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Review

Physical Therapy for Adults with Heart Failure

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ABSTRACT. Heart failure (HF) is a complex clinical syndrome caused by structural and/or functional abnormalities that results in significant disease burdens not only to the patients and their families but also to the society. Common symptoms/signs of HF include dyspnea, fatigue, and exercise intolerance, which significantly reduce the quality of life of individuals. Since the coronavirus disease 2019 (COVID-19) pandemic in 2019, it has been found that individuals with cardiovascular disease are more vulnerable to COVID-19-related cardiac sequelae including HF. In this article, we review the updated diagnosis, classifications, and interventional guidelines of HF. We also discuss the link between COVID-19 and HF. The latest evidence about physical therapy for patients with HF in both the stable chronic phase and acute cardiac decompensation phase is reviewed. Physical therapy for HF patients with circulatory support devices is also described.

Key words: CHF, COVID-19, ADHF, Rehabilitation, HF

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Heart failure (HF) is a complex clinical condition caused by structural and/or functional abnormalities or cardiac injury[1]. The diagnosis of HF requires both the presence of HF symptoms/signs and the objective evidence of cardiac dysfunction/injury. Symptoms and signs of HF include shortness of breath, fatigue, persistent coughing or wheezing, peripheral edema, lack of appetite, and elevated resting heart rate (HR). The objective diagnosis tests of HF include echocardiography, natriuretic peptide (NP), electrocardiogram (ECG), and chest X-ray (CXR)[2]. Echocardiography is the key assessment of cardiac function that provides information on ventricular systolic function, cardiac chamber sizes, wall motion, and eccentric/concentric left ventricular hypertrophy (LVH). Plasma NPs such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are produced from cardiac tissue when the cardiac tissue is stretched by pressure or volume overload. Thus, elevated NP (NT-proBNP ≥125 pg/mL or BNP ≥35 pg/mL) suggests increased cardiac wall stress[2,3]. The ECG reveals abnormal cardiac electrophysiology such as arrhythmias, LVH, atrial fibrillation, and the widened QRS complex (the Q wave, the R wave, and the S wave). Last, CXR is often used to help the differential diagnosis of HF[2].

The etiology of HF is various, including coronary artery disease, hypertension (HTN), valvular heart disease, arrhythmias, cardiomyopathy, congenital heart disease, pericardial disease, infection, drug-induced cardiotoxicity (such as anticancer medications anthracyclines and trastuzumab), metabolic/autoimmune diseases, and neuromuscular disease[2]. The pathophysiology of HF can be described from the structural and functional perspectives. From a structural perspective, HF is classified into left-sided or right-sided HF. Left-sided HF reduces cardiac output, increases fluid retention in the atrium, and eventually results in pulmonary congestion and edema. Right-sided HF results in systemic (venous) congestion. The dominant symptoms of left-sided HF are dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and cough. The dominant symptoms of right-side HF are jugular venous distention, peripheral edema, ascites, and pleural effusion[4,5]. From the functional perspective, HF is classified into systolic HF or diastolic HF. Systolic HF is characterized by impaired cardiac contractility, resulting in reduced cardiac

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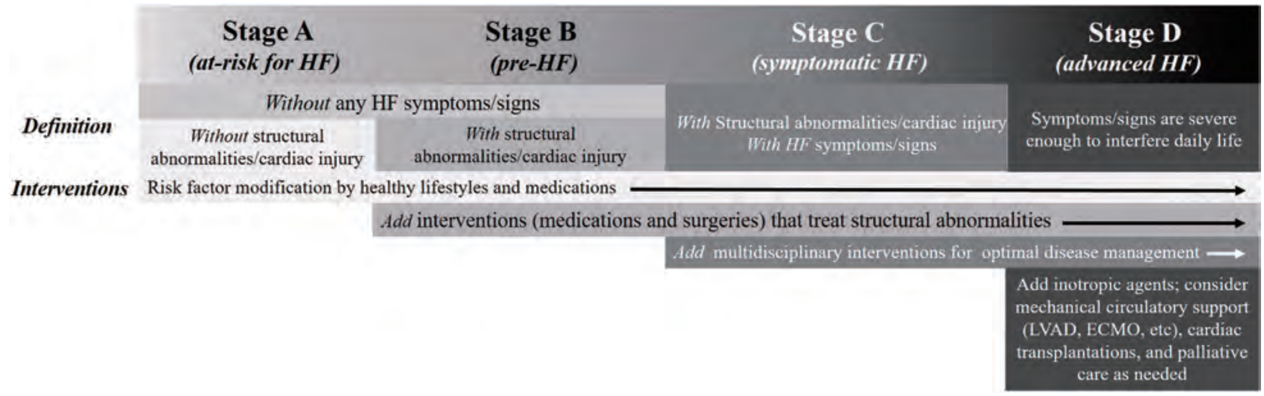

Fig. 1. The definition and suggested interventions for patients with HF at different stages
HF, heart failure; LVAD, left ventricular assist device; ECMO, extracorporeal membrane oxygenation

output. Diastolic HF is characterized by impaired relaxation of cardiac muscles during the ventricular filling stage, which also results in reduced cardiac output[4,6)]. No matter left-sided or right-sided HF, systolic or diastolic HF, the end result is reduced cardiac output. Reduced cardiac output not only leads to hypotension, cardiogenic shock, and organ dysfunction but also results in elevated cardiac pressure that results in pulmonary congestion and poor ventilatory efficiency[7–9)].

HF: Classification

The types of HF are classified based on the left ventricular ejection fraction (LVEF) assessed by echocardiogram. Individuals with LVEF ≤40% or ≥50% at the first diagnosis and the follow-ups are defined as those with heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), respectively[10)]. Individuals with LVEF 41%–49% at the first diagnosis and the follow-ups are defined as heart failure with mildly reduced ejection fraction (HFmrHF). Individuals with previous LVEF ≤40% and a follow-up LVEF >40% are defined as heart failure with improved ejection fraction (HFimpEF)[10)]. HFrEF is used to be called systolic HF and HFpEF is used to be called diastolic HF. Individuals with HFrEF are usually younger than individuals with HFmrEF and HFpEF, and often occurs in individuals with a history of myocardial infarction[11)]. HFmrEF occurs more frequently in individuals with a history of diabetes mellitus, hyperlipidemia, peripheral artery disease, renal failure, dialysis, and ischemic events[11)]. HFpEF occurs more frequently in individuals with a history of HTN, depression, and cerebral vascular accidents[11)]. Compared to HFrEF, obesity and low physical activity are more associated with the risk of HFpEF[12)]. Last, compared to individuals with HFrEF, individuals with HFimpEF have a lower prevalence of ischemic heart disease, a higher prevalence of HTN, and a more favorable outcome[13)].

The stages of HF are defined by the American College of Cardiology (ACC) and the American Heart Association (AHA) as stages A, B, C, and D. Stage A indicates individuals with risk of HF (e.g., HTN, diabetes, obesity, and atherosclerotic cardiovascular diseases) but without any HF symptoms/signs and structural abnormalities/cardiac injury. Stage B indicates individuals with structural abnormalities/cardiac injury but without HF symptoms/signs. Stage C indicates individuals with both HF symptoms/signs and structural abnormalities/cardiac injury. Stage D indicates individuals whose symptoms/signs are severe enough to interfere with daily life[10)]. The treatment aim for individuals with stage A and B is primary prevention. Individuals with stage A HF should modify risk factors via healthy lifestyles (e.g., regular exercise, avoiding obesity, and not smoking) and medications (e.g., statin, beta-blockers, and renin–angiotensin system inhibitors). For individuals with stage B, treatment should add interventions that treat structural abnormalities including surgeries (e.g., valve replacement and coronary revascularization) and implantable cardioverter-defibrillator (ICD) implantation in addition to risk modification by lifestyle and medications. The treatment aims for individuals with stage C HF is improving symptoms, preventing the worsening of symptoms, and reducing mortality and morbidity. Thus, in addition to risk modification, interventions including disease management education and support from a multidisciplinary team (e.g., vaccination, adherence to medication, restriction of dietary sodium, exercise, and cardiac rehabilitation), medications (e.g., diuretics, renin–angiotensin system inhibitors, beta-blockers, and digoxin), implantable electrical interventions (e.g., ICD and cardiac resynchronization therapy), and surgeries (e.g., valve replacement and coronary revascularization) are needed. The treatment aim for individuals with stage D HF is improving functional status, quality of life (QoL), and life span. Specialty referral for advanced care is suggested (e.g., left ventricular assist device [LVAD], cardiac transplantation, and palliative care) in addition to the suggested interventions for stages A–C HF (Fig. 1)[10,14)].

The functional capacity of individuals with HF is classified by the New York Heart Association (NYHA). NYHA classification is a subjective assessment and classifies HF as I, II, III, and IV. Class I refers to individuals who do not have limitations in physical activity and can perform activities requiring ≥7 metabolic equivalents (METs) such as jogging at 8 km/h, climbing stairs rapidly or in cold weather, climbing

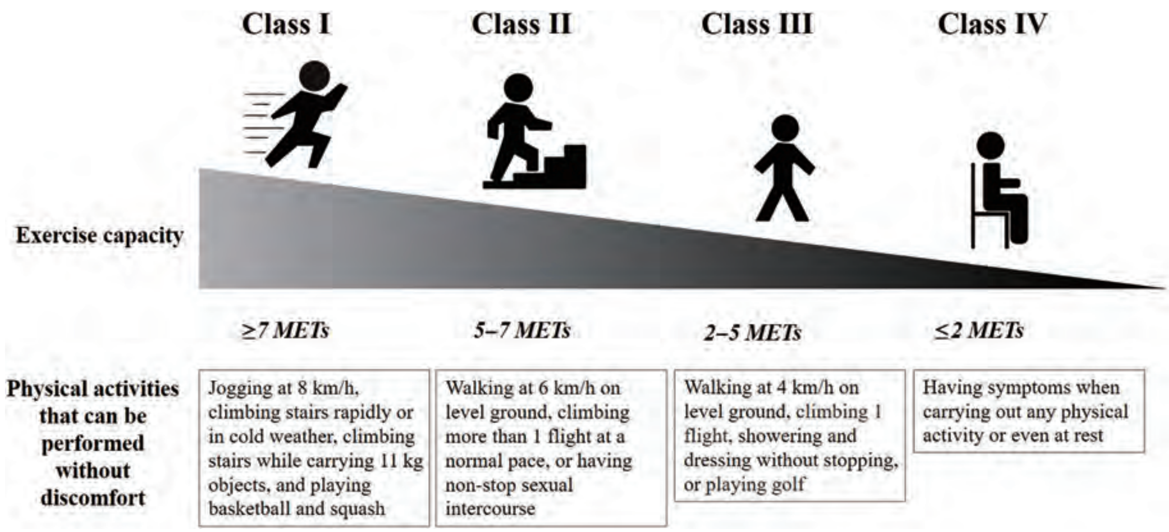

Fig. 2. NYHA functional classification

METs, metabolic equivalents; NYHA, New York Heart Association

stairs while carrying 11 kg objects, and playing basketball and squash. Class II refers to individuals who have a slight limitation of physical activity. Individuals with NYHA class II can perform activities requiring 5–7 METs (such as walking at 6 km/h on level ground, climbing more than 1 flight at a normal pace, or having non-stop sexual intercourse) without discomfort, but feel fatigued, or have palpitations or dyspnea during activities that require more than 7 METs. Class III refers to individuals who have marked limitations of physical activity. Individuals with NYHA class III are comfortable at rest, can perform activities requiring 2–5 METs (such as walking at 4 km/h on level ground, climbing 1 flight, showering and dressing without stopping, or playing golf) without discomfort, but feel fatigued, or have palpitations or dyspnea during activities that require more than 5 METs. Class IV refers to individuals who have symptoms when carrying out any physical activity or even at rest (Fig. 2)[4,10].

Depending on clinical presentations, HF is usually divided into chronic heart failure (CHF) and acute decompensated heart failure (ADHF)[2]. Individuals with CHF are under optimal medical therapy and are asymptomatic or only mildly symptomatic[15]. ADHF is a new onset or worsening of HF symptoms where individuals suffer from acute congestion symptoms, including exacerbated dyspnea and fatigue, weight gain, jugular venous distention, pulmonary or peripheral edema, or cardiogenic shock. ADHF results from a gradual increase of intraventricular pressure due to acute coronary syndrome, arrhythmias, or cardiac inflammation[10,16]. Studies found that ADHF is highly associated with high mortality and hospital readmission rates[2,5,17].

Coronavirus Disease 2019 (COVID-19) and HF

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also called COVID-19, has infected many people worldwide and caused many deaths since 2019[18]. According to the data from the World Health Organization (WHO) in April 2022, more than 632 million people confirmed COVID-19 and more than 6.5 million people died from the disease[19]. People with COVID-19 present various symptoms with different severity. Individuals with mild illness might have fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, or loss of taste and smell, but do not have dyspnea or abnormal chest imaging. Individuals with moderate illness have infections involving the lower respiratory tract and have oxygen saturation (SpO_2) ≥94% on room air. Individuals with severe illness have resting respiratory rate >30 breaths/min or SpO_2 <94% on room air. Individuals with critical illnesses have respiratory failure, septic shock, and/or multiple organ dysfunction[20]. In addition to the common symptoms stated above, some individuals develop COVID-19-related cardiac impairments during the acute onset or recovery phase. COVID-19-related cardiac impairments include acute myocardial infarction[21], myopericarditis[22], myocarditis[23], cardiomyopathy[24], and HF[25]. The reported prevalence of COVID-19-related diastolic dysfunction of cardiac muscles, decreased LVEF, pulmonary HTN, pericardial effusion, and cardiac global hypokinesis in adults is 9.9%, 2.8%, 1.8%, 1.5%, and 0.8%, respectively[26]. A follow-up study found that 2% of adults with acute COVID-19 develop HF one year after hospital admission[27]. The clinical manifestations of COVID-19-related cardiac impairments are chest pain, shortness of breath, and fatigue[21–25].

Noteworthy, individuals with cardiovascular diseases are more vulnerable to COVID-19-related cardiac sequelae and high mortality than individuals without cardiovascular diseases[28]. A study showed that 49% of individuals who died from COVID-19 had pre-existing HF[29]. The reason why individuals with cardiovascular diseases are more likely to have COVID-19-related cardiac sequelae is that the content and activity of angiotensin-converting enzyme 2 (ACE2), the key receptor of SARS-CoV-2, in cardiomyocytes are greater in individuals with cardiovascular diseases than in healthy individuals[30]. The binding of SARS-CoV-2 to ACE2 activates cellular signaling pathways and causes an immune response that leads to subsequent inflammation and myocardial injury[31,32]. Indeed, people with COVID-19-related cardiac symptoms are found to have elevated biomarkers of cardiac damage such as NT-proBNP and troponin[33–36]. Taken together, the impact of COVID-19 infection on people varies a lot, from mild to critically ill. COVID-19 infection may affect cardiac function, especially in individuals with pre-existing cardiovascular diseases.

