthy older adults.[36] Therefore, whether improvement in the 2MWD by IMT contributes to rehospitalization and death in heart failure patients as well as the 6MWD is an issue for further investigation. In the future, a multicenter, randomized, controlled trial should be conducted based on our results to further investigate the efficacy and safety of IMT in patients with severe ADHF and indications for IMT.

Conclusions

Adding IMT to the usual CR can improve the 2MWD and can be safely performed in hospitalized patients with ADHF. Thus, IMT may represent a new treatment option for CR in hospitalized patients with ADHF.

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Disclosures

The authors declare that there are no conflicts of interest.

Author Contributions

J.Y.: Conceptualization, formal analysis, funding acquisition, methodology, project administration, resources, supervision, visualization, and writing. R.T.: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, and review. Y.M.: Investigation. K.M.: Investigation. T.S.: Investigation. All authors have read and approved the final version of this manuscript.

IRB Information

The study protocol was approved by the Ethics Committee of Sendai

Medical Center (Approval no. 23-103) and the Ethics Committee of Hirosaki University Graduate School of Medicine (Approval no. T2023-028). Verbal and written informed consent was obtained from all participants in the intervention group.

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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