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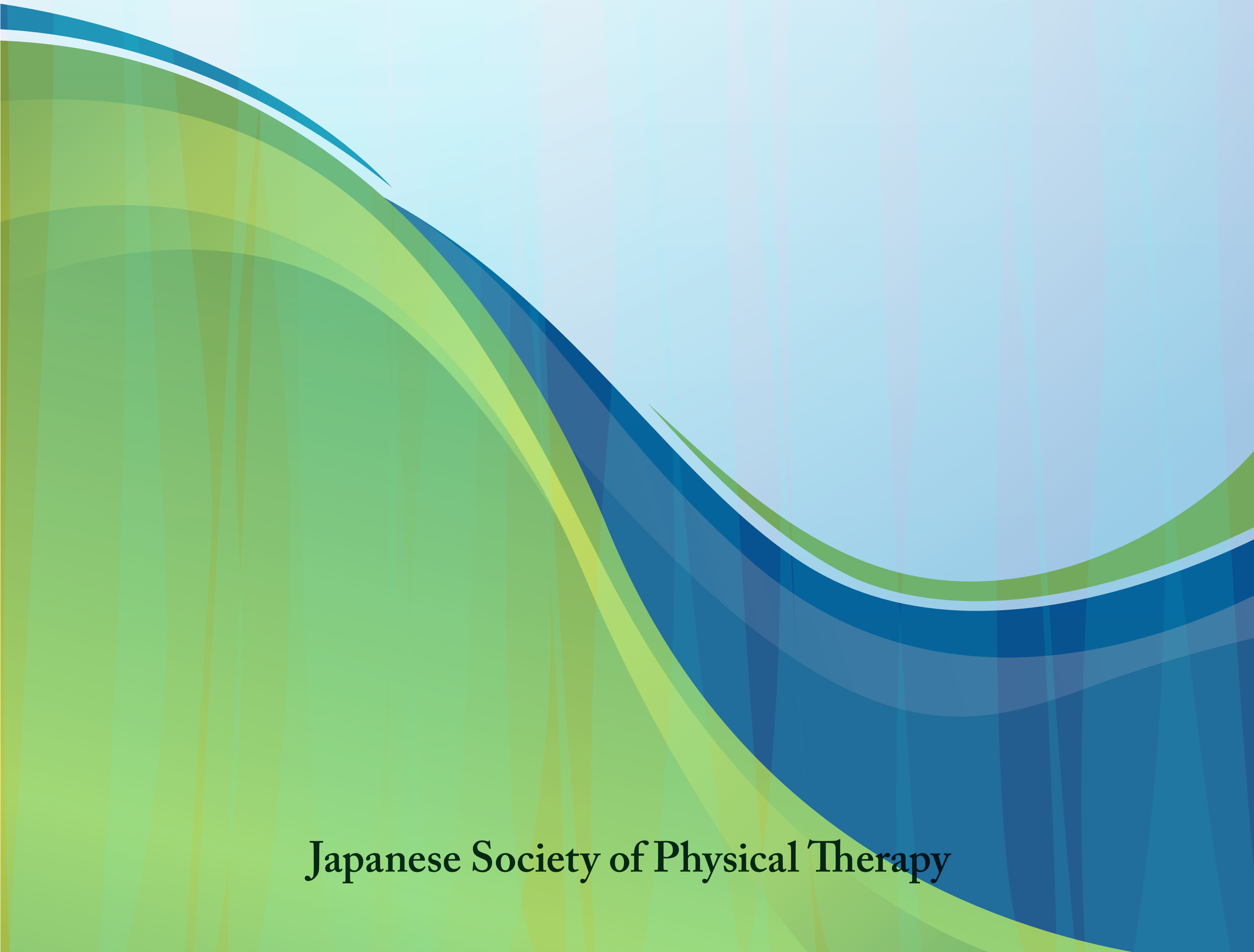

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Contents　Volume 26 Issue 2　2023

Reviews

Original Articles

PHYSICAL
THERAPY
RESEARCH

REVIEW

Rehabilitation in Animal Models of Stroke

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ABSTRACT. Objective: The purpose of this review was to evaluate the efficacy of rehabilitation strategies in animal models of stroke and their correlation with human stroke studies. Methods: General description of a stroke, functional recovery, and rehabilitation modalities were included from published studies in the field of animal models of cerebral ischemia and ischemia–reperfusion. Results: In stroke survivors, rehabilitation plays a significant role to improve motor function, cognition, and other subtle behaviors. Targeted pharmacological agents, including neuroprotective drugs, are helpful in animal models of stroke. However, no drug has yet been found that meets the criteria that would make it the Food and Drug Administration-approved treatment for human stroke. Instead, the rehabilitation of stroke in humans is limited to physical and occupational therapy, speech therapy, environmental enrichment, and social activities, as well as spiritual and family support. Conclusion: Studies on stroke injury and the significance of stroke animals' rehabilitation, including physical and pharmacological, approaches are highlighted.

Key words: Stroke, Rehabilitation, Neuroprotection, Neurorepair, Functional recovery

(Phys Ther Res 26: 39–43, 2023)

Stroke is the major cause of long-term disability worldwide. Stroke survivors suffer from long-term disability due to motor, cognitive, and subtle behavior deficits[1,2]. Varying degrees of functional deficits are prevalent for long even in patients after successful recanalization by stent-retriever devices[3] or thrombolysis by recombinant tissue plasminogen activator[4,5], indicating that the restoration of cerebral blood flow is not enough for functional recovery[6,7]. Reperfusion-induced functional deficits provide a renewed opportunity to test the efficacy of rehabilitation in animal models of transient cerebral ischemia followed and reperfusion (IR) because it mimics the stroke injury in humans after thrombolysis or endovascular thrombectomy (recanalization). Therefore, the discussion in this review will focus mainly on the animal model of transient cerebral ischemia/hypoxia and reperfusion.

Stroke comes from damaged blood vessels in the brain. The blood vessels become blocked (called "ischemic" stroke) due to a blood clot, fat deposits, or simply because the vessels become thick and hard. Sometimes, these blood vessels burst (called "hemorrhagic" stroke). An ischemic stroke cuts off the brain's oxygen and nutrients either for a short (transient stroke) or a long time (permanent stroke). The most common type of stroke, ischemic, affects nearly 700,000 people per year and the prevalence of stroke increases with the increasing aged population in the US[8]. Millions of people have to adapt to an altered life with incurable restrictions in their daily activities. Many must depend on others simply to survive. The direct annual economic burden of the stroke-related cost was projected from \$71.6 billion in 2013 to \$184.1 billion in 2030[9].

The ability to forecast stroke is critical; however, stroke by nature is unpredictable. The vascular changes that precede stroke develop stealthily and are not evident for a long time. Some of stroke risk factors include hypertension, metabolic syndrome, physical inactivity, obesity, high-fat diet, being single, being unhappy, anxiety, smoking, and being born in the wrong demographics. However, their link and the stroke-inducing deleterious mechanisms are not understood. Although stroke is not considered a genetic (inherited) disorder; however, stroke association with epigenetic (metabolome) is regarded valid. A disturbed metabolome is also observed in several peripheral organs including spleen, kidney, gut, and liver, and their function is linked with the

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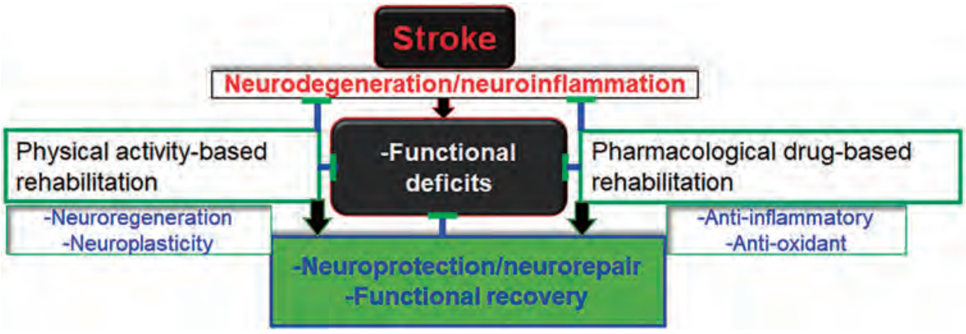

Fig. 1. Schematic showing key mechanisms of the effects of rehabilitation on animal models of stroke

Stroke (permanent ischemia or transient ischemia and reperfusion) results in oxidative burst and the activation of devastating neuroinflammatory cascades leading to neurodegeneration. If untreated, it also obstructs the mechanisms of neural regeneration and brain repair in the chronic phase of the injury. Combined effects of injury mechanisms in the acute and chronic phases lead to profound functional deficits. Functional outcomes can be improved by different rehabilitation strategies including physical-activity-based modalities and pharmacological drug-based treatment regimens.

severity of stroke. The irony is that neither an effective brain repair therapy nor metabolic disturbances after stroke are available mainly due to a limited understanding of multifactorial injurious stroke mechanisms. Furthermore, recovery from stroke injury is also restricted due to symptoms of anxiety, depression, fatigue, and pain[10–13].