About 10%–20% of COVID-19 survivors develop post-COVID-19 symptoms. A meta-analysis examined the prevalence of post-COVID-19 symptoms at different follow-up periods and found that the top two symptoms at 3–6 months, 6–9 months, 9–12 months, and longer than 12 months are fatigue/dyspnea, effort intolerance/fatigue, fatigue/dyspnea, and fatigue/dyspnea, respectively[37]. Objective measurement of physical fitness also found that individuals who recover from severe/critical COVID-19 have the lowest peak oxygen consumption (VO_2 peak) and anaerobic threshold than individuals who recover from mild/moderate COVID-19 or individuals without COVID-19[38,39]. Deconditioning due to immobilization and inactivity is the main cause of fatigue and exercise intolerance of COVID-19 survivors[40]. Nevertheless, left ventricular end-diastolic volume (LVEDV), LVEF, and cardiac output at every stage of stress exercise test are found lower in 3-month follow-up of COVID-19 survivors than in control individuals[38]. This finding suggests that cardiac sequelae might also play a role in the deceased exercise capacity of COVID-19 survivors.

Physical Therapy for Individuals with HF

Education

Education on disease self-management is critical for individuals with HF. Individuals who have better disease self-management (i.e., adherence to medications, proper diet and exercise, and monitoring any exacerbation of symptoms) have a better QoL and lower hospital readmission rate and mortality[41]. All individuals with HF should be educated on the importance of adherence to medications and recognizing the signs/symptoms of exacerbation of HF. Individuals should measure body weight daily and see a doctor when body weight increases to 0.9–1.4 kg in 24 hours or 5 kg over 3 days[4]. In terms of diet, individuals with HF are suggested to restrict dietary sodium (<2300 mg/d) and have healthy dietary patterns such as Mediterranean diet or Dietary Approaches to Stop Hypertension diet[10]. Physical inactivity is highly associated with greater mortality in people with CHF. Low physical activity (<25,000 steps/week) is a predictor of mortality for HF patients with NYHA classes II–III[42,43]. Conversely, regular exercise improves exercise capacity and QoL and reduces mortality in individuals with CHF[44]. Taken together, good disease self-management is critical for individuals with HF. In addition to stressing the importance of exercise, physical therapists should also remind individuals of other components of disease self-management.

Exercise prescription for individuals with ADHF

Physical function such as sit-to-stand and walking ability is severely impaired in older individuals with ADHF. They are also often frail, depressed, and with impaired cognition[45]. While most exercise training studies exclude individuals with ADHF, a recent Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) study provided evidence on the beneficial effects of an early and progressive rehabilitation intervention on the physical function of older adults who are hospitalized for ADHF. REHAB-HF study found that 3 months of physical rehabilitation initiated during hospitalization improved physical performance, endurance, and QoL of older individuals hospitalized for ADHF[46]. The aim of REHAB-HF is to enhance physical function of individuals with ADHF so that they can be independent in the activities of daily living[47]. Due to fragility and poor functional status of individuals, a supervised and comprehensive exercise program is suggested[45]. For all individuals, the intervention includes balance, mobility, strength, and endurance training where the proportion of each type of exercise is different based on the functional level of individuals. While the strength training accounts for about 1/3 of the overall exercise time for all individuals, a greater proportion of training time shifts from balance and mobility training toward endurance training when individuals have better functional levels. Regarding intensity, the training begins with low intensity and high frequency, and progresses to high intensity with low frequency. Specifically, during hospitalization, the intervention is 45 minutes daily where individuals are allowed to rest when they need; the target intensity is at rating of perceived exertion (RPE) ≤12[46]. After discharge, individuals attend outpatient rehabilitation 3 times per week, 60 minutes each time with target RPE 13 (somewhat hard) for endurance training and RPE 15–16 (hard) for strength training[47]. Detailed exercise prescription for different functional levels of individuals in the REHAB-HF study is shown in Table 1[46,48].

Exercise prescription for individuals with CHF

It is evident that exercise improves functional capacity and health-related QoL and reduces hospital readmissions for individuals with CHF. The American Physical Therapy Association (APTA) published a physical therapist clinical practice guideline for the management of individuals with HF in 2020 where decision flowcharts, exercise prescriptions, and the levels of evidence are well described[4]. In general, individuals without signs/symptoms of acute cardiac decompensation and uncontrolled diseases are safe to receive exercise training. Aerobic exercise (both continuous and high-intensity interval), resistance exercise, and inspiratory muscle training are recommended for individuals with CHF[4]. The exercise duration per session is 30–60 minutes.

Table 1. Comprehensive exercises for individuals with ADHF

Functional level of patients	Level 1	Level 2	Level 3	Level 4
	• Gait speed ≤0.4 m/s • Unable to stand with feet together unsupported • Unable to stand from sitting position without hand support • Can walk <2 minutes (with/without the assistive device)	• Gait speed 0.4–0.6 m/s • Can stand with feet together for 10 seconds • Can stand from sitting position without hand support at least one time • Can walk 2–10 minutes (with/without the assistive device)	• Gait speed 0.6–0.8 m/s • Can stand unsupported and reach forward 25.4 cm • Complete 5 times sit to stand in 15–60 seconds • Can walk 10–20 minutes (with/without the assistive device)	• Gait speed >0.8 m/s • Can perform single-leg standing for 10 seconds • Complete 5 times sit to stand ≤15 seconds • Can walk ≥20 mins (with/without the assistive device)
Mobility training	Start with slow speed and then add start/stop walking events, change directions during walking			
Balance training	Static balance: maintain standing with wider base of support Dynamic balance: reach forward and backward	Static balance: maintain standing with feet together, semi-tandem standing, tandem standing Dynamic balance: reaching forward beyond the base of support	Integrate balance training with endurance training such as walking with turning and stopping abruptly, dual task	
Strength training	Focuses on functional strengthening exercises such as sit-to-stand, calf raising, and step-up			
Endurance training	Start with repeated bouts of ambulation with rest periods as needed. Initial duration is 5–10 minutes and gradually progresses to 40 minutes.			

ADHF, acute decompensated heart failure

Exercise frequency is 3–7 days/week for aerobic exercise and inspiratory muscle training and 2–3 days/week for resistance exercise[49–55]. The intensity of aerobic exercise in the form of moderate-intensity continuous training (MICT) is 40%–70% VO_2 peak/HR peak/peak work rate or RPE 11–15[49,50]. For aerobic exercise in the form of high-intensity-interval exercise training (HIIT), patients are asked to complete 2–6 cycles of 3–4 minutes of high intensity (75%–80% heart rate reserve [HRR] or 70%–95% VO_2 peak/HR peak) with 2–3 minutes of low-intensity (40%–50% HRR or 50%–70% VO_2 peak/HR peak) exercise[51,52]. The intensity of resistance exercise begins with 40%–50% one repetition maximum (1RM) and then progressively increases to 60%–85% 1RM. Resistance exercise training usually includes 8–10 movements that involve major muscle groups. Each movement repeats 8–15 times for 2–3 sets[53,54]. The intensity of inspiratory muscle training is 30%–60% maximal inspiratory pressure[55].

Regarding the level of monitoring during exercise, it is suggested to monitor ECG and blood pressure (BP) at the beginning sessions of training for individuals with NYHA I/II until they know how to monitor signs/symptoms by themselves. For individuals with NYHA III/IV, individuals having an systolic BP drops below resting levels during the exercise test, and individuals having angina or ischemic ST depression in the ECG at exercise intensity <6 METs, more than 12 sessions of continuous ECG and BP monitoring is suggested until the safety is established[56]. Regarding the training effects of exercise, a meta-analysis found that 8–12 weeks of both MICT and HIIT improve exercise capacity and QoL of individuals with HFrEF[49–52]. The average improvement of VO_2 peak is 0.69–2.08 mL/kg/min; the average improvement in the six-minute walking distance test (6MWD) is 21–25.67 m; the average improvement in Minnesota Living with Heart Failure Questionnaire (MLHFQ) is 5.9–10.86[49–52]. Only one recent randomized clinical trial compared the effects of MICT (40 minutes/session; 5 sessions/week) and HIIT (38 minutes/session; 3 sessions/week) on individuals with HFpEF[57]. It found that the improvement of VO_2 peak and QoL after training was similar between MICT and HIIT (1.6 mL/kg/min vs. 1.1 mL/kg/min)[57]. It is important to note that while the effects of MICT and HIIT on exercise capacity are similar, HIIT seems to be more effective in heart remodeling[50–54]. Studies show that 8–24 weeks of HIIT, but not MICT, increases LVEF (1.32%) and LVEDV of patients with HFrEF[51,52]. Recent meta-analysis showed that 8–20 weeks of resistance training improves cardiac performance, muscle strength, exercise capacity, and QoL of individuals with HFrEF[53,54]. The average improvement of VO_2 peak is 2.49 mL/kg/min, the average improvement in the 6MWD is 49.94 meters, and the average improvement in MLHFQ is 8.25[53,54]. Last, daily inspiratory muscle training improves inspiratory muscle strength, exercise capacity, and QoL of individuals with HFrEF[55]. The average improvement of VO_2 peak is 3.75 mL/kg/min and the average improvement in the 6MWD is 81.2 m[55]. One point worth noting is that most studies to date focus on individuals with HFrEF or have mixed types of HF as study subjects. Since different types of HF have their unique pathology and the characteristics of patients with different types of HF are different, further research is needed to explore the possible type-specific effects of exercise training.

Physical therapy for HF patients with mechanical devices

The most common implantable devices seen in individuals with HF are ICDs and cardiac resynchronization devices (pacemakers). An ICD is often implanted in patients who have uncontrolled arrhythmia (such as ventricular tachycardia or fibrillation). An ICD delivers an electrical shock to reset the heartbeat when individuals have a life-threatening arrhythmia. A pacemaker is a cardiac resynchronization device and is often implanted in patients whose ventricles could not contract coordinately. A pacemaker delivers electrical signals to trigger the coordinated ventricular contractions, thus correcting irregular or slow heartbeats. Supervised exercise training including aerobic and resistance exercise is safe and effective for individuals with ICD and pacemakers. An exercise test is recommended to evaluate the risk of HR reaching the ICD intervention zone[58)]. The AHA suggests that the target HR of exercise is set at 10–15 beats/min lower than the ICD therapy rate threshold. The common exercise prescription for individuals with ICD and/or pacemakers is 3–5 days/week, 30–90 minutes/session, and with intensity 50%–80% VO_2 peak/80%–85% HRR[58)]. More than 3 months of HR or RPE monitoring during exercise is necessary[58,59)]. It is found that ICD discharges during exercise are very rare (0.9%) with appropriate exercise prescription and monitoring[58)]. Meta-analysis that examined the effects of supervised exercise training on HF patients with ICD and/or pacemakers showed that 8–12 weeks of both MICT and HIIT improve exercise capacity and QoL of patients[58,60)]. Importantly, individuals who receive exercise training have 7% less ICD shocks compared to individuals who do not receive exercise training[58)]. Collectively, HF patients with ICDs and/or pacemakers are safe to receive exercise training. Exercise improves the exercise capacity and QoL of this population.

For individuals with ADHF and cardiogenic shock (i.e., hypotension accompanied by hypoperfusion of organs), mechanical circulatory support devices are commonly used. Intra-aortic balloon pump is a device that helps reduce the afterload of the heart and increase cardiac perfusion, which has been the most widely used device since the 1960s[61)]. Recently, the use of ventricular assist devices (VADs) and extracorporeal membrane oxygenation (ECMO) has dramatically increased because they provide a greater level of hemodynamic support. VAD is a device that helps the pumping of the heart, thus reducing the workload of the heart. ECMO is the device that replaces the functions of the heart and lung, thus decreasing the workload of them. For critically ill individuals, joint contracture, muscle atrophy, and deconditioning are the common sequelae of bedridden. Early mobilization, including ambulation, is a safe and feasible intervention that benefits individuals' functional outcomes[62)]. A multidisciplinary team must include physicians, nurses, respiratory therapists, physical therapists, occupational therapists, and perfusionists to provide comprehensive care for critically ill individuals. Once an individual is assessed as suitable for activity by the medical team, physical therapists assess the functional level of patients and initiate early mobilization intervention, which usually requires assistance from other clinicians (such as a nurse, an occupational therapist, or a perfusionist)[62,63)]. Early mobilization exercises include range of motion exercises, resistance exercises, transfer exercises, standing, stepping, bed cycling, and ambulation where the selection of exercises is individualized based on the consciousness level, functional level, and disease severity of individuals[62,64)]. Vital signs, RPE, and circuit integrity should be monitored during the intervention. Exercise intervention is terminated when patients have hemodynamic instability, hypoxemia, dizziness, weakness, chest pain, or dyspnea[62)]. It is worth noting that for individuals with femoral access to mechanical circulatory support devices, movements that require hip flexion over 30 degrees or overextend the leg should be avoided to decrease the risk of malpositioning[65)]. Kerrigan et al. reported that 6 weeks of aerobic training (walking/cycling at 60%–80% HRR, 30 minutes/session, 3 sessions/week) improves cardiorespiratory fitness, muscle strength, and QoL of individuals who receive continuous flow LVAD implantation within 6 months[66)]. Hayes et al. reported that exercise training that includes moderate-intensity aerobic exercise and resistance training (2 sets of 10 repetitions) is feasible and safe for patients with LVAD who can walk independently. Additionally, the combined aerobic and resistance training had a trend to greater improve exercise capacity and QoL of HF patients than mobilization training (walking at moderate intensity) alone[67)]. In conclusion, HF patients with circulatory support devices can still receive physical therapy safely and effectively although equipped with circulatory support devices suggests that the patient has a significantly impaired cardiac function. Appropriate physical therapy interventions improve the physical fitness, mobility ability, and QoL of HF patients with circulatory support devices.

Conclusions

The reduced cardiac output and poor ventilatory efficiency impair exercise tolerance of individuals with HF. The current evidence supports the safety and effectiveness of self-management and individualized exercise programs for individuals with HF. With proper exercise prescription and monitoring, patients with CHF, ADHF, or circulatory support devices can get benefit from physical therapy intervention. Worth noting, since the COVID-19 pandemic in 2019, it has been found that individuals with cardiovascular diseases are more vulnerable to COVID-19-related cardiac sequelae including HF. Therefore, physical therapists should be aware of the effects of COVID-19 on the cardiac function when treating patients with COVID-19 and pre-existing cardiovascular diseases.

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PHYSICAL THERAPY RESEARCH

REVIEW

Recent Findings in Physical Exercise for Cancer Survivors

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ABSTRACT. In recent years, the number of cancer survivors has been increasing each year due to advances in the early diagnosis and treatment of cancer. Cancer survivors present a variety of physical and psychological complications due to cancer and its treatment. Physical exercise is an effective nonpharmacological treatment for complications in cancer survivors. Furthermore, recent evidence has shown that physical exercise improves the prognosis of cancer survivors. The benefits of physical exercise have been widely reported, and guidelines for physical exercise for cancer survivors have been published. These guidelines recommend that cancer survivors engage in moderate- or vigorous-intensity aerobic exercises and/or resistance training. However, many cancer survivors have a poor commitment to physical exercise. In the future, it is necessary to promote physical exercise among cancer survivors through outpatient rehabilitation and community support.

