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Original Article

Effects of cardiac rehabilitation with motion assistance from a wearable cyborg hybrid assistive limb on patients with chronic heart failure: a randomized controlled trial with a one-year follow-up

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Abstract. [Purpose] We have recently reported that using a wearable cyborg hybrid assistive limb improved the isometric knee extensor muscle strength of patients with chronic heart failure. Here, we investigated the long-term effects of a lumbar-type hybrid assistive limb for patients with chronic heart failure. [Participants and Methods] A total of 28 hospitalized patients with chronic heart failure (mean age, 73.1 ± 13.8 years) were randomly assigned to two groups: the hybrid assistive limb group or the control group, in which they performed a sit-to-stand exercise with or without the hybrid assistive limb, respectively. The cardiac rehabilitation therapy included this intervention, which was performed as many times as possible for 5–30 minutes per day for 6–10 days. Clinical assessments like lower-limb muscle strength, walking ability, etc., were measured before and after the intervention. Cardiac events were followed up for up to a year after discharge. [Results] No adverse events occurred during the study period in either group. In terms of long-term effects, the incidence of cardiac events was 23% and 45% in the hybrid assistive limb and the control groups, respectively. [Conclusion] Hybrid assistive limb-assisted exercise therapy may be a safe and feasible cardiac rehabilitation tool in patients with chronic heart failure. The lumbar-type wearable cyborg hybrid assistive limb may have a positive effect on heart failure prognosis by adding long-term exercise therapy.
Key words: Wearable cyborg hybrid assistive limb, Chronic heart failure, Cardiac rehabilitation

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INTRODUCTION

The 2017 Global Burden of Disease Study systematically analyzed and estimated that 64.3 million people globally are living with heart failure (HF)[1, 2]. Aging is one of the most important factors associated with prevalence and HF prognosis[3].

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Aging produces muscle weakness of the limbs, physical inactivity, gait disturbance, etc. causing a geriatric syndrome which results in frailty and sarcopenia[4–7]. Japan is the pioneer super-aging society in the world, and it is feared that the number of HF patients will increase and that a heart failure pandemic will occur in the future[8]. Therefore, the best exercise-based cardiac rehabilitation program for the improvement of independence in activities of daily living is expected to add to the prevention of HF exacerbation.

Cardiac rehabilitation is recommended worldwide as a means to prevent HF recurrence and worsening[9]. In general, walking and bicycle exercises as aerobic exercises are standard cardiac rehabilitation programs in chronic HF patients[10–12]. These exercise therapies are unavailable to many patients, especially those with severe HF in whom skeletal muscle functions are too severely compromised to endure an exercise-based regimen[13]. It is, therefore, necessary to establish safer and more effective exercise therapies for the elderly and HF patients with frailty. Functional electrical stimulation to the lower limbs and exercise using robot assistance have been performed in the clinical trial as an exercise therapy other than aerobic exercise[14, 15].

The Hybrid Assistive Limb (HAL) is the world's first wearable cyborg that supports, improves, and expands the wearer's physical functions by detecting bioelectrical signals (BES) expressed on the skin surface above the muscles when the wearer tries to generate muscle forces[16, 17]. There were many types of clinical research in terms of HAL in the last decade[18, 19]. Previous studies[18, 19] suggested that HAL intervention in patients with stroke experience can lead to improvement in the gait function and independent walking. Moreover, HAL intervention can improve balance and sit-to-stand ability in patients with locomotive syndrome. The lower limb type of HAL has been reported to improve gait function in patients with incurable neuromuscular diseases and stroke[20, 21]. Lumbar-type HAL can assist body-trunk and lower limb training[22, 23]. Our recent study suggested that patients with chronic HF had significant improvement in isometric knee extensor muscle strength after sit-to-stand exercise using lumbar-type HAL[13]. However, there have been no reports on the long-term effects of the lumbar-type HAL during sit-to-stand exercises in patients with HF. Here, the long-term effects of sit-to-stand exercises performed using the lumbar-type wearable cyborg HAL in patients with chronic HF were investigated. We hypothesize that sit-to-stand exercises for patients with HAL can reduce the rate of readmission for HF exacerbation in patients with chronic HF as a long-term effect.

PARTICIPANTS AND METHODS

This was a single-center, randomized, parallel-group, controlled trial. Our study included 28 patients who were admitted to the University of Tsukuba Hospital with chronic HF, satisfied all inclusion criteria, and did not meet any of the exclusion criteria. The inclusion and exclusion criteria have been described in our previous study[13, 24]. The enrolled patients were randomly assigned to the HAL or conventional exercise therapy (control) groups at a 1:1 allocation ratio through the minimization method using the Electronic Data Capture clinical research support system.