In developed countries, the incidence of stroke is declining, largely due to efforts to lower blood pressure and reduced smoking. However, the overall rate of stroke remains high due to the increase in the aging population. Nearly three-quarters of all strokes occur in people over the age of 65. The risk of having a stroke more than doubles each decade after the age of 55 years. Stroke is equally or more prevalent in aged women compared to aged men[14]. Younger females (before menopause) are significantly protected from stroke due likely to female sex hormones including estrogen. Most of the therapeutic approaches and rehabilitation modalities following stroke are common to both genders. Stroke in children is also among the top ten causes of death and carries often lifelong morbidity[15]. While neurons lose neuronal function in adults, neurons in children are unable to gain the function following stroke. The societal burden of childhood stroke is likely to be greater than in adults because children surviving stroke face many more years living with a disability. Both diagnosis and treatment of infant and childhood stroke are difficult[16]. Childhood stroke is caused by factors such as infection, trauma, cardiac, hematologic disorders, arteriovenous malformation, and brain tumor. A sudden compromise of neurological symptoms such as speech disturbance, limb incoordination, ataxia, headache, and altered consciousness are indicative of stroke in children and immediate medical care including thrombolytic/neuroprotective therapy is required[17].

In adult stroke survivors, rehabilitation using pharmacological drugs and/or physical activities plays a significant role in improving movement, cognition, and subtle behaviors as depicted in Figure 1. Targeted pharmacological agents including neuroprotective drugs such as minocycline[18], S-nitrosoglutathione[19–21], sodium nitrite[22], and many more[23] are successful in animal models of stroke. However, their efficacy and clinical relevance do not meet the criteria to be approved for stroke treatment. In addition to pharmacological drugs, appropriate cell infusion, therapeutic exercises, environmental enrichment, social activities, family support, and spiritual leanings also aid and accelerate functional recovery[8,24–26].

Animal research demonstrates that treatment with many neuroprotective or neurorepair agents has not provided clinically beneficial effects mainly due to the limitation of animal models (young versus aged, and permanent ischemia versus ischemia–reperfusion), biological variables, and limited understanding of differential stroke's secondary injury mechanisms in the acute versus chronic phase of stroke injury. For functional recovery, clinical trials show that neuroprotective drugs failed due to the lack of efficacy in the chronic phase[27,28]. Therefore, an ideal therapy must ameliorate acute as well as chronic phases by well-understood mechanisms.

The rehabilitation approach is essential for stroke survivors to stimulate the recovery of functions. Therefore, improvement by a therapeutic agent or rehabilitation in neurorestoration and neurobehavioral functions in animal models determines the efficacy and the clinical relevance of therapy in human stroke (Figure 1). Physical exercise-induced functional recovery in animal models of stroke translates into recovery in many stroke patients. Running exercise is widely used for the rehabilitation of stroke animals.

Justification of running on wheels motor training for physical exercise

Running on wheels resembles natural conditions more closely than any other physical modality. It promotes neurorestorative activity, decreases the mortality rate, and shows an efficient recovery of neuromotor functions following stroke[29]. Moreover, motor exercise is also reported to upregulate brain-derived neurotrophic factor expression[21) as well as to reduce the decline in cognitive function[30). Therefore, running on wheel modality for exercise using a walking wheel bed model is frequently used in animal stroke studies. In addition, rotarod, treadmill, and environmental enrichment approaches for physical exercise-based activities are common in animal models of stroke. In such studies, the severity of stroke and the degree of exercise are confounding factors. To determine the quantifiable recovery with time by rehabilitation strategies, several tasks/tests relevant to human stroke are performed in animal models of stroke as described in the following.

Evaluation of functional recovery in rat/mouse models of stroke

1) Modified neurological severity score (mNSS)

Neurological function measurements are performed as previously described from our laboratory[31). The test is sensitive to unilateral cortical injury because it reflects multiple asymmetries, including postural, sensory, and forelimb and hindlimb use asymmetries. A detailed description of this functional test has been previously reported[32). In our studies, mNSS is scaled from 0 to 12 with 0 as normal and maximal deficit score as 12[19), which reflects combined sensorimotor, beam balance, and reflex abnormal movement functions[31).

2) Foot-fault test

Animals are tested for forelimb movement dysfunction while walking on elevated metal grids with randomly missing support bars. With each weight-bearing step, the forelimb can fall or slip between the metal support bars, which is recorded as a foot fault. The total number of forelimb steps and the total number of foot faults are recorded as described[33).

3) Cylinder test

Exploration is a natural behavior of rodents. The cylinder test is used to determine rodents' exploratory behavior using sensorimotor function following stroke[34). It measures forelimb asymmetry in experimental animals. The asymmetry causes behavioral deficits in the contralateral forelimb of the injured IR animals. Animals reared onto their hind limbs and touched the cylinder wall with forelimb placement to balance themselves while exploring their surroundings. The animal is placed in a Plexiglas cylinder and videotaped as described. Touches of both affected and unaffected paws and paw-dragging are analyzed[20).

4) Forelimb placing test

The forelimb placing test scores the animals' ability to place their forelimb on a tabletop in response to whisker, visual, tactile, or proprioceptive stimulation. The test reflects function and recovery in the sensory-motor systems. Animals are held by their torsos with forelimbs hanging freely. A score of 1 is given each time the rat places its forelimb on the edge of the tabletop in response to the vibrissae stimulation. Percentage of successful placing responses are determined (number correct × 10). The lateral tactile placing is similar to the whisker placing, except that the placing response is induced by gently contacting the lateral side of the forelimb to the edge of the tabletop, whereas forward tactile placing is induced by contacting the frontal side of the forelimb to the edge of a tabletop. The scale is scored as described[35).

5) Body swing test

This test reflects the symmetry of striatal function[19,36). A normal animal typically has an equal number of swings to the contralateral side. Each rat is held along the vertical axis (defined as no more than 10° to either the left or the right side) approximately one inch from the base of its tail and elevated an inch above a table surface. A swing is recorded whenever the rat moves its head out of the vertical axis to either side. The animals have to return to the vertical position for the next swing to be counted.

6) Adhesive removal test

The adhesive removal task is a test to assess somatosensory function and is thus used to highlight minute deficits. The test is also useful to assess even smaller recovery since it is capable of measuring long-lasting deficits. Finally, it allows for longitudinal studies through adaptation of the size of the adhesive tape according to the age of the individual tested[37). Two adhesive tapes are applied with equal pressure on each animal paw. The order of placement of adhesive (right or left) is alternated between each animal. The time to contact and to remove each adhesive test is recorded, with a maximum of 2 min as described[31).

7) Motor function tests by rotarod task

Fine motor coordination is evaluated using a rotarod task. This task is a reliable test to evaluate short-term vestibulomotor function and is widely used in animal models of IR and traumatic brain injury[38–40). Animals are trained on an automated 4-lane rotarod unit. Each animal is given 3 trials, and the mean latency of the three are calculated. Motor function tests by rotarod studies are complemented by the beam walk task as previously described[21,41).