Key words: Cancer survivor, Physical exercise, Complication, Prognosis

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The number of cancer cases is increasing every year. It is estimated that 19.3 million people worldwide were diagnosed with cancer in 2020[1)] and 28.4 million people will be newly diagnosed in 2040[1)]. In Japan, there were approximately 1,012,000 new cancer cases in 2020[2)]. In recent years, advances in cancer screening and treatment have led to improved survival rates and an increase in the number of cancer survivors[2,3)]. Furthermore, about half of the growing number of cancer survivors are elderly adults[2)]. The number of elderly cancer survivors will continue to grow as the population ages.

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Complications for Cancer Survivors

Cancer treatment is selected based on the type of tumor, site, stage, and pathological diagnosis. In addition, cancer treatment can affect nontarget tissues[4)] and cancer cells also adversely affect bodily functions[5)]. Therefore, cancer survivors experience various complications due to the effects of cancer and its treatment (Fig. 1).

A previous study has reported breast cancer survivors to have lower upper body muscle strength than healthy controls[6)]. Another study reported that 26 cancer survivors had significantly lower hand grip strength than age-matched healthy controls[7)]. These reports indicate that cancer survivors may have reduced muscle strength compared to healthy controls.

Cancer survivors may also have impaired balance function. In a study by Schmitt et al., cancer survivors exhibited longer mediolateral root mean square and increased center of pressure velocity compared to healthy controls[8)]. Another previous study reported that cancer survivors had lower Mini-Balance Evaluation Systems Test scores and longer Timed Up and Go test times compared to healthy controls[7,9)]. With eyes open, the area of the center of pressure was significantly larger in cancer survivors than in healthy controls[9)]. These findings

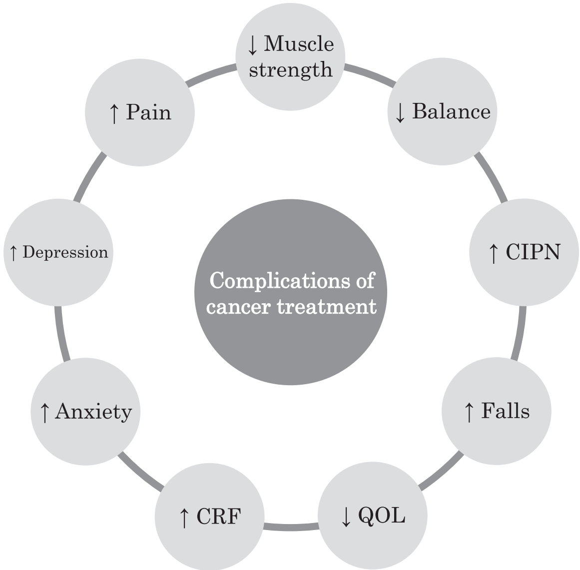

Fig. 1. Various complications of cancer treatment in cancer survivors

CIPN, chemotherapy-induced peripheral neuropathy; QOL, quality of life; CRF, cancer-related fatigue

indicate that cancer survivors have impaired balance function compared to healthy individuals. This lower balance function in cancer survivors may be related to chemotherapy-induced peripheral neuropathy (CIPN). CIPN presents primarily with sensory and motor neuropathy in the hands and feet[10]. A meta-analysis of 31 studies of 4179 cancer survivors showed that the prevalence of CIPN is 68.1% at one month, 60.0% at three months, and 30.0% at six months after chemotherapy[11]. CIPN also negatively affects physical functions such as upper and lower extremity function[12,13], gait[12,14], and balance function[14,15], and is one of the main concerns of cancer survivors.

Cancer survivors present with various physical symptoms, including pain, fatigue, and anxiety. The prevalence of pain in cancer survivors is 39.3% after curative treatment, 55.0% during anticancer therapy, and 66.4% during advanced/metastatic/terminally ill stages[16]. Cancer-related fatigue (CRF) is prevalent among cancer survivors and may continue to be experienced long after treatment[17]. Additionally, a study of the prevalence of anxiety and depression in 1154 adult cancer survivors showed that at six months post diagnosis, the prevalence of anxiety and depression was 22% and 13%, respectively, and then 21% and 13%, respectively, at 12 months[18].

Cancer survivors' complications negatively affect their quality of life (QOL). Previous studies have shown that cancer survivors have a lower QOL than healthy controls[19], and there is a significant association between muscle strength and QOL[19]. Kober et al. reported that cancer survivors with peripheral neuropathy had poorer balance function and lower QOL scores than those without peripheral neuropathy, particularly in the physical function domain[13]. On the other hand, another study reported that balance function in cancer survivors might have little effect on QOL[20]. Therefore, cancer survivors' muscle strength may more significantly impact their QOL than their balance function.

Elderly cancer survivors, as well as adult cancer survivors, present a variety of complications. In a previous study, 3766 elderly endometrial cancer survivors had more difficulty with walking and/or balance than an age- and race-matched group of women with no cancer history[21]. Another report showed that elderly breast cancer survivors had lower short physical performance battery scores, longer chair stand times, and lower grip strength than women of the same age without cancer[22]. Thus, elderly cancer survivors may have poorer physical function than healthy elderly adults.

Falls are a significant problem for elderly cancer survivors. A systematic review of falls in elderly cancer survivors reported a fall rate of 1.52%–3.41% per 1000 patient days for inpatients and 39%–64% for outpatients[23]. Furthermore, falls in elderly cancer survivors have been shown to impact subsequent cancer treatment negatively[23].

In summary, adult cancer survivors present with various complications and reduced QOL due to cancer and its treatment. In addition, elderly cancer survivors have poor physical function and a higher risk of falls.

Effects of Physical Exercise on Complications

Physical exercise is an effective nonpharmacological treatment for complications in cancer survivors (Fig. 2). A systematic review of 16 randomized controlled trials (RCTs) of cancer survivors undergoing active treatment showed that physical exercise, including aerobic exercise and/or resistance training, improved muscle strength more than usual care[24]. Another meta-analysis, including 48 RCTs with cancer survivors (n = 3632), showed that physical exercise significantly improved cardiopulmonary function[25]. In that study, 56% of physical exercise was aerobic[25].

The effectiveness of physical exercise for CIPN has also been evaluated. A systematic review and meta-analysis of five RCTs found that physical exercise significantly improved mean CIPN scores[26]. The physical exercises included resistance, balance, sensorimotor-based, and nerve gliding exercises[26]. In contrast, another meta-analysis found no effect of physical exercise on CIPN symptoms[27]. That study showed that physical exercise significantly positively affected physical function (muscle strength, balance function) and QOL in cancer survivors with CIPN[27].

The effects of physical exercise on physical symptoms in cancer survivors have been investigated. A meta-analysis of 10 RCTs found that physical exercise significantly improved physical symptoms such as fatigue, pain, dyspnea, and insomnia in cancer survivors compared to a healthy control group[28]. The types of physical exercise included aerobic, resistance, stretching, and walking[28]. A meta-analysis on the effects of pharmacotherapy, psychotherapy, and physical exercise on CRF was conducted[29], and showed that physical exercise significantly improved CRF compared to other treatments[29]. In studies of physical exercise (n = 69), 36 involved aerobic exercises, 13 involved anaerobic exercises, and 20 involved a combination

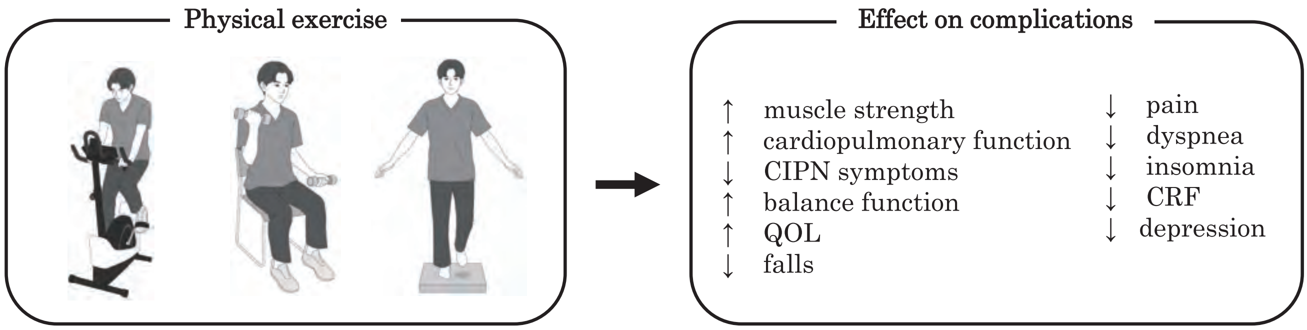

Fig. 2. Effects of physical exercise on complications in cancer survivors
CIPN, chemotherapy-induced peripheral neuropathy; QOL, quality of life; CRF, cancer-related fatigue

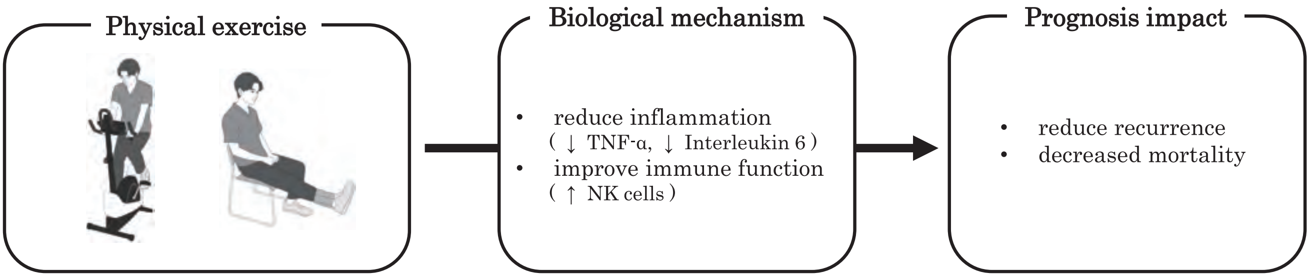

Fig. 3. Prognostic impact of physical exercise
TNF-α, tumor necrosis factor-α; NK, natural killer

of aerobic and anaerobic exercises[29]. Another meta-analysis of 37 RCTs of 2929 cancer survivors showed that physical exercise reduced depressive symptoms compared to standard treatment[30]. Exercise modalities included walking, yoga, stationary cycling, resistance bands, and weight machines[30].

Several studies have reported that physical exercise is an effective intervention for improving the QOL of cancer survivors. A meta-analysis of 16 RCTs showed that physical exercise significantly improved the QOL of cancer survivors compared to usual care[31]. Outcomes associated with QOL, such as fatigue and physical function, were also reported to improve with physical exercise[31]. In addition, another meta-analysis showed that physical exercise for cancer survivors during and after treatment significantly improved QOL and physical function compared to that for the control group[32]. Among the forms of exercise delivery in that study, supervised physical exercise was shown to have the largest positive impact on QOL and physical function[32]. Another study investigated the effects of physical exercise on various domains of cancer survivors' QOL[33], and the results showed that physical exercise improved global QOL, physical QOL, role QOL, and emotional QOL[33].

There is a lack of evidence on the effect of physical exercise on falls, a concern in elderly cancer survivors[34]. Currently, trials of physical exercise interventions are being tested in elderly cancer survivors to assess their ability to prevent falls[35].

In summary, many studies have suggested that physical exercise may improve muscle strength, cardiopulmonary function, CIPN symptoms, balance function, pain, dyspnea, insomnia, CRF, depression, and QOL in cancer survivors. Further research is needed on the effects of physical exercise on falls.

Prognostic Impact of Physical Exercise

Physical exercise has been shown to improve prognosis in cancer survivors (Fig. 3). Studies in the 2000s showed that physical activity improved the prognosis of breast and colorectal cancer survivors. For example, participation in physical activity after diagnosis reduced recurrence by 24% and mortality by 45% in breast cancer survivors[36]. Similarly, recurrence and mortality were reduced by 40% and 63%, respectively, among colorectal cancer survivors[37].

Since the 2010s, more systematic reviews and meta-analyses have been reported. A meta-analysis of 136 studies found evidence that cancer survivors with higher physical activity levels after diagnosis had reduced cancer-specific mortality[38]. In addition, a meta-analysis of RCTs on physical exercise among cancer survivors has been investigated[39]. Eight RCTs were included in the meta-analysis, and interventions were roughly classified into 2 categories: short-term interventions in the hospital (two weeks in duration) and outpatient or home-based interventions (2–8 months in duration)[9]. All physical exercises were aerobic and/or resistance training[39]. A meta-analysis revealed that physical exercise reduced cancer survivors' risk of recurrence by about 48% and the risk of mortality by about 24%[39].

The biological mechanisms for the prognostic effects of physical exercise have not yet been established. In 2016, the antitumor effects of physical exercise were demonstrated in animal studies[40]. In a mouse model, six weeks of physical exercise reduced the incidence and growth of several tumors (melanoma, liver cancer, and lung cancer)[40]. In addition,

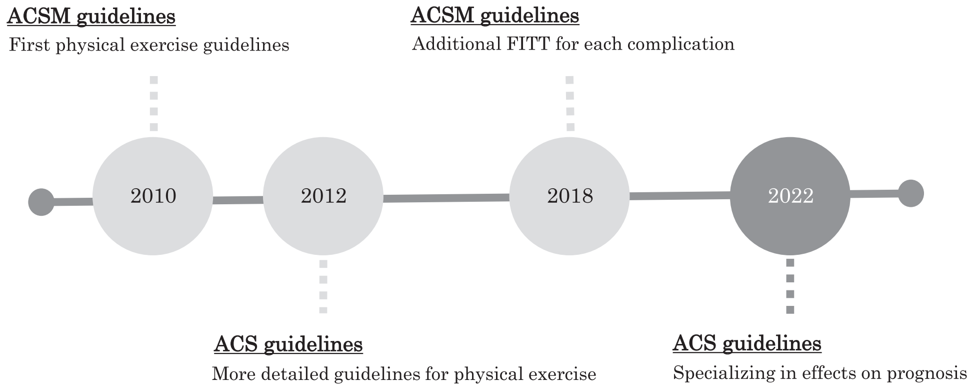

Fig. 4. History of physical exercise guidelines for cancer survivors

ACSM, American College of Sports Medicine; FITT, frequency, intensity, time, and type; ACS, American Cancer Society

physical exercise was shown to regulate tumor growth by increasing the number of natural killer (NK) cells[40]. The mobilization of NK cells involved interleukin-6, released from muscles as a result of physical exercise[40].

Studies of cancer survivors suggest that physical exercise may maintain NK cell function[41]. However, there is currently limited evidence to support the effects of physical exercise on NK cells in cancer survivors[42]. On the other hand, evidence for an anti-inflammatory effect of physical exercise in cancer survivors is becoming more evident[43]. A meta-analysis of 26 RCTs showed that physical exercise reduces inflammatory markers, particularly C-reactive protein levels and tumor necrosis factor-α production[43]. The anti-inflammatory effects of physical exercise were more pronounced in prostate and breast cancer survivors[43], and the most effective physical exercise program was a combination of aerobic and resistance training[43].