All patients who participated in this study[13] were investigated one year after discharge. The Tsukuba University Clinical Research Review Board approved this study (TCRB18-023). The study protocol was registered with the Japan Registry of Clinical Trials (jRCTs032180105).

Patients in the HAL group performed the sit-to-stand exercise with the lumbar-type HAL for 5–30 min a day between 6–10 days (Fig. 1). The patients in the control group performed the sit-to-stand exercise without HAL for the same duration according to the same schedule (Fig. 1). In previous studies, the duration of HAL intervention was set to 20–40 minutes[25–27]. However, as this was an exploratory study, we set the range of intervention time as 5–30 minutes, including rest time between exercises. In both groups, the exercise duration was more than 5 minutes on the first day and was gradually increased to

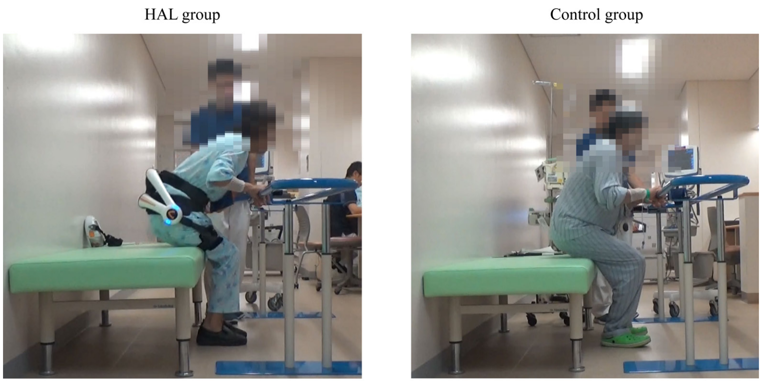

Fig. 1. Sit-to-stand exercise with and without a lumbar-type wearable cyborg HAL.
HAL: hybrid assistive limb.

suit the patient's physical fitness and familiarity with the sit-to-stand exercise. The goal of the sit-to-stand exercise with/without HAL was to improve the patient's sit-to-stand ability and help them achieve a symmetrical posture while sitting and standing. The physical therapist checked the patient's heart rate, systolic and diastolic blood pressures, and subjective ratings of exercise intensity on the Borg scale every minute during the exercise therapy. The intervention method in both groups has been described in detail in our previous study[13, 24)]. Patients in both groups implemented physical therapy, except for this intervention, as mentioned in the "Rehabilitation Guidelines for Cardiovascular Disease Patients" published by the Japanese Circulation Society in 2012[28)].

Patients wore the lumbar-type HAL (HAL-FB02-SSSJP) during the intervention in only the HAL group. Electrodes attached to the skin covering the lumbar erector spinae muscles can detect the action potentials of nerves and muscles as BES when patients wore the HAL. Therefore, it can sense the wearer's intent to perform the sit-to-stand action. As a result, patients can do sit-to-stand exercises using motion assistance from HAL. Physical therapists can adjust the torque tuner of the HAL from level 1 to 5, according to the posture and motion of the patient. Details of the HAL's operating modes and principles can be found in previous studies[17, 24, 29)].

The short-term outcomes were measured before and after the intervention as clinical assessments; results were previously reported[13)]. The long-term outcomes (as a prognosis, one year after discharge) evaluated in the present study were the incidence of all rehospitalization and rehospitalization due to exacerbation of HF and mortality.

The Kaplan–Meier method was used for survival analysis. The log-rank test was performed to compare the long-term effects between the two groups. All statistical analyses were conducted using SPSS (version 26.0) (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p<0.05$.

RESULTS

Figure 2 shows the flowchart. In this study, 28 patients who had difficulty with normal walking speeds (approximately 80 m/min) were enrolled in the study and randomized into two groups. No adverse events occurred during the study period in either group. Four patients (one in the HAL group and three in the control group) were discharged early from the hospital for reasons