8) Learning/Memory tests (Morris water maze [MWM])

Spatial learning and memory deficits in rodents are investigated using a water maze paradigm[38,42,43) similar to that originally described by Morris[44) and extensively used in experimental stroke. Spatial learning is assessed by training the animals to locate a hidden, submerged platform using extra maze visual information. It should be noted that a variety of parameters and outcomes are measured in this computerized video system, including swim speed, latency to find the platform, path length, and percentage of time in each quadrant. Differences in swimming speed indicate differences in motor function, whereas path length (time and distance to find platform) measurements determine cognitive processes as described[45]. Working memory is also examined by comparing repeated trials on the same day[38]. To minimize the confounding effects of motor deficits on spatial learning/memory and to complement with MWM data, a well-recognized memory test "Novel Object Recognition" (NOR) is used.

9) Memory test (NOR)

This test determines nonspatial hippocampal-mediated memory and is based on an animal's spontaneous ability to explore a novel object. The advantages of the test is that it is independent of motor function and it is quick and simple to perform[46]. Animals are habituated twice for 5 min to the NOR apparatus to familiarize the testing environment. On the test day, each animal is again allowed to explore two identical objects for 5 min (trial phase). After resting for 4 h, the animal is brought to the box and allowed to explore a familiar and a novel object for 5 min. Both trials and test phases are recorded and analyzed. Object exploration is defined as the animal sniffing or touching the objects but not by leaning against, standing on, turning around, or sitting on the objects. Discrimination index ([time spent exploring the novel object-time spent on exploring the familiar object]/ total exploration time) is calculated for each of the animals during the test phase as previously described[20,47].

10) Gait analysis

CatWalk system gait analysis has been validated in neuroscience research and experimental procedures for several neurological disorders including stroke, and it is an excellent method for tracking gait disruption with time due to stroke injury[48]. The Catwalk system represents a rapid and sensitive way to objectively quantify several gait parameters such as position, pressure, and surface area of each paw. The mouse traverses a glass plate voluntarily (toward a goal box), while its footprints are captured by video. The software with the system subsequently visualizes the prints and calculates statistics related to print dimensions and the time and distance relationships between footfalls.

Conclusions

Stroke is associated not only with significant mortality but also with morbidity, dementia, depression, fatigue, pain, as well as a great financial burden. Unfortunately, an effective therapy neither for neuroprotection nor for functional recovery (rehabilitation) following stroke is available. Although a large number of rehabilitation modalities are available for human stroke, many of them are much less effective due to social and personal factors and varying severity of injury in stroke patients. To advance the field and to investigate more relevant therapy to stroke in humans, rehabilitation studies using neuroprotective drugs and physical activities in animal models of stroke are required to continue using new and novel cellular/molecular mechanism-based approaches. A combination of both strategies is anticipated to provide greater and accelerated rehabilitation in stroke survivors.

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Conflict of Interest: The author declares that he has no conflict of interest.

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REVIEW

Physical Therapy Combined with Transcranial Magnetic Stimulation Therapy: Treatment Practice Considering the Effect of Reducing Upper Limb Spasticity on Gait

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ABSTRACT. We perform physical therapy combined with repetitive transcranial magnetic stimulation (rTMS) in stroke patients with hemiplegia in the maintenance phase with the intent of improving the support of paralyzed leg. In gait evaluation in patients with hemiplegia, it is important to assess elements related to coordination carefully. rTMS therapy is effective in alleviating the tension of upper limbs. As rTMS helps upper-limb swing to become evident during gait, it makes trunk rotation necessary for left–right coordination appear more easily. As a result, rTMS has potential for improved upper-limb swing or trunk rotation. Post-rTMS therapy may prepare for the environment suitable for hip extending the stance phase of the paralyzed side. In physical therapy, it is advisable to practice standing up, maintaining standing posture or walking by making good use of these effects. We conduct practices in combination with the following: standing up focusing on load evenly distributed on both sides, standing on slant-board training, which enables forward shift of center of mass, walking by fixating upper limbs to the back of the body with the intent of extending the stance phase of the paralyzed side, and increasing trunk rotation. It is also necessary to discuss the combination with injection with botulinum toxin, which suppresses spasticity of ankle plantar flexors with the physician. Gait is associated with a variety of factors and has significant intrapatient and interpatient variations. In this regard, physiotherapists are required to develop a treatment program based on a quantitative evaluation, especially, in patients with hemiplegia.

Key words: Repetitive transcranial magnetic stimulation, Hemiplegia, Physical therapy, Rehabilitation

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We have so far performed physical therapy combined with repetitive transcranial magnetic stimulation (rTMS) in stroke patients with hemiplegia in the maintenance phase actively with the intent of improving the support of paralyzed leg naturally.

Gait is described as the efficient spatial shift in the center of gravity (COG)[1]. COG can be translated into the center of mass (COM) of a body, and it is discriminated from the center of pressure produced by the ground reaction force at times. Human can walk forward by putting force on the ground by plantar aspect, controlling joints ideally, preventing the body from swaying right to left or up and down, and reaction force applied to the ground. Gait can be divided into two phases: “stance phase” and “swing phase” in terms of kinetics, which is dynamic characteristics of gait. The stance phase represents about 60% of the gait cycle, while the swing phase occupies around 40% of it. The double stance phase represents about 20%. Each gait cycle begins at initial contact with a stance phase, followed by loading response, mid stance, and terminal stance, and proceeds through a swing phase: pre-swing, initial swing, mid swing, and terminal swing. Thus, it is common to observe and analyze the gait based on this cycle step by step[2]. The flow of repeating the stance phase following the swing phase is a major characteristic of the standard gait. As this rhythmical gait cycle is disrupted in patients with hemiplegia,

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evaluating the coordination carefully is the first step toward the treatment of hemiplegia.

Getting Faster Maximum Gait Speed Is Not a Treatment Effect

Kinematic motion analysis is a key to approach for gait provided by physiotherapists. On the other hand, spatiotemporal analysis is also clinically useful and is widely used for the diagnosis and judgement of the treatment effect. The most well-known evaluation method is the 10-meter walk test used to measure walking speed over 10 m3). For the relationship between the gait speed and the gait function in hemiplegic patients, <0.4 m/s predicts household walking, 0.4 to 0.8 m/s predicts limited community walking, and >0.8 m/s predicts unlimited community walking4). A change of getting faster gait speed by using differences between pretreatment and posttreatment is often used as a measure of improvement. However, in terms of kinematic motion analysis, this outcome measure should be interpreted very carefully. This is why 10-meter walk is measured with a maximum effort in most cases. For gait in healthy people, when the gait speed becomes faster, both the stance phase and the double stance phase decrease and the swing phase increases. If it were hemiplegic patients, it might lead to the further decrease in the stance phase of paralyzed leg than in the healthy individual. Alternating the stance phase and the swing phase smoothly is coordination. Rebuilding smooth performance is a treatment goal in physical therapy. However, the supporting phase of paralyzed leg may be increasingly decreased because patients have a conscious desire to increase gait speed. As the reduced supporting time of the paralyzed leg causes loss of activities without fail, leading to the atrophy of paralyzed muscles, it must be avoided. Also, it is necessary to keep in mind to develop a program to enable COM shift and joint control smoothly, not only to extend the supporting period of the paralyzed leg. We herein report changes in the gait of hemiplegic patients using rTMS, which we actively perform in our hospital as well as physical therapy.

Evaluation in Performing Physical Therapy in Combination with rTMS

The gait of hemiplegic patients is characterized by increased stance phase and decreased swing phase when compared with healthy individuals5–7), which causes asymmetric gait patterns. Also, it is known to increase the double stance phase gradually8–10). Hemiplegic patients have difficulty with rotation toward the opposite direction of pelvis and chest11). As rTMS therapy is effective in alleviating the tension of upper limbs12), it helps upper-limb swing to become evident during gait and makes trunk rotation necessary for left–right coordination appear more easily13). As a result, rTMS has potential for improved upper-limb swing or trunk rotation. Post-rTMS therapy may prepare for the environment suitable for extending the stance phase of the paralyzed side. In hemiplegic patients, it is difficult to support the load due to the impaired function of ankle plantar flexors or toe flexor muscles in the COM shift to forefoot in the terminal stance of the paralyzed side14). In the physical therapy, it is necessary to develop a kinetic therapy that enables the movement of ankle plantar flexors during the prone hip extension and the slightly flexed position of the knee and the shift of the COM anteriorly by focusing on the shift of the body weight to forefoot in the stance phase of the paralyzed side.