In summary, physical exercise has been shown to influence the prognosis of cancer survivors. Recently, meta-analyses using RCTs, not only cohort studies, have been conducted, and the evidence in this area is growing. On the other hand, the biological mechanisms of the exercise effect have not been established and require further study. Cancer recurrence is a significant concern for most cancer survivors[44]. Therefore, physical therapists need to provide physical exercise to improve the prognosis of cancer survivors in the future.

Physical Exercise Guidelines for Cancer Survivors

The American Cancer Society (ACS) and the American College of Sports Medicine (ACSM) have published recommendations on physical exercise for cancer survivors[45–49]. This chapter presents several guidelines (Fig. 4).

In 2010, the ACSM developed the first physical exercise guidelines for cancer survivors[46]. These guidelines reported strong evidence that physical exercise improves physical fitness, physical functioning, QOL, and CRF. However, there was insufficient evidence to establish a recommended amount of physical exercise. Therefore, based on the Physical Activity Guidelines for Americans, the guidelines recommend at least 150 minutes of aerobic exercise per week and resistance training at least two days per week.

In 2012, the ACS published more detailed recommendations for physical exercise[47]. Adult cancer survivors are recommended to perform 150 minutes per week of aerobic exercise at a moderate intensity or 75 minutes per week at a vigorous intensity, plus resistance training for major muscle groups at least two days per week. Elderly cancer survivors should follow the recommendations of adult cancer survivors if possible, but if there are limitations, it is recommended that they exercise whenever possible and avoid prolonged physical inactivity.

In 2019, the ACSM released new physical exercise recommendations for cancer survivors[48]. These guidelines provided recommendations and frequency, intensity, time, and type (FITT) for various complications in cancer survivors. Specifically, they reported strong evidence to support the effectiveness of physical exercise for anxiety, depressive symptoms, CRF, health-related QOL, lymphedema, and physical function. The guidelines also provided moderate evidence for bone health and sleep and insufficient evidence for cardiotoxicity, CIPN, cognitive function, falls, nausea, pain, sexual function, and treatment tolerance. For FITT, the introductions focused mainly on outcomes in the strong evidence category. For most, 30 minutes of aerobic exercise three times a week is an effective exercise prescription. Resistance training, which consists of two or more sets of 8–15 repetitions at 60% or more of the maximum number of repetitions per session at least twice a week, has also been equally effective. Because cancer survivors have sequelae and comorbidities, individualized goals are recommended.

In 2022, the ACS published the latest recommendations for physical exercise[49]. The purpose of these ACS guidelines was to provide recommendations for physical exercise (including nutrition) to improve prognosis. For physical exercise, the studies included systematic reviews, meta-analyses, cohort studies, and RCTs (sample sizes of at least 200 participants) published in 2018 or later. The review revealed that nine studies met the inclusion criteria and that physical exercise is recommended for breast, colorectal, and prostate cancer survivors to improve prognosis. There is currently limited evidence for the prognostic impact of physical exercise on survivors of gynecologic, lung, hematologic, and pediatric cancers. In addition, these guidelines recommend 150–300 minutes per week for adult cancer survivors at moderate intensity, 75–150 minutes of physical exercise at vigorous intensity, and resistance training at least two days per week. Children and adolescents should perform at least one hour of moderate- or vigorous-intensity physical exercise daily. Compared to the 2012 ACS guidelines, the recommended amount of physical exercise has been increased, and recommendations for cancer survivors in the adolescent and young adult generation have been added.

In summary, the guidelines for physical exercise for cancer survivors recommend that physical exercise should include aerobic exercise, resistance training, or a combination of both. In recent years, the guidelines have also shown that physical exercise can improve the prognosis of cancer survivors. Recommended physical exercise is provided, but cancer survivors have various complications and should be evaluated individually.

Future Directions

Physical exercise is a critical nonpharmacological therapy to improve complications and prognosis in cancer survivors. However, most cancer survivors lack compliance with physical exercise[50–52]. A previous study reported that in 102 cancer survivors, the amount of physical exercise significantly decreased after cancer diagnosis and remained decreased during treatment[50]. Another report indicated that only 38% of 72 cancer survivors were able to meet 90 to 150 minutes of moderate to vigorous exercise per week and only 10% were able to perform resistance training twice per week[51]. The amount of physical exercise over ten years for 631 breast cancer survivors was also studied, and the results showed that 7.8% met the guidelines for physical exercise at all follow-up periods[52]. Thus, many cancer survivors lack compliance with physical exercise.

ACSM guidelines recommend supervised physical exercise for cancer survivors[48]. However, in Japan, outpatient rehabilitation for cancer survivors is not covered by medical fees, and the implementation rate of outpatient rehabilitation is 39.1%[53]. Therefore, a medical fee revision is needed to promote outpatient cancer rehabilitation.

Elderly cancer survivors have limited mobility[54]. Therefore, community support is essential for cancer survivors. However, only 39.1% of the hospitals in Japan designated as cooperative cancer treatment centers have regional cooperation[53], and only 9.8% have established a regional cooperation path[53]. In the future, regional cooperation should be promoted to support cancer survivors regarding physical exercise.

Conclusions

Cancer survivors present not only physical complications, such as low muscle strength and balance function, but also psychological complications, such as anxiety, depression, and CRF, as a result of cancer and its treatment. Furthermore, these complications negatively affect QOL. Elderly cancer survivors likewise present a variety of complications, and falls are a significant problem. Physical exercise can improve physical and psychological complications in cancer survivors. Recently, physical exercise has even been shown to improve the prognosis of cancer survivors. The ACSM and ACS guidelines for cancer survivors recommend physical exercises such as aerobic exercise and resistance training to improve complications and prognosis. However, most cancer survivors lack compliance with physical exercise. To promote physical exercise among cancer survivors, inpatient rehabilitation alone is insufficient. In the future, outpatient rehabilitation and community support should be used to promote physical exercise among cancer survivors after discharge.

Conflict of Interest: The authors declare no conflict of interest.

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PHYSICAL THERAPY RESEARCH

ORIGINAL ARTICLE

Characteristics of Older Patients with Heart Failure Readmitted due to Acute Exacerbations within the Past Year

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ABSTRACT. Objective: We aimed to examine the relationship between physical performance and readmission among older patients with heart failure (HF) over the past year. Methods: This retrospective cohort study included 325 patients with HF who were aged ≥65 years and were hospitalized for acute exacerbation between November 2017 and December 2021. We investigated age, sex, body mass index, length of hospital stay, initiation of rehabilitation, New York Heart Association (NYHA) class, Charlson comorbidity index (CCI) score, medications, cardiac/renal function, nutrition, maximal quadriceps isometric strength, grip strength, and Short Physical Performance Battery (SPPB) score. Data were analyzed using the χ^2 test, Mann–Whitney U test, and logistic regression analysis. Results: Altogether, 108 patients met the inclusion criteria and were divided into the non-readmission (n = 76) and readmission (n = 32) groups. The readmission group exhibited longer hospital stay, more severe NYHA class, higher CCI score, higher brain natriuretic peptide (BNP) levels, lower muscle strength, and lower SPPB score compared to the non-readmission group. In the logistic regression model, BNP level and SPPB score were independent factors associated with readmission. Conclusion: BNP level and SPPB score were associated with readmission in patients with HF within the past year.

Key words: Heart failure, Older adults, Readmission, Short Physical Performance Battery, Brain natriuretic peptide

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The number of older adults is increasing throughout the world. In Japan, it has been reported that older adults account for 28.4% of the total population[1,2)]. An increase in the incidence of heart failure (HF) due to aging has become a major problem. According to a previous study, the estimated prevalence of HF in the United States is 5.1 million, which is predicted to increase to 8 million by 2030[3)]. A previous Japanese study estimated that the total number of patients with left ventricular dysfunction in Japan (both systolic and diastolic dysfunction) would increase from 979,000 in 2005 to 1,284,000 by 2030[4)]. Patients with HF encounter problems such as increased readmission rates, increased medical costs, and multiple short-term hospitalizations[5,6)].

HF is a major cause of hospitalization and death among older adults worldwide[7)]. Factors related to readmission of patients with HF include exacerbation of HF as well as various conditions such as respiratory diseases, kidney diseases, psychiatric diseases, bone and joint diseases, and diabetes[8,9)]. Shiraishi et al. reported that 5.4% of the patients with HF were readmitted within 30 days, while 26.2% of them were readmitted within 1 year[10)]. In addition, according to the Rationale and Design of Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD), the readmission rate among patients with HF was as high as 35% within 1 year[11)], indicating a high risk of readmission among these patients within 1 year. Furthermore, patients with HF have to bear high medical costs, and it has been reported that patients with higher serum N-terminal pro-brain natriuretic peptide levels have to bear higher medical costs associated with hospitalization[12,13)]. Thus, reducing the readmission rate of patients with HF would reduce the medical costs.

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In recent years, many reports have shown that the Short Physical Performance Battery (SPPB) is useful for functional evaluation of older patients, and a meta-analysis revealed that an SPPB score of <10 points is an excellent predictor of all-cause mortality[14–16]. In addition, the SPPB score has also been reported to predict future decline in the activities of daily living (ADLs) among older adults[17]. The SPPB score at discharge may be useful in predicting future decline in the ADLs and readmission among patients with HF.

Therefore, we hypothesized that the SPPB score may be a strong predictor of readmission among patients with HF, and patients with HF having low SPPB scores would have been repeatedly hospitalized and discharged within the past year.

Methods

Participants

The present study was a single-center cross-sectional study. This retrospective cohort study included 325 patients with HF admitted to a community-based hospital in Kumamoto, Japan, for acute exacerbations from November 2017 to December 2021. An experienced cardiologist diagnosed acute decompensated HF based on the Framingham criteria and Japanese guidelines[18]. The inclusion criteria were age ≥65 years and ability to walk with assistance at discharge. Patients who did not consent to participation, patients who died during hospitalization, patients who were transferred to another hospital, and patients in a poor general condition that could have caused difficulties while conducting the measurements were excluded from this study. All participants in this study underwent cardiac rehabilitation.

Investigations

Patient characteristics and clinical parameters at discharge such as age, sex, body mass index (BMI), length of hospital stay, initiation of rehabilitation, New York Heart Association (NYHA) class, Charlson comorbidity index (CCI) score, comorbidities, medications, left ventricular ejection fraction (LVEF), brain natriuretic peptide (BNP), creatinine (Cr), blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), hemoglobin (Hb), albumin (Alb), geriatric nutritional risk index (GNRI) score, maximal quadriceps isometric strength (QIS), grip strength, and SPPB score were investigated by reviewing the medical records. LVEF was not measured at discharge in many patients. Therefore, we used the data at admission. According to the Japanese guidelines, it has been shown that 60%–80% of the patients with HF having reduced ejection fraction and 60%–90% of the patients with HF having preserved ejection fraction have HF with unchanged LVEF[19].

Assessment of the NYHA class, maximal QIS, and grip strength

We evaluated the maximal QIS, grip strength, and NYHA class at discharge. The NYHA class was determined by an experienced cardiologist and a physiotherapist specializing in cardiac rehabilitation.

The maximal QIS was measured using a handheld dynamometer (Mobie MT-100; SAKAI, Tokyo, Japan). Patients sat on a chair with their arms folded and knees flexed at 90°. The pad position was established at 30 mm above the lateral malleolus in all patients. Knee extension strength was measured twice on both the right and the left sides with maximum force. We used the maximum value multiplied by the leg length and divided by the body weight (Nm/kg).

Grip strength was measured to evaluate the upper limb muscle strength. A digital grip force meter (Grip D T.K.K. 5401; Takei Scientific Instruments, Niigata, Japan) was used to measure grip strength. The measurements were performed according to the method recommended by the Ministry of Education, Culture, Sports, Science, and Technology[20]. However, since many patients were unstable in the standing posture, measurements were performed in the sitting position. The maximum grip strength was measured twice on each side and the highest value was used.

Assessment of the SPPB score

The SPPB score was assessed based on standing balance, 4-m walking velocity, and time to rise five times from the seated position[14]. Participants were asked to hold each of the three standing positions, namely closed-leg standing, semi-tandem stance (heel of one foot touching the base of the toe of the other foot), and full tandem stance (heel of one foot directly touching the other toe) for 10 s during the assessment for balance. Walking velocity was measured using a 4-m walk performed at the patient's usual pace. Participants were allowed to use canes or walkers. For measurement of time to rise from the seated position, participants sat on a chair with their arms folded across their chest and stood up five times consecutively as quickly as possible. The time taken to complete this maneuver was measured.

These tasks were assigned scores from 0 to 4 according to the established methods. The scores from the three tasks were added to obtain the total SPPB score (range: 0–12). A higher score indicated better physical performance.

Statistical analysis

Continuous variables such as patient characteristics and clinical parameters were expressed as mean ± standard deviation. Categorical variables were expressed as numbers (percentages). Normality of distribution for continuous variables was evaluated using the Shapiro–Wilk test. Patients with HF were divided into two groups based on readmission within the past year. Baseline characteristics and physical function were compared using the Mann–Whitney U test and χ^2 test. Logistic regression analysis was performed to evaluate whether patient characteristics, clinical parameters, and physical function at discharge were associated with readmission within the past year. A model was constructed using a stepwise forward selection procedure based on Akaike's information criterion. The explanatory variables used in this model were those that showed statistical significance in the univariate analysis ($P < 0.05$).

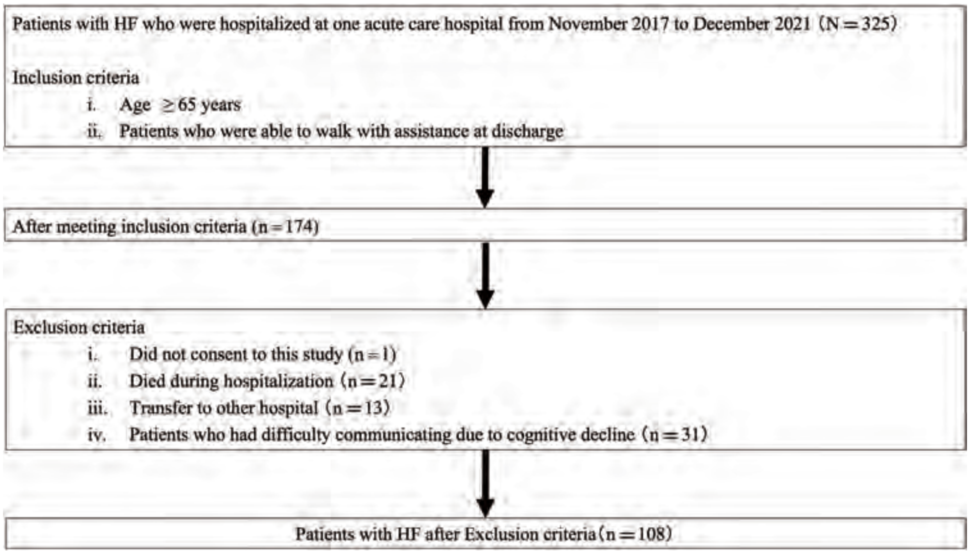

Fig. 1. Flowchart of patient selection
HF, heart failure

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Core Team, 2022). Specifically, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics[21].