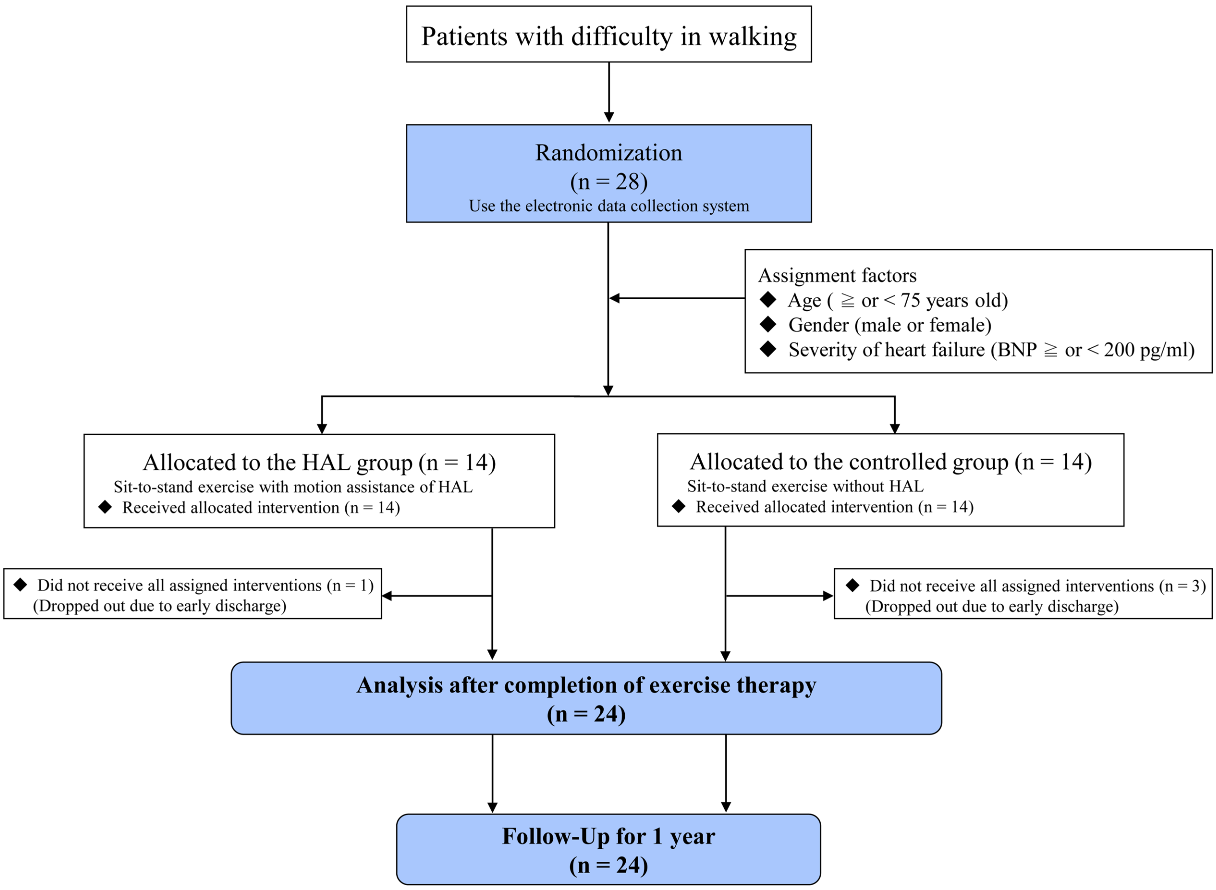

Fig. 2. Study flowchart.
HAL: hybrid assistive limb; BNP: B-type natriuretic peptide.

unrelated to this study. These patients were excluded from the analysis, and data on the remaining 24 patients (13 in the HAL group and 11 in the control group) were analyzed. All 24 patients were able to be followed up 1 year after discharge (Fig. 2).

The two groups had no differences in mean age, height, body mass index, left ventricle ejection fraction, and HF severity at baseline assessment. The specific numbers and values for both groups are described in our previous report[13]. The total number of intervention days in the HAL group did not differ significantly from that in the control group (7.2 ± 1.5 and 6.8 ± 1.3 days, respectively; p=0.53). There was no difference in the total number of stand-up exercises performed by the two groups (629 ± 463 in the HAL group; 485 ± 237 in the control group; p=0.42)[13] during the study period.

The long-term outcomes (prognosis in 1 year discharge) between the two groups showed no observable significant difference. All rehospitalization incidence was 54% (n=7) in the HAL group and 73% (n=8) in the control group (p=0.29). In the HAL group, three patients had HF exacerbation, one had a head injury due to a fall, two had gastrointestinal bleeding, and one had dyspnea due to pneumonia. In the control group, however, five patients had HF exacerbation, one had suspected intestinal bleeding, one was hospitalized for left ventricular assist device insertion, and one had educational hospitalization for glycemic control due to diabetes mellitus. The rehospitalization incidence due to HF exacerbation was 23% (n=3) in the HAL group and 45% (n=5) in the control group (p=0.30) (Fig. 3). Also, the mortality rate was 8% (n=1) in the HAL group and 9% (n=1) in the control group (p=0.93). The causes of death were cardiac amyloidosis (HAL group; n=1) and HF (control group; n=1).