Most of the patients give a priority to the stability and touch the ground by the entire plantar aspect to avoid touching the ground by toe or in inversion position of the foot. In order to touch the ground by the entire plantar aspect, it is required to extend the stance duration of the lower limb on the non-paralyzed side and attempt touching the ground slowly as if choosing a touching place. For this purpose, it is also necessary to allow the patient heel to touch the ground using orthosis as needed. Patients with partial loss of sensation of plantar flexors tend to bend forward inevitably because they use visual compensation by looking at their foot. Hemiplegic patients rely on their vision to maintain standing balance when compared with healthy individuals15). The use of a mirror is useful not only in entering sensory information but also in correcting their posture. It is recommendable to hear sensory impairment from them and provide feedback accordingly, and prepare the environment that allows patients to learn somatic positional relationship and how to apply force as much as possible by exploiting all their residual sensations. It is also important to establish the environment for feedback by setting gait width as narrow as possible.

Load applied to the forefoot on the paralyzed side may induce knee buckling because the load line shifts ahead of the axis of the knee. As patients always feel fear of knee buckling, they tend to prevent their weight from shifting forward as much as possible. The way of applying their body weight without fear is a strategy of locking knee joint in extension position. The patients can acquire the stability of their gait when the knee joint is locked in the extension position during the stance phase. The stronger the recoil is generated in locking, the more frequently genu recurvatum will be induced. The stance phase will inevitably occur without participation of knee extensors. As a result, it causes atrophy in quadriceps not in proportion to exercise volume. Once one remembers locking, it is difficult to correct. In case of severe paralysis, there are not a few patients who cannot support their weight without locking. It is essential to judge how much they can achieve by practicing standing up or walking from the early stage while attempting maximum sensory integration. It is necessary to prepare as much information that can be given to patients as possible as follows: providing visual feedback by making the utmost use of a mirror, giving appropriate support for the upper limb on the non-paralyzed side, and providing feedback using knee brace or surface electromyography in order not to transfer to knee hyperextension in the end range.

Physical Therapy to Be Conducted as a Therapeutic Method Following rTMS

We provide a program that can exploit the effectiveness of rTMS therapy in addition to stretching following rTMS at our university. We describe herein our practical physical therapy.

Standing-up practice focusing on left and right loads

Standing-up motion is a motion that shifts COM upward smoothly until the standing position is taken by putting the COM on the base of support consisting of buttock through plantar aspects of both feet. Patients with hemiplegia often stand up depending on the extremity on the non-paralyzed side dominantly[16,17]. When paralysis becomes severe, it is extremely difficult to apply a load on the forefoot on the paralyzed side. Patients perform standing-up motion while applying their weight evenly distributed over both legs using visual feedback. Also, the decrease in load efficiency on the limb on the paralyzed side was assessed. A full-length mirror is always installed in front of patients in order to enter the information properly. A straight line is drawn on the mirror, and a seal is applied on the patient body as a mark. Patients consciously practice so that the mark on their body can move upward smoothly along with the line on the mirror. This practice helps patients reset load sensation between right and left legs, which they so far have felt. In this practice, patients can easily take in information on left–right coordination by placing a soft ball between their knees. Similarly, they can realize tension of both hands and compensatory body motion more easily by folding their arms. As the tension of upper limbs is likely to elevate during the practice, it is important to position a therapist on the paralyzed side or posteriorly so that he or she can relax as much as possible and his or her feeling of fear for applying a load on the paralyzed side can be removed. Giving a sense of assurance to patients, “Never fall” is a mandatory condition in conducting the training. The training with parallel bars can also give a sense of assurance to them. It is also important to take data on ground reaction force in standing up and provide correct information for patients.

Standing on slant-board training (SST)

It is required to change potential energy to kinetic energy efficiently to shift the COM anteriorly. Generally, the gait that can be explained by the inverted pendulum model has a high energy efficiency[18]. For hemiplegic patients, as attention is required for their anxiety about applying a load on the paralyzed limb, the load application on the extremity on the non-paralyzed side dominantly, knee buckling or toe’s getting caught, the COM is often positioned at the rear of the non-paralyzed limb. The lower limb muscle weakness affects the reduced force of shifting the COM anteriorly toward the paralyzed side[19,20]. We often employ the SST (Fig. 1) as one of the programs following rTMS in order to facilitate the shift of the COM anteriorly as physical therapy. The SST allows patients to shift the COM anteriorly easily by taking the standing position on the slant board. It is expected to exert an effect that hemiplegic patients whose COM is shifted backward can move more easily. A study reports that the SST is effective in improvement of walking ability not only for hemiplegic patients[21] but also for patients with Parkinson’s disease[22]. We performed SST combined with rTMS in hemiplegic patients and reported that the COM in walking was shifted forward[23]. The SST enables the COM to shift forward in patients who feel anxiety for applying a load to the forefoot on the paralyzed side due to sensory disorder in the lower limb on the paralyzed side.

Fig. 1. Standing on slant-board training

The treatment is to maintain a standing posture on a slope with a toe up. In the subsequent standing position on the level ground, the weight center position deviated forward. This has been verified and reported in patients with hemiplegia and Parkinson’s disease.

Walking practice by fixating upper limbs to the back of the body in shoulder extension and internal rotation position

A treadmill is a device used for walking practice at a constant speed. Hemiplegic patients develop asymmetric walking pattern due to the shortened support phase of the paralyzed side[24]. Walking practice using a treadmill increases step length[25,26]. A device with ground reaction force sensor can give a variety of information on walking related to ground contact to therapists or patients. A lot of patients have a fear for moving belt. As is the case with hemiplegic patients with sensory disorder or disturbance of sensation who feel fear about the moving belt, this also

Fig. 2. Normal gait practice (left) and gait practice with the upper limb immobilized on the back in shoulder extension internal rotation (right)

applies to elderly people with reduced postural control function. It is necessary to adjust the speed and take time to determine the appropriate speed.

We develop and provide the NEURO (NovEl Intervention Using Repetitive TMS and Intensive Occupational Therapy) program consisting of rTMS, physical therapy, and occupational therapy in patients who have a high tendency to bend due to upper limb spasticity. In the NEURO protocol during 2 weeks of hospitalization, each subject received daily 40-min low-frequency rTMS and 240-min intensive therapeutic exercise. The rTMS was directed at the primary motor cortex of the patient's healthy hemisphere at 2400 pulses a day at a low frequency of 1 Hz. The stimulation intensity was set at 90% of the resting motor threshold for the first dorsal interosseous muscle of the non-paralyzed side. The therapeutic exercise was a combination of one-to-one training for 120 min and self-exercising for 120 min. In physical therapy, we have intervention by utilizing the effect of reducing spasticity follow rTMS with the intent of gait reconstruction.

It is demonstrated that walking practice by fixating upper limbs to the trunk using an arm sling (Fig. 2) enables load application to the paralyzed side more easily and that it extends the stance duration[27)]. However, a posture by positioning the upper limb anterior to the body with an arm sling shifts the COM backward. To deal with, we employ walking practice by fixating upper limbs to the back of the body with the belt. Fixating upper limbs to the back of the body inevitably shits the COM forward. The shoulder extension and internal rotation position are not frequently used in hemiplegic patients during walking. This training method is expected to improve the shift of COM forward, trunk rotation, and application of load to the paralyze side as well as load evenly distributed on both sides shown with a symbol of butterfly illustrated during normal walking (Fig. 3).