Ethical consideration

This study was approved by the Ethics Committee of the Medical Corporation Tanakakai Musashigaoka Hospital (no. H30-3) and complied with the principles of the Declaration of Helsinki.

Results

Patient characteristics and clinical parameters

A flowchart of patient selection is shown in Figure 1. Among 325 patients hospitalized with HF, 174 met the inclusion criteria. Sixty-six patients were excluded for not providing consent (n = 1), death during hospitalization (n = 21), transfer to another hospital (n = 13), and poor general condition that might have caused difficulties in measurements (n = 31). Finally, 108 patients were included and divided into the non-readmission group (n = 76) and readmission group (n = 32). Table 1 shows the clinical characteristics of all patients and the results of the comparison between the groups.

The mean age of the patients was 85.5 ± 7.2 years, and 50% were female. Altogether, 34 patients were over 90 years of age. There were no significant differences in age, sex, BMI, and time from admission to the start of rehabilitation between the readmission and non-readmission groups. Patients in the readmission group had a significantly longer hospital stay compared to those in the non-readmission group. All patients enrolled in this study were classified into NYHA classes II and III. The readmission group exhibited significantly higher severity of NYHA class than the non-readmission group.

Significant differences were observed in the CCI scores between the groups. However, the incidence of comorbidities such as hypertension, diabetes, atrial fibrillation, valvular disease, and ischemic heart disease was not significantly different between the groups.

No significant differences were observed in the use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or diuretics between the readmission and non-readmission groups.

No significant differences were observed in the LVEF, Cr level, BUN level, or eGFR. However, BNP was significantly higher in the readmission group than in the non-readmission group. No significant differences were observed in the Hb level, Alb level, or GNRI between the groups.

The maximal QIS, grip strength, and SPPB were significantly lower in the readmission group than in the non-readmission group.

Independent factors associated with readmission

Table 2 shows the results of the logistic regression analysis. The NYHA class, BNP level, maximal QIS, grip strength, and SPPB score were selected as explanatory variables and analyzed using stepwise selection. BNP level and SPPB score were identified as independent factors associated with readmission within the past year.

Discussion

In the present study, we examined the factors associated with readmission of patients with HF within the past year in Japan, which is becoming a super-aging society. Reportedly, ADLs are associated with readmission in Japan, and the presence or absence of sarcopenia affects the prognosis[22–25]. The

Table 1. Comparison between the two groups of clinical parameters, comorbidity, medication, cardiac function, laboratory data, nutrition, and physical function of all participants

	All (N = 108)	Non-readmission (n = 76)	Readmission (n = 32)	P-value
Clinical parameter				
Age (years)	85.5 ± 7.2	84.5 ± 7.8	87.7 ± 4.9	0.058
Sex (female), number (%)	54 (50.0)	41 (53.9)	19 (59.4)	0.292
BMI (kg/m^2)	22.1 ± 4.2	22.1 ± 4.5	21.9 ± 3.5	0.719
Length of hospital stay (days)	30.0 ± 17.6	28.2 ± 16.5	34.4 ± 19.1	0.042
Initiation of rehabilitation (days)	6.0 ± 4.6	6.0 ± 5.1	5.9 ± 3.0	0.206
NYHA (I/II/III/IV), number	0/68/40/0	0/54/22/0	0/14/18/0	0.007
Comorbidity				
CCI	2.7 ± 1.3	2.5 ± 1.4	3.1 ± 1.0	0.008
HT, number (%)	91 (84.3)	61 (80.3)	30 (93.8)	0.090
DM, number (%)	71 (65.7)	49 (64.5)	22 (68.8)	0.825
Af, number (%)	66 (61.1)	42 (55.3)	24 (75.0)	0.082
Ischemic heart disease, number (%)	63 (58.3)	43 (56.6)	20 (62.5)	0.671
Valvular disease, number (%)	64 (59.3)	43 (56.6)	21 (65.6)	0.402
Medication				
β-blocker, number (%)	58 (53.7)	40 (52.6)	18 (52.3)	0.833
ACE-I/ARB, number (%)	54 (50.0)	41 (53.9)	13 (40.6)	0.292
Diuretic, number (%)	84 (77.8)	56 (73.7)	28 (87.5)	0.135
Cardiac function				
LVEF (%)	59.8 ± 14.1	59.6 ± 14.2	60.4 ± 13.8	0.724
Laboratory data				
BNP (pg/mL)	319.8 ± 225.8	284.0 ± 216.3	404.9 ± 225.0	0.010
Cr (g/dL)	1.3 ± 0.6	1.2 ± 0.5	1.4 ± 0.7	0.157
BUN (g/dL)	26.9 ± 13.3	26.1 ± 13.4	28.9 ± 13.0	0.142
eGFR (mL/min/1.73 m^2)	42.7 ± 17.3	44.4 ± 17.5	38.7 ± 16.1	0.176
Hb (g/dL)	11.5 ± 1.9	11.6 ± 2.0	11.3 ± 1.7	0.514
Nutrition				
Alb (g/dL)	3.4 ± 0.5	3.4 ± 0.5	3.3 ± 0.4	0.060
GNRI	89.3 ± 8.9	89.9 ± 9.3	88.0 ± 7.8	0.180
Physical function				
Maximal QIS (Nm/kg)	0.8 ± 0.3	0.9 ± 0.3	0.7 ± 0.3	0.015
Grip strength (kg)	17.5 ± 6.1	18.3 ± 6.2	15.5 ± 5.5	0.034
SPPB	6.6 ± 3.6	7.5 ± 3.5	4.5 ± 3.0	<0.001

Values are presented as mean ± standard deviation or number (percentage).

BMI, body mass index; NYHA, New York Heart Association functional classification; CCI, Charlson comorbidity index; HT, high blood pressure; DM, diabetes mellitus; Af, atrial fibrillation; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; Cr, creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; Alb, albumin; GNRI, Geriatric Nutritional Risk Index; QIS, quadriceps isometric strength; SPPB, Short Physical Performance Battery

readmission group in the present study exhibited higher NYHA class, more comorbidities, higher BNP levels, and lower physical function and physical performance than the non-readmission group. Furthermore, BNP level and SPPB score were identified as independent risk factors for readmission in the multivariate analysis. The mean age of patients in the present study was 85.5 ± 7.2 years, which was higher than that reported in previous studies[22–24]. In Japan, no definite view has been obtained about the effect of cardiac rehabilitation on older patients with HF, and the influence of physical performance of older patients with HF on the risk of readmission within the past year is unknown. The main finding of the present study was that physical performance affected the risk of readmission within the past year in older patients with HF having an average age of 85 years or above, suggesting the importance of cardiac rehabilitation in these patients.

BNP is a cardiac hormone synthesized in the ventricles and a biomarker that sensitively reflects the load on the

Table 2. Odds ratio of factors related to hospital readmission by logistic regression analysis

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Length of hospital stay	1.020	0.996–1.040	0.100			
NYHA	3.160	1.340–7.430	0.008			
CCI	1.330	0.977–1.820	0.069			
BNP	1.000	1.000–1.000	0.013	1.000	1.000–1.000	0.039
Maximal QIS	0.123	0.024–0.623	0.011			
Grip strength	0.923	0.857–0.995	0.036			
SPPB	0.773	0.674–0.886	<0.001	0.776	0.674–0.895	<0.001

OR, odds ratio; CI, confidence interval; NYHA, New York Heart Association; CCI, Charlson comorbidity index; BNP, brain natriuretic peptide; QIS, quadriceps isometric strength; SPPB, Short Physical Performance Battery

ventricles[26–29]. Previous studies have reported that a high BNP level at discharge is associated with higher readmission rates and mortality[30]. BNP is secreted by the myocardium in response to wall stress, and it is affected by various factors. For example, obesity lowers the BNP levels, whereas aging, atrial fibrillation, and worsening renal function increase the BNP levels[31–34]. There was no significant difference in BMI and renal function between the readmission non-readmission groups in the present study. In addition, BNP level was found to be an independent risk factor for readmission in the multivariate analysis. However, the odds ratio was 1.000 (95% confidence interval: 1.000–1.000), and further research is needed to determine how BNP affects readmission in patients with HF.

Patients with HF having low physical performance are more likely to be readmitted due to the increased cardiac load required for daily activities after discharge. Additionally, patients with HF may have decreased physical performance after discharge and may be readmitted due to events such as cardiovascular diseases, respiratory diseases, exacerbation of orthopedic diseases, and falls[22]. Previous studies have reported a relationship between readmission and ADLs[22], which is influenced by physical performance (such as that determined using the SPPB score) and may result in a decline in ADLs due to inactivity caused by decreased physical capacity. A previous study reported that the SPPB score is a useful predictor of future decline in ADLs among older adults[17]. Therefore, the SPPB score at discharge is considered an important factor for predicting the risk of readmission. Long-term inactivity during hospitalization makes daily life after discharge difficult due to deterioration of physical function including muscle strength and exercise tolerance and concomitant deterioration of ADLs. Therefore, it is important to improve physical function, physical performance, and ADLs by introducing cardiac rehabilitation during acute treatment of patients to reduce the risk of readmission.

In Japan, people aged ≥90 years are defined as "super-elderly"[35]. The present study included 34 patients aged ≥90 years, accounting for more than 30% of all patients. Our data may be important for preventing readmission among older adults with HF. Reports of early readmission (90–180 days) after discharge have increased over the past few years[22,24,36], but very few studies have followed patients for longer periods. It is clear that Japanese patients with HF are at a high risk of readmission within 1 year[13]. The readmission rates in previous studies were 5.4% within 30 days, approximately 20% within 90 days, approximately 24% within 180 days, and 26%–35% within 1 year; and the risk of readmission increased with increasing observation period[10,11,22,36]. Therefore, continued follow-up after preventing early readmission is important. Moreover, results of the present study suggest the importance of cardiac rehabilitation to maintain physical performance. However, in Japan, there is insufficient evidence on the effectiveness of cardiac rehabilitation in older patients with HF, and very few studies have investigated the relationship between physical performance and readmission. Thus, further research is required on this topic.

Limitations

This study has some limitations. It was a single-center study with a small sample size. To avoid sampling bias, we randomly selected participants from both the groups. Based on the inclusion and exclusion criteria, only 33.2% of the patients with HF who were hospitalized for acute exacerbations were included in this study. Therefore, the results of this study may not be generalizable to other patients with severe HF. A detailed evaluation of frailty and body composition could not be conducted. Frailty and sarcopenia have been shown to affect the prognosis of patients with HF[37,38]. Therefore, detailed assessment of frailty and sarcopenia may be necessary. The present study did not evaluate left ventricular diastolic function. The effects of cardiac rehabilitation interventions have not been investigated. Determining the effects of cardiac rehabilitation is an important issue in Japan, where the average age of the population is expected to increase in the future. Studies that consider the interventional effect of cardiac rehabilitation are required to prevent readmission.

Conclusion

Patients who were readmitted due to exacerbation of HF within the past year exhibited longer hospital stays, multiple comorbidities, higher NYHA class, higher BNP levels, and lower physical performance than those from the non-readmission group. In addition, the multivariate analysis showed that BNP level and SPPB score were associated with readmission for HF.

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PHYSICAL THERAPY RESEARCH

ORIGINAL ARTICLE

A Standing Low-frequency Vibration Exercise Device for Improving Balance in Community-dwelling Older Adults: A Single-blind Randomized Controlled Trial

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ABSTRACT. Objective: This study aimed to compare the effects of the standing low-frequency vibration exercise device (SLVED) and walking training on balance ability on an unstable surface in community-dwelling elderly people. Methods: Thirty-eight older adults were randomly allocated to the SLVED sessions: the intervention group (n = 19), and the walking sessions: the control group (n = 19). Each group session lasted 20 min and was performed twice a week for 12 weeks. Standing balance was assessed by the change in center-of-gravity sway of the participant standing on foam rubber with eyes open (EO) and eyes closed (EC). The primary outcome measures were the root mean square (RMS) values of the center of foot pressure in the mediolateral and anteroposterior directions and the RMS area. Secondary outcome measures were the results of the 10-m walking time test (10 MWT), five-times sit-to-stand (5T-STS) test, and timed up-and-go (TUG) test. Results: Analysis of variance showed a significant group × time interaction for the TUG test. Significant improvements were observed in Y-RMS for EO condition; RMS, X-RMS, Y-RMS, and RMS area for EC condition; and 10 MWT, 5T-STS test, and TUG test for the main effect of the time factor. Conclusion: SLVED for intervention in community-dwelling older adults showed a greater improvement than walking training in the TUG test. In addition, SLVED improved the Y-RMS for the EO condition on foam rubber; RMS, X-RMS, Y-RMS, and RMS area for the EC condition on foam rubber in standing balance; and the 10 MWT and 5T-STS test, suggesting that it has similar effects to walking training.

Key words: Older adults, Standing low-frequency vibration exercise device, Standing balance

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Falls can reduce activities of daily living and increase nursing care due to trauma, such as fractures in older adults[1)]. Therefore, preventing falls in the elderly is essential to extend life expectancy and maintain quality of life. Previous studies have reported that a program comprising both balance training and muscle-strengthening exercises is effective at preventing falls in the elderly[2,3)]. However, most balance exercises are static and dynamic balance tasks in which the sensory input and ground surface are altered. These programs lack specificity for active community-dwelling older adults and may lack efficacy in reducing and preventing falls. To achieve effective balance training, it is essential to set tasks with an appropriate level of difficulty based on the subject's ability.