DISCUSSION

This is a randomized controlled trial of chronic HF patients to investigate the short-term and long-term effects of the lumbar-type HAL. The sit-to-stand exercise using HAL was demonstrated to significantly improve the isometric knee extensor muscle strength after intervention in chronic HF patients[13]. The results also suggested that the HAL-assisted exercise therapy may serve as a safe and feasible cardiac rehabilitation tool without increasing B-type natriuretic peptide (BNP) in chronic HF[13]. There was no significant difference in the occurrence of cardiac events between the HAL and control groups during 1 year after discharge. Although patients with HF were not included, a previous pilot study reported that participants with locomotive syndrome exhibited improvement in balance and sit-to-stand ability after lumbar-type HAL intervention[19]. There have been no reports on the long-term effects of lumbar-type HAL during sit-to-stand exercises in patients with HF and locomotive syndrome.

Schoenrath et al. suggested that robot-assisted gait therapy with the Lokomat system was feasible and safe in HF patients, according to the previous research using robot-assist technology[30]. Furthermore, Schoenrath et al. compared the effects of the Lokomat system robot-assisted gait therapy and standard physical therapy for patients after cardiac surgery[31]. There was no significant difference in the amount of change in the 6-min walking distance (6MWD) and the amount of change in the knee extensor muscle strength between the two groups, although both groups had significant improvement in 6MWD, and knee extensor muscle strength[31]. Both groups significantly improved 6MWD and short physical performance battery after the intervention in our study[13]. The BNP was significantly improved after intervention in the HAL group, while BNP in the control group tended to improve[13]. No adverse events occurred during the study period in either group of our study. A total of four patients dropped out due to early discharge before the termination of the predefined period of exercise intervention. A total of 24 patients completed the exercise intervention and follow-up assessments (1 year after discharge). Therefore, our results suggest that sit-to-stand exercise using a HAL is safe and feasible for chronic HF.

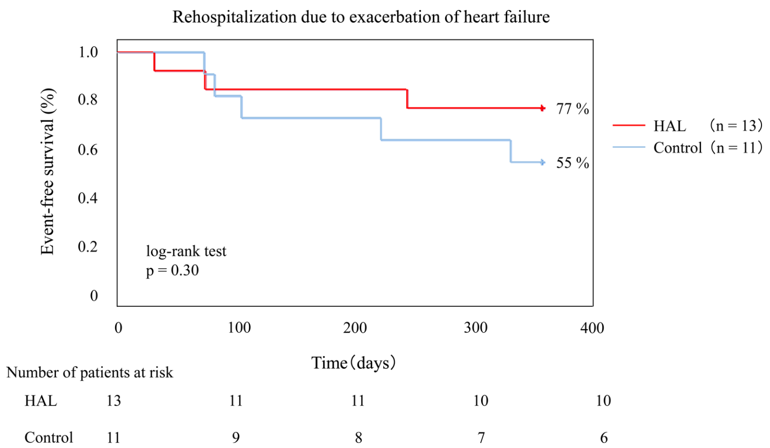

Fig. 3. Kaplan–Meier curves comparing rehospitalization due to heart failure exacerbation after exercise therapy during 1 year follow-up between the HAL group and the control group.
HAL: hybrid assistive limb.

There are numerous muscle strength training methods for HF patients. In general, resistance training, repetitive sit-to-stand exercise, squat exercise, and neuromuscular electrical stimulation (NMES) are conducted in exercise-based cardiac rehabilitation[32–34]. Quittan et al. performed NMES in chronic HF patients for 8 weeks to increase knee extensor muscle strength[32]. The maximal isometric knee extensor muscle strength increased by 20% from 294.3 ± 19.6 N to 354.14 ± 15.7 N ($p=0.04$)[32]. Our study performed the sit-to-stand exercise with a lumbar type of HAL approximately for 1–2 weeks in patients with chronic HF. As a result, the isometric knee extensor muscle strength improved significantly in the HAL group, increasing by approximately 21% from 0.29 ± 0.11 to 0.35 ± 0.11 kgf/kg ($p<0.01$) after the intervention[13]. Although not directly comparable, our study found a similar improvement in knee extensor muscle strength in a shorter period than in previous studies[32]. Kono et al. reported that knee extensor muscle strength is an independent factor determining exercise capacity, especially in elderly HF patients with sarcopenia, and provided useful information on exercise prescription[35]. Knee extensor muscle power is an independent predictor for rehospitalization in HF patients with reduced ejection fraction[36]. Therefore, physical therapists need to focus on improving knee extensor muscle strength in patients with HF.