Physical therapy combined with botulinum toxin

rTMS is known to reduce upper limb spasticity. While rTMS is reported to have a treatment effect on the lower limbs in terms of improvement in the gait speed[28)], the improvement in gait patterns represents a challenge. We have so far investigated the impact of rTMS to the upper limbs on the lower limb function and also the effect of the combination with physical therapy. Some studies report that the spasticity of ankle plantar flexors has a huge impact on asymmetric walking pattern[29,30)]. It is shown that the use of botulinum toxin in rehabilitation therapy increases the walking ability of hemiplegic patients due to its effect to alleviate the spasticity of ankle plantar flexors significantly[31)]. In particular, the use of botulinum toxin in combination with rTMS has a high potential for realizing the load application in ankle dorsiflexion during the stance phase. It may be necessary to reconsider the indication or change in orthoses by controlling the movement of lower limb orthoses and understanding the impact of knee or hip joint during the terminal stance phase due to load application to the forefoot precisely. If sensory disorder is mild, it is possible to learn and apply a load in the ankle dorsiflexion position again.

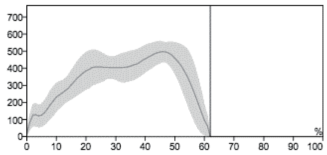
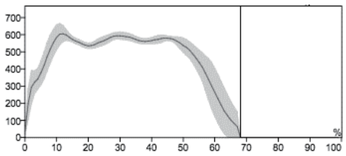
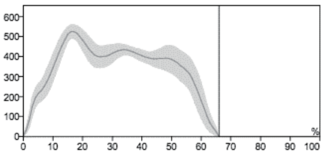
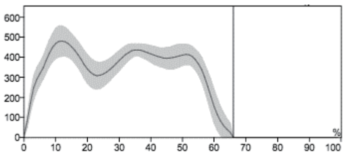
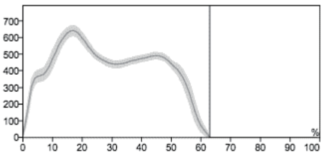
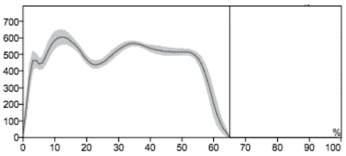
	Left / Butterfly sign / Right	Average Force(N)	
Before intervention		 Max force1: 407.9N, 24% from gait cycle Max force2: 496.5N, 46% from gait cycle	 Max force1: 606.5N, 12% from gait cycle Max force2: 579.5N, 45% from gait cycle
After 1 week		 Max force1: 525.8N, 17% from gait cycle Max force2: 434.2N, 34% from gait cycle	 Max force1: 480.9N, 12% from gait cycle Max force2: 436.4N, 35% from gait cycle
After 2 weeks		 Max force1: 641.0N, 17% from gait cycle Max force2: 490.8N, 45% from gait cycle	 Max force1: 605.2N, 12% from gait cycle Max force2: 566.3N, 35% from gait cycle

Fig. 3. Butterfly sign and change in floor reaction force

After 1 and 2 weeks, the data are from walking with the belt immobilization removed. The butterfly sign was gradually drawn and a bimodal effect could be seen in the floor reaction force.

Improvement of Functional Impairment and Role of Physical Therapy Combined

In hemiplegic patients, recovery refers to the restoration of a function back to a normal state, whereas compensation refers to the substitution with a different state before its onset[32). Most patients with paralysis experience compensation. For kinetic therapy, it is required to choose a learning theory or trade-off concept on a case-by-case basis. Motor learning theory is a concept of neuropsychology aiming at automatization by giving the knowledge results (correct information) appropriately and by repeating practice. The motor learning theory is applied to a wide range of treatments. There are very few cases where physiotherapists assess whether patients can practice motor learning after being provided correct information. Motion analysis based on observations works out problems by breaking into more simple motion and comparing that with compound motion consisting of combination of individual simple motions. One must understand that the patients are always in the unstable state due to reduced separation motion or sensory disorder seen in paralysis. A program is needed to choose muscles whose activities should be suppressed or those whose activities should be elevated or for long-term planning of learning on the position of the COM.

Conclusions

It is no exaggeration to say that independent gait depends on whether patients can live an independent life. In the aging society, rTMS stands as one of the therapeutic approaches to acquire smooth gait, which is widely recognized. Rationale is required for physical therapy performed in combination with rTMS. There are quite a few physical therapy modalities with unclear content despite advanced rehabilitation medicine. In rehabilitation medicine as aftertreatment program, one should keep in mind to understand which is physical therapy and to perform a certain treatment tailored to individual patient's life by learning the patient lifestyle in the process of assessing meticulously and collecting information. It is important to provide therapy that physiotherapists can do after patients understand what paralysis is.

Conflict of Interest: The author declares no conflicts of interest.

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PHYSICAL
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ORIGINAL ARTICLE

Characteristics and Related Factors of One-year Transition in Exercise Tolerance Following an Emergency Declaration due to the Coronavirus Disease 2019 Pandemic in Patients on Phase III Cardiac Rehabilitation

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ABSTRACT. Objective: This study aimed to understand the long-term transition of exercise tolerance in patients on phase III cardiac rehabilitation (CR) and clarify the characteristics of patients with a high risk of declined exercise tolerance during the first emergency declaration. Methods: Patients who participated in phase III outpatient CR before the first emergency declaration and those who performed cardiopulmonary exercise testing were at ≥2-time points: before and at 3 or 12 months post-emergency declaration. Exercise tolerance transition at 3-time points was analyzed, and whether different social background factors affected the peak oxygen uptake ($\dot{V}O_2$) transition method remains to be examined. Results: A total of 101 (median age 74.0 years, 69% men), and both peak $\dot{V}O_2$ and anaerobic threshold (AT) significantly declined from pre-declaration to 3 months post-declaration but recovered to levels likely similar from pre-declaration at 12 months (peak $\dot{V}O_2$: from 17.3 to 16.7 to 18.7 mL/min/kg; AT: from 11.8 to 11.2 to 11.6 mL/min/kg). Further, patients with multiple comorbidities at pre-declaration had a significantly lower peak $\dot{V}O_2$ at 3 months (−1.0 mL/min/kg, $p = 0.025$) and it remained significantly low in those with a slower gait speed at 12 months after lifting the emergency declaration (−2.5 mL/min/kg, $p = 0.009$). Conclusion: The emergency declaration declined the exercise tolerance in patients on phase III CR but improved to pre-declaration levels over time, but more likely declined in patients with multiple comorbidities during pre-declaration and those with low-gait speeds were less likely to improve their declined exercise tolerance.

Key words: COVID-19, Peak $\dot{V}O_2$, Comorbidity, Gait speed

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The coronavirus disease 2019 (COVID-19) is affecting the world severely, causing high global morbidity and mortality rates. The World Health Organization declared COVID-19 as a pandemic in March 2020, and the Japanese government declared a state of emergency on April 7, 2020. Consequently, people were forced to restrict their outings and social activities, which significantly stagnated their activities.

A previous study on an older population in Japan reported a 26.5% reduction in physical activity during the emergency declaration[1)]. Another study on patients with heart failure in the Czech Republic also found that the national

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lockdown for COVID-19 infection control restricted most outdoor activities, except for a few activities, such as shopping for daily necessities, which reduced approximately 1100 steps per day in physical activity[2]. Furthermore, a previous study on phase III cardiac rehabilitation (CR) patients reported that reduced physical activity time and exercise tolerance were associated with emergency declaration[3].

On the other hand, a previous study on community-dwelling elderly people has shown that decreased physical activity with the emergency declaration shows a tendency to improve again[4]. Furthermore, exercise intolerance due to training interruption has been reported to improve again with training resumption[5]. Therefore, the emergency declaration is expected to be lifted to improve exercise tolerance again, as it was in the pre-pandemic life, as soon as the epidemic situation improves. However, whether declined exercise tolerance was improved by the emergency declaration and whether the difference between those who improved and unimproved remain unclear. In addition, clarifying the method for screening people at risk of declined exercise tolerance and recommending appropriate physical activities required similar infection control measures due to the emergence of further mutant strains and unknown viruses. It will be valuable knowledge for the development of intervention programs.

Therefore, this study aimed to determine how exercise tolerance in patients on phase III CR changes before the first emergency declaration to 1 year after lifting restrictions and determine the characteristics of patients with low exercise tolerance even after the lifting of the emergency declaration.