Progressive balance exercises to prevent falls in daily life include step and equipment training. Step training can contribute to falling prevention by performing "correct," "fast," and "directional" steps[4)]. In addition, step practice under unstable conditions has been developed[5)]. However, there is a trade-off between the difficulty of balance training and the risk of falling, and step training has a higher risk of

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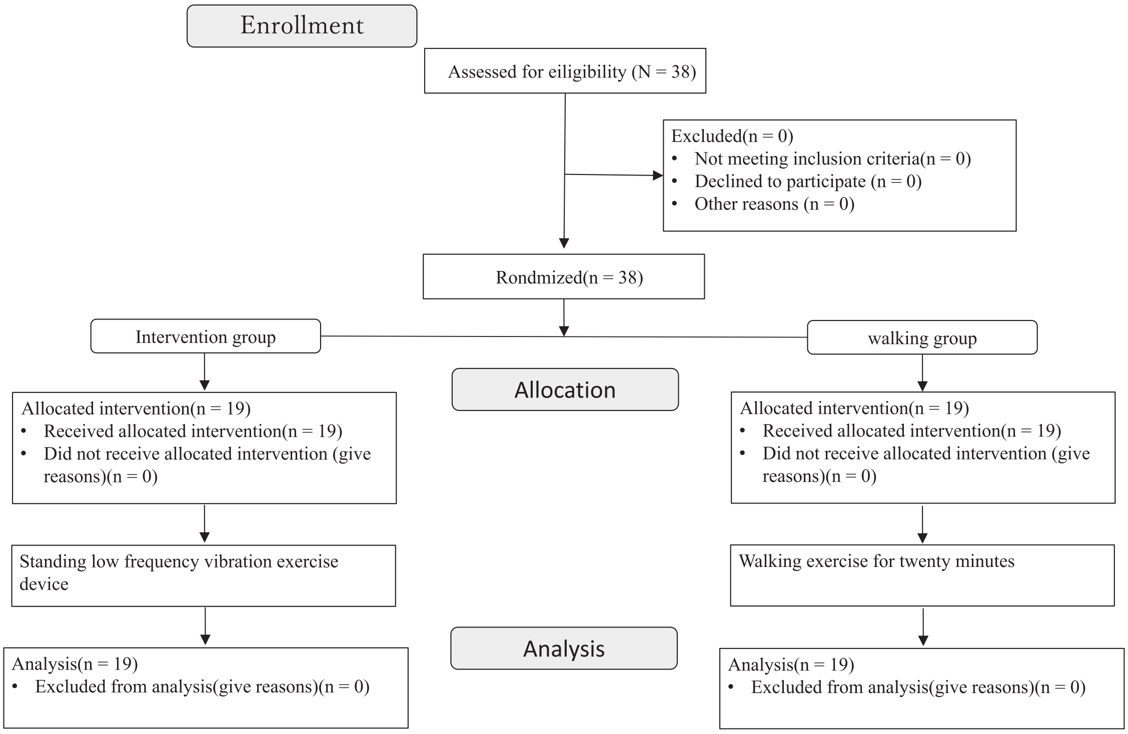

Fig. 1. Flow diagram of the study

Participants were randomly allocated to the intervention group (SLVED) or walking group (walking exercise for twenty minutes).

SLVED, standing low-frequency vibration exercise device

falling than static or dynamic balance tasks. Safe and effective balance-training equipment has been developed to address these issues. In addition, vibration stimulation interventions have been applied to improve balance.

A systematic review reported that a focused vibration device could effectively decrease the risk of falls and improve balance in the elderly[6,7]. It was also reported that direct vibratory stimulation helped standing balance in community-dwelling older adults with eyes closed (EC)[8]. However, previous stimulation methods, such as local stimulation of the Achilles tendon to activate sensation and stimulation from the sole in the standing position, are difficult to apply in combination with walking. Recently, passive exercise devices have been designed to improve walking ability. One product employing this method is the standing low-frequency vibration exercise device (SLVED)[9]. The primary characteristic of SLVED is that it focuses on the movement of the lower limbs during the walking motion and incorporates the composite motion of (1) rocking stimulus in the left–right direction to shift the center of pressure (COP) to the stance leg side; (2) back-and-forth movement stimulus in the opposite phase; and (3) plantar dorsiflexion motion of the ankle joint to kick the ground during the terminal stance. A prior study showed that balance training with SLVED increases walking speed and improves ankle plantar dorsiflexion muscle strength and one-legged stance with EC condition[9]. Thus, although the effects of SLVED on the motor system have been verified, its effects on sensory strategies in postural control have not been investigated. The modified Clinical Test of Sensory Interaction and Balance measures body sway in four different conditions to assess the dominance of the visual, somatosensory, and vestibular senses in controlling standing posture[10]. It has also been suggested that the Berg Balance Scale static standing on a hard floor and sit-to-stand is not suitable for assessing balance ability in older adults with high activity levels[11]. In contrast, the percentage of those unable to perform foam rubber static standing for 30 s in the EC condition, where the floor surface is unstable, increases in those over 60 years of age, and cutoff values for fall risk have also been reported[12]. Therefore, we consider that the static standing balance of foam rubber could be used to evaluate the balance ability in sensory strategies of active community-dwelling older adults.

The SLVED was developed as a balance-training device that allows the safe performance of movements that simulate walking. Therefore, this study aimed to compare the effects of SLVED and walking training on standing balance on an unstable surface in community-dwelling older adults with walking independence in a randomized controlled trial.

Methods

Study design

The study was designed as a 12-week single-blind randomized controlled trial with parallel arms, in which the raters were blinded. A flowchart describing the recruitment of participants and the study flow is presented in Figure 1. The participants were randomly assigned to SLVED sessions (intervention group) or walking sessions (control group) using a random number table created using the Rand function in Excel, and adjusted for sex and age. The assessments were conducted on day 1 (baseline and before session 1) and after 12 weeks, on day 7.

Participants

We enrolled 38 mentally capable people aged 65 years and older who could walk independently without the use of assistive aids. The exclusion criteria were as follows: history of neurological disease or orthopedic disease of the trunk and lower limbs, movement disorders, or diseases limiting their activities. Demographic characteristics included age, height, weight, body mass index, and Hasegawa Dementia Scale-Revised (HDS-R).

Participants provided written informed consent after receiving an explanation of the study. The study was begun after obtaining approval from the ethical review committee of International University of Health and Welfare to which we belong (approval number: 19-Ifh-088).

Outcome measures

The primary outcomes to measure an improvement in the standing balance of participants with eyes open (EO) and EC conditions were the root mean square (RMS) amplitude of COP trajectories over time, in both the mediolateral (COP-X) direction for calculating X-RMS and anteroposterior (COP-Y) direction for calculating Y-RMS. The RMS area was also calculated.

The Twingravicoder G-6100 (ANIMA, Tokyo, Japan) and foam rubber CGT balance pad (IP-B6000, size: 540 mm × 478 mm × 74 mm; Inter Reha, Tokyo, Japan) were used to measure standing balance. These devices were used to measure the change in the degree of COP sway of the participant standing on the foam rubber under EO and EC conditions. The system recorded COP trajectories over time in both the mediolateral (COP-X) and anteroposterior (COP-Y) directions, at a sampling frequency of 20 Hz for 1 minute. One measurement was taken for each EO and EC condition. Participants stood on the foam rubber with both feet together. For the EO condition test, a target diameter of approximately 2 cm was placed 2 m in front of the subject at the eye level. A researcher instructed each participant to stand as still as possible while looking forward and keeping their arms relaxed at their sides. Participants were instructed to focus on the target as the recordings were taken. The steps for the EC condition test were the same, but without viewing the target. The RMS value (cm) of the amplitude was calculated for the COP, the X-RMS value (cm) of the amplitude was calculated for COP-X, and the Y-RMS value (cm) of the amplitude was calculated for COP-Y. The RMS area (cm^2) was calculated as the area of a circle ($\pi \times RMS^2$), with the RMS value as the radius.

Secondary outcome measures were the 10-m walking time test (10 MWT), five-times sit-to-stand (5T-STS) test, and timed up-and-go (TUG) test. During the 10 MWT, a stopwatch

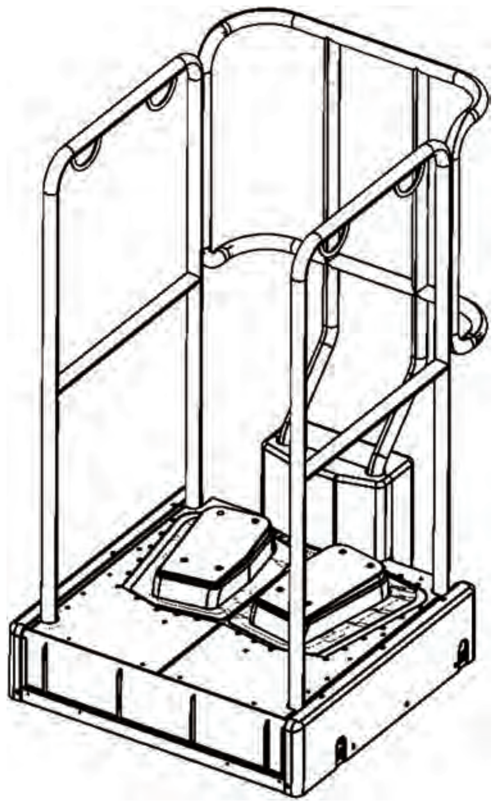

Fig. 2. Original standing low-frequency vibration exercise device

was used to measure time while the participants walked at the maximum speed. The maximum 10 MWT was measured twice, and the best of the two results was used[13]. The 5T-STS test is used as an index of lower-limb muscle strength in the elderly[14,15]. In this test, the time taken for the participant to perform five STS repetitions on a standardized armless chair (0.40 m height) is measured. The participants were instructed to perform STS repetitions as rapidly as possible from a chair sitting position to a full standing position, with arms crossed over the chest. For the STS test, a stopwatch was used to measure the time until the participants sat down in their chairs after the fifth stand-up session to the nearest 0.01 s.

To measure TUG, the participant stood up from the armchair, walked 3 m, turned around, walked again, and recorded the time it took to sit down using a stopwatch[16]. The TUG test was performed twice, and the best of the two results was used.

Intervention

A physiotherapist monitored both groups twice a week for 12 weeks. Participants in the intervention group stood on the SLVED for 15 minutes, for two sessions a week, totaling 24 sessions, while participants in the control group walked at a fast pace for 20 minutes, for two sessions a week, for a total of 24 sessions. A physiotherapist monitored both groups during the intervention. The SLVED 3D system Rakuraku Balance (Cotoho, Osaka, Japan) was set to shake participants at a frequency of 1.6 Hz (Fig. 2). The distance between the left and right footplates was 25 cm and the foot angle was 10°. The range of motion of the step on which the feet were placed was 10 mm forward and backward, 38 mm right and left, 5.5° plantar flexion, and 10.5° dorsiflexion. The footplate movement consisted of backward translation and dorsiflexion while shifting the center of gravity in the left and right movements, and forward translation and plantar flexion on the opposite side, which was performed in the reverse phase on the left and right sides. Subjects were instructed to maintain a standing position on their left and right footplates.

Statistical analysis

Statistical analyses were performed using SPSS Statistics (version 25.0; IBM, Armonk, NY, USA). A non-paired t-test was conducted to compare the demographic characteristics and baseline outcomes between the intervention and control groups. In addition, analysis of variance (ANOVA) with a split-plot design was performed for comparison before and after the intervention (time factor), comparison of the intervention groups (group factor), and interaction (time × group).

The effect sizes (eta squared, η_p^2) were calculated for the main and interaction effects. The eta-squared (η_p^2) value of the ANOVA tests indicated effect sizes following Cohen's guidelines (0.01, small; 0.06, medium; 0.14, large)[17]. A corresponding paired t-test was performed to compare outcomes before and after the intervention. Cohens' d was used to measure the effect size, with values of 0.14, 0.4, and 0.75 indicating small, medium, and large effects[18]. The significance level was set at 5%.

Results

Flow of participants through the trial

Thirty-eight people (8 males, 30 females; 77.6 ± 4.0 years) were screened, all of whom met the study criteria, signed an informed consent form, and were subsequently enrolled in the study. This cohort was split into the intervention and control groups (n = 19 each), and all participants completed the relevant intervention and measurement periods (Fig. 1).

The demographic characteristics (Table 1) and baseline values of the outcome measures (Tables 2 and 3) were comparable between the groups, except for the TUG and RMS area under the EC condition. In the baseline comparison, the RMS area under the EC condition of the intervention group was larger than that of the control group (p = 0.032). In addition, the TUG test of the control group was performed earlier than that of the intervention group (p = 0.010).

Primary outcomes: changes in standing balance on an unstable surface

We found no interaction between the time and group factors of the COP sway test for any items under either the EO or EC conditions. We found a significant time factor and main effect for Y-RMS (F (1, 36) = 5.392, p = 0.026, η_p^2 = 0.130) for participants in the EO condition, and RMS (F (1, 36) = 8.483, p = 0.006, η_p^2 = 0.191), X-RMS (F (1, 36) = 7.532, p = 0.009, η_p^2 = 0.173), Y-RMS (F (1, 36) = 7.078, p = 0.012, η_p^2 = 0.164), and RMS area (F (1, 36) = 6.656, p = 0.014, η_p^2 = 0.156) for participants in the EC condition. Furthermore, we observed a significant group factor and main effect for the RMS area for participants in the EC condition (F (1, 36) = 4.554, p = 0.040, η_p^2 = 0.112).

Table 1. Participants' characteristics

	Intervention	Control	p-value
Number (male/female)	19 (4/15)	19 (4/15)	
Age, year	78.0 (3.8)	77.4 (3.8)	0.641
Height, m	1.54 (9.4)	1.53 (9.6)	0.907
Weight, kg	55.5 (8.2)	55.2 (9.7)	0.929
BMI, kg/m^2	23.5 (3.1)	23.3 (3.8)	0.885
HDS-R	25.1 (2.8)	26.3 (2.8)	0.194

Average (standard deviation), non-paired t-test

BMI, body mass index; HDS-R, Hasegawa Dementia Scale-Revised

In the intervention group, RMS, X-RMS, Y-RMS, and the change in RMS area from baseline to the end of the exercise sessions for participants in the EC condition showed significant improvements, with a medium effect (RMS, p = 0.006, d = 0.52; X-RMS, p = 0.011, d = 0.55; Y-RMS, p = 0.010, d = 0.44; RMS area, p = 0.007, d = 0.54) (Table 2).

In the control group, there was no significant difference between the pre- and post-intervention COP sway tests under either the EO or EC conditions for any items.

Secondary outcomes

10 MWT

We found no interaction between the time and group factors in the 10 MWT. However, a large and significant time effect (F (1, 36) = 11.145, p = 0.002, η_p^2 = 0.236) was observed at 10 MWT. The post-hoc test also showed a statistically significant improvement in the intervention group, with a moderate effect (d = 0.50), but no significant difference in the control group (Table 3).

5T-STS test

We found no interaction between the time and group factors in the 5T-STS test. We found a significant time effect (F (1, 36) = 52.067, p <0.001, η_p^2 = 0.591) for the 5T-STS test. In addition, post-hoc testing revealed a statistically significant improvement over time, with a medium effect (d = 0.57) in the intervention group and a large effect (d = 0.83) in the control group (Table 3).