The lumbar-type HAL facilitates sit-to-stand exercises by supporting the hip extension[24, 29]. Patients with cardiac disease who have limited mobility and exercise tolerance may be able to implement the required exercise more stably, naturally, and accurately when receiving motion assistance from the HAL[13, 24]. Von et al. reported knee extensor muscle activity is increased during lumbar-type HAL use[37]. Kotani et al. reported that the exercise using lumbar-type HAL may be a safe and promising treatment for frailty patients in the cohort study[23]. We speculate that quadriceps muscle activity increased and knee extension muscle strength improved in the sit-to-stand exercise using HAL, although the lumbar-type HAL effect has not been currently clarified. Exercise with the lumbar-type HAL may have conferred a high motor learning effect by promoting brain, nerve, and muscle activity through the hypothesized mechanism of interactive biofeedback[23, 29]. Sit-to-stand exercises using HAL might be a new tool for cardiac rehabilitation in chronic HF patients.

Belardinelli et al. reported that for long-term cardiac rehabilitation effectiveness in HF, the training group (initially three times a week for 8 weeks, then twice a week for 1 year) had significantly fewer hospitalizations and cardiac events due to worsening HF than the non-exercise training group[38]. The latest Cochrane Review revealed that exercise-based cardiac rehabilitation probably reduces the risk of all-cause hospital admissions and may reduce HF-specific hospital admissions[33]. The relatively high rate of rehospitalization in our study might be attributable to the higher age of the included patients.

In conclusion, HAL-assisted exercise therapy may serve as a safe and feasible cardiac rehabilitation tool for patients with chronic HF. Long-term exercise therapy with lumbar-type wearable cyborg HAL may have a positive effect on the prognosis of HF. No significant difference in cardiac events (rehospitalization due to HF exacerbation) was observed between the two groups during the 1 year follow-up period in our present study. We believe that the reason why there was no significant difference in the occurrence of cardiac events was largely due to the short period of exercise therapy along with the small sample size. Age, gender, and HF severity (BNP) were set as the allocation factors in this study[13, 24]. The suppression of cardiac events is affected by many confounding factors (diet therapy, lifestyle guidance, medication management, etc.) other than exercise therapy. We need to add cases by implementing this intervention at multiple centers in the future. Functional assessments were not blinded and thus were potentially open to observer bias is another limitation of this study. We confirmed the occurrence of cardiac events and readmission of the patients using their medical records in terms of follow-up with no functional assessment. Therefore, there are unclear long-term effects of lumbar-type HAL on the quality of life, functional capacity, and clinical outcomes in the patients with chronic HF patients. In our next study, we plan to collect data on cognitive function in addition to body function. Finally, we need to investigate the appropriate specific exercise parameters (length of the intervention period, intensity, frequency, duration of exercise therapy session, and type of exercise therapy) using a lumbar-type HAL for chronic HF.

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Conflict of interest

Hiroaki Kawamoto is an associate professor at the University of Tsukuba, a cofounder, a shareholder, and an outside director of the university venture company CYBERDYNE Inc. (Ibaraki, Japan). Yoshiyuki Sankai (YS) is an inventor of the world's first wearable cyborg HAL, a founder, a stockholder, and the CEO of a university venture company, CYBERDYNE, the manufacturer of the wearable cyborg HAL. YS's conflict of interest is strictly managed by the board of directors of CYBERDYNE and the University of Tsukuba, according to the national university rules. The patents of HAL belong to the University of Tsukuba, and CYBERDYNE pays a patent royalty to the University of Tsukuba according to national university rules. CYBERDYNE was not involved in the study design, in the collection, analysis, or interpretation of the data, in the writing of the report, in the financial/nonfinancial support, or in the decision to submit the paper for publication. This information is fully described in the consent forms. The following authors report no conflicts of interest: Hiroki Watanabe, Akira Koike, Hidenori Kato, Naoto Kawamatsu, Takako Ichinohe, Takeshi Machino, Isao Nishi, and Masaki Ieda.

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