Methods

Study design and participants

This multicenter retrospective cohort study enrolled patients from four urban medical institutions in Japan (Itabashi Heart Clinic, Iwatsuki Minami Hospital, Kisen Hospital, and Sonoda Third Hospital) who had participated in phase III outpatient CR before the first emergency declaration (from April 7 to May 25, 2020). Patients who underwent a cardiopulmonary exercise test (CPET) approximately 6 months before the emergency declaration (from October 1, 2019 to April 6, 2020) were analyzed. Patients took the CPET test at either or both of the following time points: approximately 3 months (from May 26, 2020 to August 31, 2020) or 12 months (May 26, 2021 to August 31, 2021) after lifting the emergency declaration. The exclusion criteria were as follows: nonindependence in activities of daily living, disagreement to participate, and respiratory exchange ratio (RER) <1.0 in CPET before the emergency declaration[6].

This study was conducted in compliance with the “Declaration of Helsinki” and “Ethical Guidelines for Medical Research Involving Human Subjects.” The study protocol was reviewed and approved by the ethical review board of Iwatsuki Minami Hospital (approval no. 33). Consent was obtained from the participants using an opt-out method.

Evaluation of exercise tolerance and physical function

Participants underwent CPET on a bicycle ergometer in an upright sitting position. A work rate protocol was created using a short-duration ramp test[7] and an exercise load electrocardiography program tailored based on physical function. During CPET, expiratory gas analysis was continuously performed through breath-by-breath respiratory gas exchange measurements. Two facilities used the CPEX-1 system (Inter Reha, Tokyo, Japan) and the other two used the Aero Monitor AE-310S (Minato Medical Science, Osaka, Japan) as the breath-by-breath gas analyzers. Peak oxygen uptake ($\dot{V}O_2$) was defined as the highest $\dot{V}O_2$ value obtained during the last minute of CPET. Anaerobic threshold (AT) was detected using the V-slope method[8]. CPET was terminated only if the patient requested or if the physician stopped the test for medical reasons, including the occurrence of symptoms or high-risk traits, such as decreased systolic blood pressure of >10 mmHg with increasing workload (persistently below baseline), high-risk ST changes, and sustained ventricular tachycardia[9].

Hand-grip strength was measured using a grip strength meter in a standing position. Two measurements were performed on each side, and the maximum value (kg) was used as the representative value. For the gait speed test, the time taken for a usual 4 or 5 m gait was measured twice, the fastest value taken, and m/s calculated.

Medical record information

The following clinical characteristics were obtained from the patients’ medical records: age, sex, body weight, body mass index (BMI), family structure, employment status, Walk Score as a living environment, disease, comorbidity, β-blocker oral status, and left ventricular ejection fraction.

The number of CR participation was examined in patients during the emergency declaration. The frequency of participating in the outpatient CR program during the emergency declaration period was also investigated. During the first emergency declaration, CR was performed at each facility to achieve infection control measures. The program followed the rehabilitation guidelines for cardiovascular diseases and primarily consisted of warming up, aerobic exercises, resistance training, and cooling down[10].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation when assuming a normal distribution or as median (interquartile range) when not assuming a normal distribution, and the categorical variables are expressed as frequency (%).

Linear mixed-effects models were used to compare exercise tolerance, body weight, and BMI before and 3 months and 12 months after the emergency declaration. The calculated estimated marginal means of peak $\dot{V}O_2$, AT, peak RER, body weight, and BMI were used to illustrate changes during measurement. To further confirm the impact of the emergency declaration, a similar analysis was conducted from

January 1, 2020 to April 6, 2020, only for participants who took the CPET prior to the emergency declaration.

Then, an unpaired *t*-test was performed to compare the peak $\dot{V}O_2$ before the emergency declaration in the presence and absence of background factors. The presence of a background factor is defined as 1, whereas the absence of a background factor is defined as 0. Gender was defined as 1 for men and 0 for women, household composition as 1 for those living alone and 0 for those living together, and the employment status as 1 for workers and 0 for nonworkers. The presence or absence of multiple comorbidities was defined as having three or more or two or fewer comorbidities, respectively, with 1 having three or more comorbidities and 0 having two or fewer comorbidities[11]. For the living environment, the Walk Score, an index used for evaluating neighborhood walkability, is defined as a low value for <90 points, with 1 for <90 points and 0 for ≥90 points[12,13]. Grip strength and usual gait speed were used as physical functions at pre-emergency declaration. According to the revised Japanese version of the Cardiovascular Health Study (J-CHS) criteria, grip strength is defined as low grip strength of <28 kg for men and <18 kg for women, with normal grip strength being higher. The usual gait speed is defined as a slow gait speed when showing <1.0 m/s and as a normal gait speed when showing >1.0 m/s[14]. The low grip strength group was set to 1, the normal grip strength group was set to 0, the slow gait speed group was set to 1, and the normal gait speed group was set to 0.

Next, background factors were found to be associated with peak $\dot{V}O_2$ changes from the pre-emergency declaration to 3 months and 12 months after lifting. A linear mixed-effects model was used, with an objective variable as peak $\dot{V}O_2$ and background factors (sex, household composition, employment status, comorbidity, living environment, grip strength, and usual gait speed), and the interaction terms during measurement as explanatory variables separately. All background factors were used before the pre-emergency declaration. Adjustment variables were age, sex (except when sex was entered in the interaction term), and peak $\dot{V}O_2$ pre-emergency declaration. As a result, this generated point estimates (unstandardized coefficients) and 95% confidence intervals for the difference at 3 and 12 months after lifting the emergency declaration for those with a background factor of 1 versus those without a background factor of 0. Further, using the estimated marginal mean, the transition during measurement of the peak $\dot{V}O_2$ with and without background factor is illustrated.

The significance level was set to p <0.05 in all statistical analyses. The Stata/BE 17.0 (College Station, TX, USA) was used for statistical analysis.

Results

Among the 119 enrolled participants, 18 were excluded (3 who needed assistance with activities of daily living, 1 who refused to participate, and 14 with an inadequate load on CPET). Finally, the data of 101 people were analyzed. A total of 38 participants were able to perform CPET at both 3 and 12 months after the emergency declaration was lifted, 90 were able to perform CPET after 3 months, and 11 were able to perform CPET after 12 months. The median age of the participants was 74.0 (67.0–80.0 years), and 69 (69%) were men. Participants' primary disease for CR was myocardial infarction in 25 (24.8%), angina pectoris in 22 (21.8%), cardiac surgery in 13 (12.9%), chronic heart failure in 33 (32.7%), aortic disease in 1 (1.0%), peripheral artery disease in 3 (3.0%), and transcatheter aortic valve implantation in 4 (4.0%). The median left ventricular ejection fraction of participants was 60.0% (49.0%–64.0%), and 75 (74.3%) of them were taking β-blockers. Furthermore, 62 (61.4%)

Table 1. Clinical characteristics

	Overall (*n* = 101)
Age, years	74.0 (67.0–80.0)
Men, *n* (%)	69.0 (68.3)
Body weight (kg)	60.4 ± 11.3
BMI	23.4 (20.8–25.4)
Disease, *n* (%)	
Myocardial infarction	25 (24.8)
Angina pectoris	22 (21.8)
Postcardiac surgery	13 (12.9)
Chronic heart failure	33 (32.7)
Aortic disease	1 (1.0)
Peripheral artery disease	3 (3.0)
Post TAVI	4 (4.0)
Comorbidity, *n* (%)	
Hypertension	85 (84.1)
Dyslipidemia	71 (70.3)
Former or current smoker	56 (55.4)
Diabetes mellitus	41 (41.0)
Cardiovascular disease	33 (32.7)
Chronic kidney disease	26 (25.7)
Orthopedic disorders	25 (24.8)
Malignant tumor	11 (10.9)
Cerebrovascular disease	7 (6.9)
Respiratory disease	2 (2.0)
LVEF, %	60.0 (49.0–64.0)
β-blocker medication, *n* (%)	75 (74.3)
Multiple comorbidities 3 or more, *n* (%)	62 (61.4)
Worker, *n* (%)	32 (31.7)
Living alone, *n* (%)	25 (24.8)
Walk Score, points	80.0 (67.0–88.0)
Number of CR during the emergency declaration, times	4.0 (2.0–6.0)