TUG test

We found a significant medium time × group interaction effect (F (1, 36) = 4.190, p = 0.048, η_p^2 = 0.104). Furthermore, a significant, large group and time effect (group: F (1, 36) = 6.861, p = 0.013, η_p^2 = 0.160; time: F (1, 36) = 14.834, p = 0.002, η_p^2 = 0.292) were also observed. Comparison of TUG before and after exercise showed a large effect on the improvement after 24 sessions of exercise in the

Table 2. Changes from pre and post for all groups of gravity sway test in EO and EC

	Intervention			Control			F-value					
	Pre	Post	d	Pre	Post	d	Time	η_p^2	Group	η_p^2	Time × Group	η_p^2
EO												
RMS, cm	1.38 (0.07)	1.32 (0.06)	0.23	1.34 (0.05)	1.31 (0.06)	0.11	2.135	0.056	0.101	0.003	0.328	0.009
X-RMS, cm	0.94 (0.05)	0.93 (0.05)	0.04	0.88 (0.04)	0.92 (0.05)	0.19	0.685	0.008	0.006	0.008	0.685	0.019
Y-RMS, cm	1.00 (0.06)	0.93 (0.05)	0.35	1.00 (0.05)	0.92 (0.05)	0.34	5.392#	0.130	0.006	0.000	0.019	0.001
RMS area, cm^2	6.26 (0.70)	5.65 (0.54)	0.23	5.78 (0.45)	5.59 (0.54)	0.09	2.055	0.054	0.132	0.004	0.590	0.016
EC												
RMS, cm	2.26 (0.16)	1.94 (0.12)*	0.52	1.90 (0.07)	1.78 (0.09)	0.37	8.483##	0.191	3.471	0.088	1.475	0.039
X-RMS, cm	1.57 (0.11)	1.34 (0.08)*	0.55	1.31 (0.06)	1.20 (0.08)	0.35	7.532##	0.173	3.706	0.093	1.059	0.029
Y-RMS, cm	1.61 (0.12)	1.41 (0.09)*	0.44	1.37 (0.05)	1.30 (0.06)	0.34	7.078#	0.164	2.667	0.069	1.375	0.037
RMS area, cm^2	17.38 (2.41)	12.67 (1.51)**	0.54	11.68 (0.83)†	10.33 (1.03)	0.33	6.656#	0.156	4.554#	0.112	2.653	0.054

Average (standard error), ANOVA: #p <0.05, ##p <0.01

Significant difference between pre and post (paired t-test): *p <0.05, **p <0.01

Comparing groups in baseline (non-paired t-test): †p <0.05

Effect size (η_p^2), ANOVA (0.010: small, 0.060: medium, 0.140: large)

Effect size (Cohen's d), pre vs post (0.15: small, 0.40: medium, 0.75: large)

EO, eyes open; EC, eyes closed; RMS, root mean square; ANOVA, analysis of variance intervention group (p <0.001, d = 1.01) but no significant difference in the control group (Table 3).

Discussion

In this randomized controlled trial, we compared the effects of SLVED and walking training on standing balance in foam rubber, STS test, gait, and TUG test in community-dwelling older adults. ANOVAs revealed a significant group × time interaction for the TUG test. The main effect of the time factor was found in standing balance for both the EO and EC conditions on foam rubber, 10 MWT, 5T-STS test, and TUG test. In addition, the intervention group showed statistically significant improvements from baseline in RMS, X-RMS, Y-RMS, RMS area with EC, 10 MWT, 5T-STS test, and TUG test. These results suggest that SLVED has a similar effect to walking training in community-dwelling older adults.

We found that TUG test was observed for medium interaction effects, and the large-effect group factor and control group were faster than the intervention group at baseline. For participants tested under the EC condition, the RMS area showed a medium group factor effect, which was larger in the intervention group than in the control group at baseline. During the TUG test, participants stood up from a chair, walked, and performed 180-degree turn movements. There were no differences between the groups at baseline in the 10 MWT, which is a measure of walking ability, or the 5T-STS test, which is a measure of standing movement. Therefore, the two groups were considered to have similar walking and sit-to-stand abilities. However, there was a group difference in the RMS area under the EC condition, which is a measure of postural control by the vestibular system. These results suggest that this difference may influence the interaction of vestibular function in the TUG test during turning.

A main effect of time was observed on the foam rubber standing balance with EO and EC conditions, 10 MWT, 5T-STS test, and TUG test. In addition, the simple main effect in the intervention group showed statistically significant improved outcomes from medium to large effects for RMS, X-RMS, Y-RMS, and RMS area with the EC condition, 10 MWT, 5T-STS test, and TUG test. These results agree with those of a previous study that reported that vibratory stimuli applied to the plantar region exert beneficial effects on balance in women aged 60 years or older, with greater efficacy in anterior displacement, postural control of the anteroposterior axis, and EC condition[8]. Standing balance with the EC condition on foam rubber modifies somatosensory input from the plantar surface and increases dependence on vestibular sensation[12,19]. During postural control, the visual image is maintained by the vestibulo-ocular reflex (VOR), in which the vestibular senses receive head movements, and the eyes move at the same speed in opposite directions. VOR adapts in a speed-dependent manner at frequencies above 0.3 Hz, and VOR adaptation training has been reported to be

Table 3. Changes from pre and post for all groups of 10 MWT, 5T-STS test and TUG test

	Intervention			Control			F-value					
	Pre	Post	d	Pre	Post	d	Time	η_p^2	Group	η_p^2	Time × Group	η_p^2
10 MWT, s	5.6 (0.3)	5.1 (0.2)**	0.50	5.2 (0.1)	5.0 (0.1)	0.31	11.145##	0.236	1.771	0.047	1.485	0.040
5T-STS test, s	8.0 (0.4)	6.9 (0.4)**	0.57	7.3 (0.3)	6.3 (0.3)**	0.83	52.067#	0.591	1.492	0.040	0.138	0.004
TUG test, s	7.7 (1.6)	6.4 (0.7)**	1.01	6.6 (0.7)†	6.2 (0.7)	0.47	14.834##	0.292	6.861#	0.160	4.190#	0.104

Average (standard error), ANOVA: #p <0.05, ##p <0.01

Significant difference between pre and post (paired t-test): **p <0.01

Comparing groups in baseline (non-paired t-test): †p <0.05

Effect size (η_p^2), ANOVA (0.010: small, 0.060: medium, 0.140: large)

Effect size (Cohen's d), pre vs post (0.15: small, 0.40: medium, 0.75: large)

10 MWT, 10-m walking time test; 5T-STS, five-times sit-to-stand; TUG, timed up-and-go; ANOVA, analysis of variance

more effective at medium frequencies (1.3 Hz)[20]. A previous study reported that the average daily gait cycle of elderly Japanese individuals is 1 Hz[21]. SLVED participants maintained a standing position on the footplate with EO during compound movements at a frequency of 1.6 Hz. This shows that SLVED with EO may elicit VOR to maintain the visual image and stimulate vestibular sensation in response to head movements linked to footplate movements. As a result of the stimulation, vestibular function to control head movements was improved, and body sway was reduced while participants stood on an unstable surface.

In both groups, the 5T-STS test had a simple main effect and significant improvement (intervention group: moderate effect, control group: large effect). Walking is known to improve knee extension torque[22], which likely explains these results. A previous study investigating locomotive syndrome in Japanese individuals reported a 5T-STS of 8.25 ± 2.23 s in healthy elderly participants[23]. Tankisheva et al. reported that local vibration treatment of the mid thigh and around the hip for six months increased knee extension muscle torque in postmenopausal women[24]. Bellomo et al. reported that global sensorimotor and high-intensity focused vibration for 8 weeks increased knee extension muscle torque in elderly individuals with sarcopenia[25]. The 5T-STS test has been reported to be an indicator of knee extension muscle strength[14] and balance ability in patients with vestibular disorders[26]. These results suggest that SLVED and walking training improved lower-extremity muscle strength and balance ability during standing and sitting in older adults.

Participants standing on foam rubber with EO condition were dependent on vision, which was the main effect observed in the Y-RMS, an index of body sway in the anterior-posterior direction that decreased after the intervention. In the device used in this study, the left–right inverse phase of the ankle plantar dorsiflexion and hip extension movements by foot support was similar to the lower limb movements during walking[9]. Therefore, it is assumed that holding the standing position with the EO condition on the device adapts to the anterior-posterior movement of the body. A previous study reported that anterior–posterior body swaying appears in the standing position with visual stimuli in which the visual landscape flows back and forth[27]. In addition, it has been reported that the relationship between the distance of the gazing index and body sway in the upright position increases with distance[28]. Thus, anteroposterior body sway is affected by visual information. However, it has been reported that ankle plantar flexors and dorsiflexors contribute to ankle plantar flexion and dorsiflexion strategies, respectively[29,30]. These results suggest that the main effects of ankle plantar dorsiflexion and visual stimulation in the anteroposterior direction were reduced in participants in the EO condition in the control and intervention groups. However, since there was no simple main effect before and after the intervention in each group, it was assumed that the effect was small in community-dwelling older adults.

Conclusion

This study compared the effects of SLVED and walking training on foam rubber standing balance, 5T-STS test, 10 MWT, and TUG test in older adults living in the community. The results showed that SLVED had similar effects as walking training on foam rubber standing with EC condition, walking, 5T-STS test, and TUG test in participants. The specific SLVED protocol used in this study can be considered safe and suitable for mobility and balance training programs in community-dwelling older adults.

The limitations of this study include the bias in TUG test and balance assessment at baseline at random assignment and the lack of investigating vestibular function assessment as a factor. Further studies with larger sample sizes, taking into account allocation adjustment by the main outcome, and somatosensory and vestibular function assessments should be conducted to verify our findings. In addition, training time and frequency should be increased with a passive exercise-assisting device.

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PHYSICAL
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ORIGINAL ARTICLE

Exertional Desaturation Is More Severe in Idiopathic Pulmonary Fibrosis Than in Other Interstitial Lung Diseases

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ABSTRACT. Objective: Interstitial lung disease (ILD) is classified into several disease groups. Among them, idiopathic pulmonary fibrosis (IPF) has higher incidence and poor prognosis; therefore, it is important to characterize specific IPF symptoms. Exercise desaturation is a strong factor related to mortality in patients with ILD. Thus, the purpose of this study was to compare the degree of oxygen desaturation between IPF and other ILD (non-IPF ILD) patients during exercise, using the 6-minute walk test (6MWT). Methods: This retrospective study included 126 stable patients with ILD who underwent 6MWT in our outpatient department. The 6MWT was used to assess desaturation during exercise, 6-minute walk distance (6MWD), and dyspnea at the end of exercise. In addition, patient characteristics and pulmonary function test results were recorded. Results: Study subjects were divided into 51 IPF patients and 75 non-IPF ILD patients. The IPF group had significantly lower nadir oxygen saturation determined by pulse oximetry (SpO_2) during 6MWT than the non-IPF ILD group (IPF, 86.5 ± 4.6%; non-IPF ILD, 88.7 ± 5.3%; $p = 0.02$). The significant association between the nadir SpO_2 and IPF or non-IPF ILD grouping remained even after adjusting for gender, age, body mass index, lung function, 6MWD, and dyspnea ($\beta = -1.62$; $p < 0.05$). Conclusion: Even after adjusting for confounding factors, IPF patients had lower nadir SpO_2 during 6MWT. Early assessment of exercise desaturation using the 6MWT may be more important in patients with IPF compared with patients with other ILDs.

Key words: Idiopathic pulmonary fibrosis, Interstitial lung disease, 6-minute walk test, Oxygen desaturation

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Interstitial lung disease (ILD) comprises a group of diverse diseases that damage the lung parenchyma through inflammation and fibrosis. ILD is divided into several disease groups, with different treatment goals and assessment methods[1)]. Idiopathic pulmonary fibrosis (IPF) is the most frequent form of ILD and has a very poor prognosis with a median survival time of 2–3 years from diagnosis[2)]. In contrast, non-IPF ILDs, such as idiopathic nonspecific interstitial pneumonia (NSIP), connective tissue disease-associated ILD, and hypersensitivity pneumonitis, usually have a better prognosis than IPF[3)]. Hence, it is important to characterize the specific symptoms in IPF patients compared with those in non-IPF ILD patients.

Chronic hypoxemia influences prognosis in patients with ILD. Many patients with ILD present with severe desaturation during exercise even if they do not have hypoxemia at rest[4,5)]. The 6-minute walk test (6MWT) is an inexpensive and simple test that assesses desaturation during exercise and has been shown to be reproducible in patients with ILD[6,7)]. Desaturation during exercise is a strong risk factor for mortality in ILD patients[5,6,8–12)] and is also associated with quality of life[13,14)]. A few studies have

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assessed the difference in desaturation during exercise between IPF patients and non-IPF ILD patients, but no adjustment was made for some important confounding factors[5,15]. Moreover, several studies reported controversial results on whether desaturation during exercise is more severe in patients with IPF[16,17]; hence, this relationship remains unclear. Clarifying the differences in desaturation during exercise between patients with IPF and patients with non-IPF ILD will be useful in determining how to evaluate IPF patients and help determine the appropriate treatment strategy.

Therefore, the purpose of this study was to compare the degree of oxygen desaturation in IPF and non-IPF ILD patients during exercise, using the 6MWT.

Methods

Study design and study population

This retrospective study included 195 stable patients with ILD who underwent the 6MWT as part of an examination at our outpatient clinic at Kobe City Medical Center West Hospital (Japan) between April 2016 and March 2020. No respiratory rehabilitation was performed before or after 6MWT because it was performed to assess physiological status of the patients. Among these, patients with long-term oxygen therapy, active coronary artery disease, other severe comorbidities, and missing data were excluded. The classification of ILD, including the diagnosis of IPF, was made using the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement[1]. Assessment items for the analyses were age, gender, the modified British Medical Research Council (mMRC) scale, comorbidities, treatment, smoking status, 6MWT, and pulmonary function tests.

This study was approved by the Institutional Review Board (Clinical Research) of Kobe City Medical Center West Hospital with waiver of informed consent because of its retrospective nature (June 25, 2019: project approval number 19-006).

6-minute walk test

The subjects performed 6MWT on a flat, 25-m walking course according to the ATS statement[18]. Patients were instructed to walk as much as possible in 6 min. Oxygen saturation determined by pulse oximetry (SpO_2) during 6MWT was continuously recorded using a pulse oximeter with a finger probe (WristOx 3150; Nonin Medical, Plymouth, MN, USA) and 6MWT analysis software (WristOx 2; Star Product, Tokyo, Japan). To minimize errors in SpO_2 measurement, patients were instructed to hold the finger with the pulse oximeter attached to the front of their chest while walking. SpO_2 was also measured at rest for 1 min prior to the test and for 3 min immediately after. Patients were asked to rate their dyspnea every minute during 6MWT, using the modified Borg scale scores by selecting a number from 0 to 10, with 0 being no appreciable dyspnea and 10 being maximal sustained dyspnea[19]. From the 6MWT, 6-minute walk distance (6MWD), rest SpO_2, nadir SpO_2, ΔSpO_2 (rest SpO_2 − nadir SpO_2), maximum heart rate, and modified Borg scale scores during 6MWT were obtained.

Pulmonary function tests

All patients were subjected to pulmonary function tests by spirometry (Autospirometer System 7; MINATO, Osaka, Japan) according to the method described in the ATS 1994 update[20]. Vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume in 1 s (FEV_1) were evaluated. Predicted normal values for the Japanese population were derived from reference values of the Japanese Respiratory Society[21] for VC, FVC, and FEV_1.

Analysis

Statistical analysis was performed with EZR Ver. 1.38 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Subjects were categorized into the IPF group or the non-IPF ILD group. Continuous variables were presented as mean ± standard deviation and were compared using unpaired t, Welch's t, and Mann–Whitney U tests between the two groups. A simple regression analysis was performed to examine the relationship between the nadir SpO_2 and IPF or non-IPF ILD groups. Additionally, multiple regression analysis was performed with the nadir SpO_2 as the dependent variable and IPF diagnosis as the independent variable to evaluate the relationship after adjusting for potential covariates. Dummy variables were created with patients with IPF as 0 and non-IPF ILD as 1. These were entered into the regression analysis. Gender, age, body mass index (BMI), chronic obstructive pulmonary disease (COPD) or non-COPD, 6MWD, %VC, and mMRC scale scores were included as confounders because they are assumed to be involved in desaturation[22,23]. p-value <0.05 was considered significant.

Results

Among 195 patients with ILD who underwent 6MWT, 18 patients were on long-term oxygen therapy and 51 cases had missing data. Therefore, 126 cases were included in the analysis. Fifty-one patients (40%) were diagnosed with IPF and the other 75 patients (60%) had non-IPF ILD. Non-IPF ILD included collagen disease, n = 12 (16.0%); hypersensitivity pneumonitis, n = 10 (13.3%); idiopathic pleuroparenchymal fibroelastosis, n = 6 (8.0%); asbestosis, n = 6 (8.0%); idiopathic NSIP, n = 3 (4.0%); sarcoidosis, n = 2 (2.7%); cryptogenic organizing pneumonia, n = 1 (1.3%); and unclassifiable, n = 35 (46.7%). Figure 1 shows the flow chart showing exclusion and categorization of patients.

Table 1 summarizes the patient characteristics according to the IPF or non-IPF ILD grouping. No significant

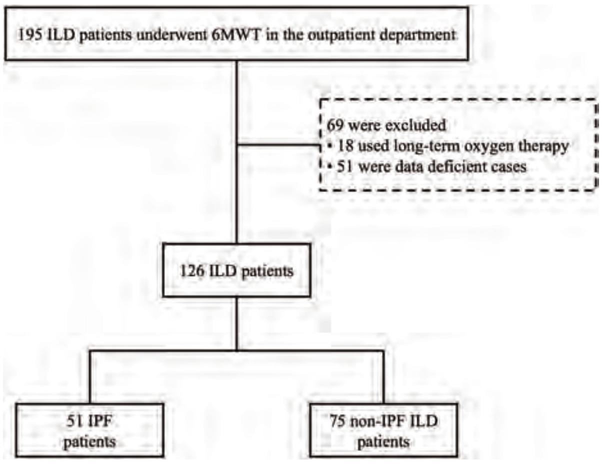

Fig. 1. Flow chart showing exclusion and categorization of patients

ILD, interstitial lung disease; 6MWT, 6-minute walk test; IPF, idiopathic pulmonary fibrosis

Table 1. Characteristics of patients according to the IPF or the non-IPF ILD grouping

Variables	IPF (n = 51)	non-IPF ILD (n = 75)	*p*-value
Gender (male), n (%)	37 (72.5)	48 (64.0)	0.42
Age (year)	72.9 ± 8.3	71.7 ± 9.4	0.47
BMI (kg/m^2)	23.6 ± 3.6	23.1 ± 3.9	0.41
mMRC (0/1/2/3/4)	2/20/20/8/1	8/29/23/15/0	0.50
Smoking status			0.57
Current, n (%)	10 (19.6)	17 (22.7)	
Previous, n (%)	30 (58.8)	37 (49.3)	
Never, n (%)	11 (21.6)	21 (28.0)	
Comorbidities, n (%)			
Hypertension	12 (23.5)	21 (28.0)	0.72
Hyperlipidemia	5 (9.8)	8 (10.7)	1.00
Diabetes	13 (25.5)	15 (20.0)	0.61
COPD	5 (9.8)	7 (9.3)	1.00
Lung cancer	5 (9.8)	7 (9.3)	1.00
Treatment, n (%)			
Corticosteroid	0 (0)	11 (14.7)	0.01
Immunosuppressive therapy	0 (0)	6 (8.0)	0.10
Anti-fibrotic therapy	8 (15.7)	0 (0)	0.002
Pulmonary function tests			
VC (L)	2.2 ± 0.6	2.2 ± 0.8	0.49
VC (%pred)	69.3 ± 16.3	71.4 ± 17.5	0.50
FVC (L)	2.1 ± 0.7	2.2 ± 0.8	0.46
FVC (%pred)	71.5 ± 18.6	72.7 ± 18.6	0.73
FEV_1 (L)	1.8 ± 0.5	1.8 ± 0.6	0.80
FEV_1 (%pred)	75.3 ± 18.9	74.9 ± 17.7	0.91

Data presented as n (%), or mean ± standard deviation

IPF, idiopathic pulmonary fibrosis; non-IPF ILD, interstitial lung disease other than IPF; BMI, body mass index; mMRC, modified British Medical Research Council; COPD, chronic obstructive pulmonary disease; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s

Table 2. Results of the 6MWT according to IPF or non-IPF ILD grouping

Variables	IPF (n = 51)	non-IPF ILD (n = 75)	*p*-value
6MWD (m)	410.6 ± 116.8	408.9 ± 119.6	0.94
Rest SpO_2 (%)	95.7 ± 1.3	95.6 ± 1.9	0.61
Nadir SpO_2 (%)	86.5 ± 4.6	88.7 ± 5.3	0.02
ΔSpO_2 (%)	9.3 ± 4.0	6.9 ± 4.4	0.002
Maximum pulse rate (bpm)	114.8 ± 15.8	110.9 ± 16.1	0.19
Modified Borg scale score*	2(0–10)	2(0–10)	0.49

Data are presented as mean ± standard deviation

*The modified Borg scale score at the end of 6MWT

6MWT, 6-minute walk test; IPF, idiopathic pulmonary fibrosis; non-IPF ILD, interstitial lung disease other than IPF; 6MWD, 6-minute walk distance; SpO_2, oxygen saturation of determined by pulse oximetry; ΔSpO_2, difference in SpO_2 rest to nadir

differences were observed in %VC (IPF: 69.3% ± 16.3%, non-IPF ILD: 71.4% ± 17.5%; $p = 0.50$) and %FVC (IPF: 71.5% ± 18.6%, non-IPF ILD: 72.7% ± 18.6%; $p = 0.73$), between the IPF group and the non-IPF ILD group. In addition, no significant differences were observed in the other pulmonary function measures or patients characteristics between the two groups, with the exception of treatment modalities used for IPF and non-IPF ILD.

Table 2 presents the results of the 6MWT according to the IPF or the non-IPF ILD grouping. The IPF group had significantly lower nadir SpO_2 during 6MWT than the non-IPF ILD group (IPF: 86.5% ± 4.6%, non-IPF ILD: 88.7% ± 5.3%; $p = 0.02$). The IPF group also had significantly higher ΔSpO_2 during 6MWT than the non-IPF ILD group (IPF: 9.3% ± 4.0%, non-IPF ILD: 6.9% ± 4.4%; $p = 0.002$). In contrast, no significant difference was observed in the dyspnea scale at the end of 6MWT (IPF, 2 [range, 0–10]; non-IPF ILD, 2 [range, 0–10]; $p = 0.49$) and the 6MWD (IPF: 410.6 ± 116.8 m, non-IPF ILD: 408.9 ± 119.6 m; $p = 0.94$) between the two groups.

Figure 2 shows the change in SpO_2 over time during the 6MWT.

Simple regression analysis revealed a significant association (B = −2.20, $p = 0.02$) between nadir SpO_2 and IPF or non-IPF ILD grouping (Table 3: Model 1). The significant association (B = −1.62, $p < 0.05$) remained even after adjustments for gender, age, BMI, COPD or non-COPD, 6MWD, %VC, and mMRC scale score (Table 3: Model 2).

Discussion

In this study, we used the 6MWT to characterize the severity of desaturation during exercise in ILD patients. The results demonstrated that IPF patients had significantly lower nadir SpO_2 during 6MWT than non-IPF ILD patients,

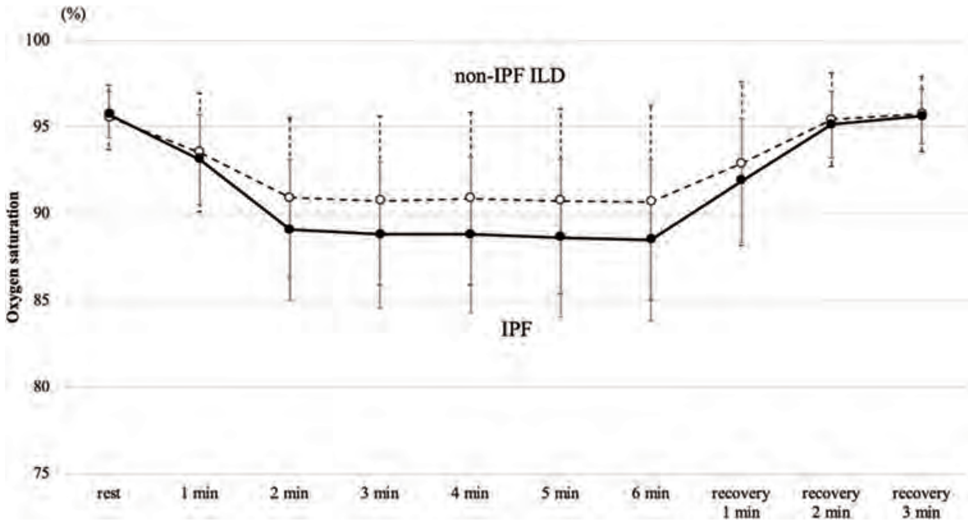

Fig. 2. Mean SpO_2 of the point reached for each minute during the 6-min walk test (solid line, IPF; dotted line, non-IPF ILD)

non-IPF ILD, interstitial lung disease other than IPF; IPF, idiopathic pulmonary fibrosis; SpO_2, oxygen saturation determined by pulse oximetry

Table 3. Univariate and multivariate analyses of association between nadir SpO_2 and IPF or non-IPF ILD

Variables	SpO_2 (nadir) at 6MWT							
	Model 1			Model 2				
	B	95% CI	*p*-value	B	β	95% CI	*p*-value	VIF
IPF or non-IPF ILD	−2.20	−3.99 to −0.41	0.02	−1.62	−0.14	−3.21 to −0.03	<0.05	1.03
Gender (male or female)				1.55	0.14	−0.18 to −3.27	0.08	1.10
Age (year)				−0.07	−0.13	−0.18 to −0.03	0.20	1.49
BMI (kg/m^2)				−0.36	−0.27	−0.58 to −0.15	0.001	1.10
COPD or non-COPD				−3.65	−0.21	−6.51 to −0.79	0.01	1.19
6MWD (m)				−0.01	−0.22	−0.02 to −0.00	0.04	1.88
%VC				0.11	0.39	0.07 to −0.17	<0.001	1.23
mMRC[†]				−1.13	−0.20	−2.09 to −0.16	0.02	1.26

Model 1. Results of simple regression analysis

Model 2. Results of multiple regression analysis with nadir SpO_2 at 6MWT as the objective variable, IPF or non-IPF ILD as the explanatory variable, and gender, age, BMI, COPD or non-COPD, 6MWD, %VC, and dyspnea as confounding factors

[†]Dyspnea was assessed with the mMRC scale.

SpO_2, oxygen saturation of determined by pulse oximetry; IPF, idiopathic pulmonary fibrosis; non-IPF ILD, interstitial lung disease other than IPF; 6MWT, 6-minute walk test; CI, confidence interval; VIF, variance inflation factor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; 6MWD, 6-minute walk distance; VC, vital capacity; mMRC, modified British Medical Research Council

although there was no difference in dyspnea scale results and 6MWD. In addition, even after adjusting for various potential confounding factors such as gender, age, BMI, COPD or non-COPD, 6MWD, %VC, and mMRC scale scores, IPF patients had lower nadir SpO_2 during 6MWT. Therefore, desaturation during exercise can be severe in IPF patients regardless of dyspnea, physical function, lung capacity, and other factors.

The results of this study indicate that patients with IPF tended to have severe desaturation during exercise despite not having hypoxemia at rest. Holland et al. reported that nadir SpO_2 in 6MWT was significantly lower in the IPF group than that in the non-IPF ILD group[15)]. Their finding supports our results, but the study did not adjust for any confounding factors. Another study comparing SpO_2 during 6MWT between patients with IPF and patients with idiopathic NSIP reported that there was no significant difference[5)]. Although there were only two cases of idiopathic NSIP in the present study, the results could not be simply compared, and it is necessary to classify non-IPF ILD patients in detail and compare the results using 6MWT in the future.

We performed the 6MWT to assess desaturation during exercise in patients with ILD. In two previous studies, wherein a bicycle ergometer was employed as an exercise stress test, IPF patients were shown to exhibit more severe desaturation during exercise than non-IPF ILD patients[16,17]. Although these results were similar to our findings, 6MWT is a more clinically feasible and simpler exercise stress test than using a bicycle ergometer. In addition, they also did not adjust for confounding factors. Therefore, this study expanded on the results of these two studies and indicated that similar results can also be obtained with 6MWT, which is simple and easy to administer in the clinical settings.

More severe desaturation during exercise in patients with IPF might be explained by more severe diffusion limitation. IPF is a progressive disease, and diffusing capacity for carbon monoxide (DL_{CO}) is more likely to decline earlier compared with %FVC. In fact, it was reported that patients with IPF had lower DL_{CO} than patients with non-IPF ILD[17,24]. Ventilation–diffusion inequality and diffusion limitation play an important role in desaturation at rest and during exercise[25]. A number of studies showed that low DL_{CO} is strongly associated with desaturation during exercise. For example, Du Plessis et al. reported that DL_{CO} was a predictor of nadir SpO_2 during 6MWT among ILD patients[22]. In another study of 300 patients with ILD, a simple regression analysis identified DL_{CO} as the explanatory factor for decreased oxygen saturation during exercise[26]. Therefore, we speculated that early decline in DL_{CO} in IPF patients could lead to more severe desaturation during exercise. However, this study did not have sufficient data on DL_{CO}, which is a future challenge.

Desaturation during exercise is a strong prognostic indicator in patients with IPF[8,9]. Our results indicated that IPF patients have more severe exercise desaturation compared with non-IPF ILD patients. Therefore, early assessment of exercise desaturation using 6MWT may be useful, especially in patients with IPF who do not have hypoxemia at rest. In addition, the 6MWT does not require much time or complex equipment to implement; therefore, the test is easy to perform clinically.

Our study has some limitations. First, this was a single-center cross-sectional study and may not represent the general characteristics of IPF patients. Therefore, further multicenter studies with larger samples are needed. Second, we did not evaluate the presence of pulmonary hypertension, right heart pressure, or other circulatory dynamics. It has been reported that patients with pulmonary hypertension present with severe exercise hypoxia[27,28]. For that reason, these can be confounding factors. However, in the present study, there was no difference in the maximum pulse rate during the 6MWT, which is related to the circulatory response during exercise, so the difference in circulatory dynamics may not have been significant between IPF and non-IPF ILD patients.

Conclusion

The results of this study showed that even after adjusting for confounding factors, IPF patients had lower nadir SpO_2 during 6MWT. Early assessment of exercise desaturation using the 6MWT might be more important in patients with IPF than in patients with non-IPF ILD. Even if the resting SpO_2 is good, it may be important to perform 6MWT more aggressively in patients with IPF to detect a decrease in oxygen saturation during the test, which is a prognostic factor at an early stage.

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