Continuous variables are expressed as mean with standard deviation in parenthesis or median with interquartile range in parenthesis

BMI, body mass index; TAVI, transcatheter aortic valve implantation; LVEF, left ventricular ejection fraction; CR, cardiac rehabilitation

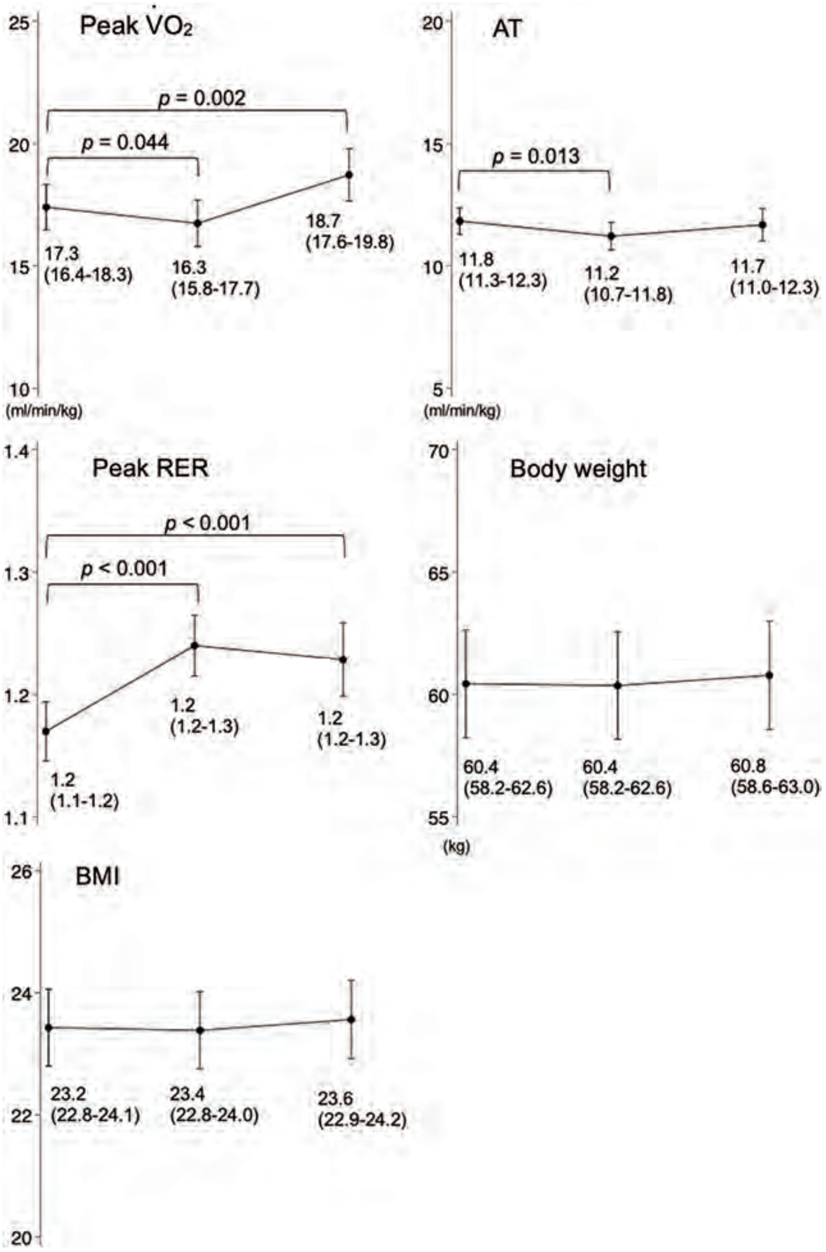

Fig. 1. Exercise tolerance and body composition before the emergency declaration, 3 months after lifting, and 12 months after lifting

Values are, in order, estimated marginal mean values before the emergency declaration, 3 months after lifting the emergency declaration, and 12 months after lifting the emergency declaration.

$\dot{V}O_2$, oxygen uptake; AT, anaerobic threshold; RER, respiratory exchange ratio; BMI, body mass index

had three or more comorbidities, 32 (31.7%) were working, and 25 (24.8%) were living alone. Participants had a median Walk Score of 80.0 (67.0–88.0), and the median number of patients who participated in the outpatient CR during the emergency declaration was 4 (2.0–6.0) (Table 1).

Figure 1 shows changes in the peak $\dot{V}O_2$, AT, peak RER, body weight, and BMI at pre-emergency declaration, 3 months after lifting, and 12 months after lifting. The peak $\dot{V}O_2$ significantly decreased from 17.3 mL/min/kg to 16.3 mL/min/kg at 3 months ($p = 0.044$) and to 18.7 mL/min/kg at 12 months after lifting the emergency declaration, a significant increase compared to that in pre-emergency declaration ($p = 0.002$). The AT significantly decreased from 11.8 mL/min/kg to 11.2 mL/min/kg at 3 months after lifting the emergency declaration ($p = 0.013$) compared to pre-emergency declaration. Notably, body weight and BMI did not change. There were 56 participants who performed CPET prior to the emergency declaration from January 1, 2020 to April 6, 2020. The trends in peak $\dot{V}O_2$ and AT were compared to the analysis with 101 participants and the trends were the same (Appendices 1 and 2; all supplementary files are available online).

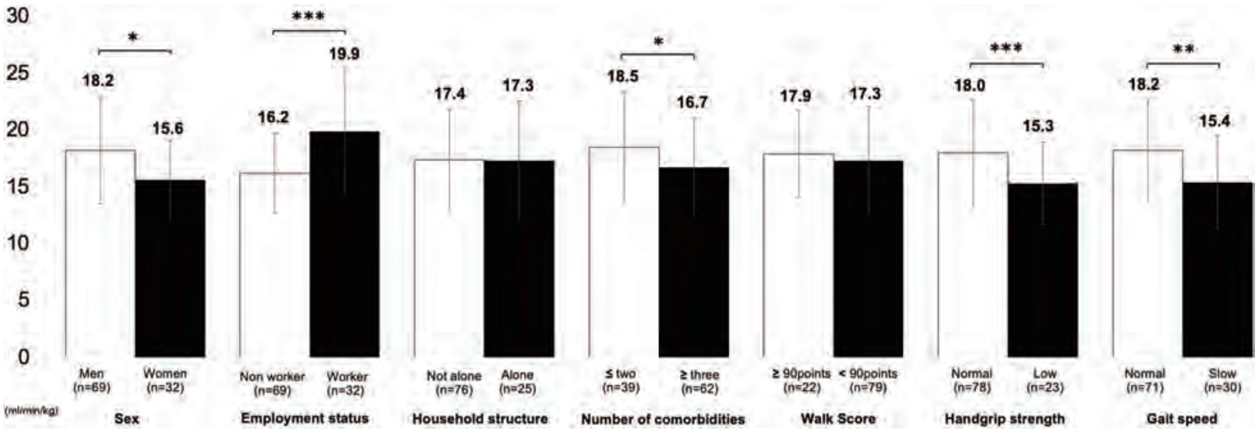

Fig. 2. Peak $\dot{V}O_2$ before the emergency declaration classified by background

Error bars indicate 95% CI.

*: p <0.05, **: p <0.01, ***: p <0.001

$\dot{V}O_2$, oxygen uptake; CI, confidence interval

Table 2. Results of the interaction between peak $\dot{V}O_2$ transition and background factors × evaluation period in the linear mixed-effects model

Background factor	Evaluation period*	Coefficient Background factor × Evaluation period	95% CI	*p*
Men	3 months after lifting	–1.27	–2.62, 0.08	0.066
	12 months after lifting	0.78	–0.89, 2.45	0.361
Worker	3 months after lifting	–0.38	–1.74, 0.99	0.588
	12 months after lifting	–0.27	–2.04, 1.49	0.761
Living alone	3 months after lifting	–0.93	–2.42, 0.56	0.223
	12 months after lifting	–0.16	–1.99, 1.67	0.863
Number of comorbidities (≥3)	3 months after lifting	–1.46	–2.73, –0.18	0.025
	12 months after lifting	–0.22	–1.82, 1.39	0.788
Walk Score (<90 points)	3 months after lifting	–1.36	–2.92, 0.20	0.087
	12 months after lifting	–1.05	–3.16, 1.05	0.326
Low handgrip strength (men <28 kg, women <18 kg)	3 months after lifting	0.56	–0.99, 2.21	0.479
	12 months after lifting	–1.01	–2.73, 0.71	0.248
Slow gait speed (<1.0 m/s)	3 months after lifting	–0.10	–1.47, 1.28	0.891
	12 months after lifting	–2.18	–3.81, –0.55	0.009

*Estimated the difference of changes in the evaluation period with background factor (1) against no background factor (0), based on the period before the emergency declaration

$\dot{V}O_2$, oxygen uptake; CI, confidence interval

Figure 2 shows the peak $\dot{V}O_2$ during the pre-emergency declaration for each background factor. Comparing men with women (15.6 ± 4.7 vs. 18.2 ± 4.7 mL/min/kg, $p = 0.006$) and workers with nonworkers (16.2 ± 3.5 vs. 19.9 ± 5.4 mL/min, $p < 0.001$), the peak $\dot{V}O_2$ was high, and a statistically significant difference was observed. Furthermore, when comparing patients with low grip strength and those with normal grip strength (18.0 ± 4.6 vs. 15.3 ± 3.5 mL/min/kg, $p = 0.012$), those with slow gait speed and those normal (18.2 ± 4.5 vs. 15.4 ± 4.0 mL/min/kg, $p = 0.005$), and those who had three or more comorbidities (18.5 ± 4.8 vs. 16.6 ± 4.2 mL/min/kg, $p = 0.049$) and those who had two or fewer comorbidities, the peak $\dot{V}O_2$ was low, and a statistically significant difference was observed.

Table 2 shows the unstandardized coefficients, 95% confidence intervals, and p-values calculated by imputing the interaction term between the presence and absence of background factors × time of evaluation to the linear mixed-effects model. Moreover, the estimated marginal mean based on the results is shown in Figure 3. At 3 months after the lifting of the emergency declaration, based on the values before the emergency declaration, those with ≥3 comorbidities had significantly lower peak $\dot{V}O_2$ than those ≤2 (−1.46 mL/min/kg, $p = 0.025$). At 12 months after lifting the emergency declaration, patients with a slow gait speed before the emergency declaration had a significantly lower peak $\dot{V}O_2$ than those with a normal gait speed (−2.18 mL/min/kg, $p = 0.009$).

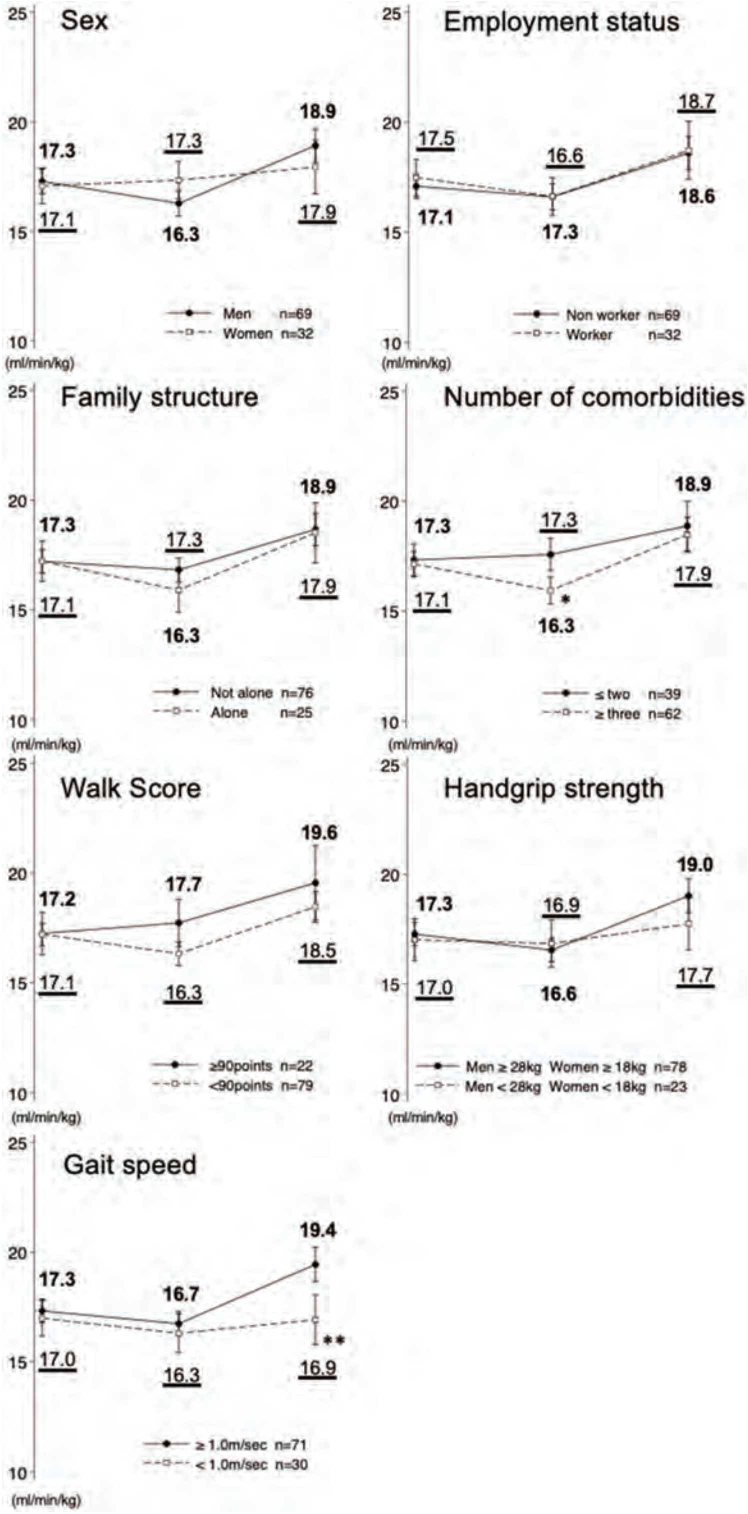

Fig. 3. Peak $\dot{V}O_2$ background at each evaluation point

Values are, in order, estimated marginal mean values before the emergency declaration, 3 months after lifting the emergency declaration, and 12 months after lifting the declaration.

Error bars indicate 95% CI.

The results show that there were significant differences between the groups over time, based on the time before the emergency declaration.

*: $p < 0.05$, **: $p < 0.01$

$\dot{V}O_2$, oxygen uptake; CI, confidence interval

Discussion

This is the first study to verify the transition of exercise tolerance and related factors in patients on phase III CR from before to 12 months after lifting the emergency declaration. The results showed that both the peak $\dot{V}O_2$ and AT decreased in the overall participants 3 months after lifting the emergency declaration but improved to the level before the emergency declaration and continued till 12 months after lifting the emergency declaration. The peak $\dot{V}O_2$ transition was significantly lower in participants with ≥3 comorbidities than in those with ≤2 comorbidities at 3 months after lifting. At 12 months after lifting the emergency declaration, those with slower gait speeds before the emergency declaration were less likely to improve their peak $\dot{V}O_2$ than those with normal gait speeds.

Previous studies in patients on phase III CR have reported that physical activity was positively correlated with the peak $\dot{V}O_2$15) and that a decreased physical activity time during the emergency declaration period was associated with decreased exercise tolerance3). Conversely, a previous study of patients with chronic heart failure reported that physical function and frailty worsened before and after interrupting the outpatient CR due to emergency declaration but improved again when outpatient CR was resumed16). Furthermore, a previous study of elderly community-dwelling people reported that the amount of physical activity declined after the emergency declaration showing a tendency to improve again from 3 months after lifting the emergency declaration4). Generally, exercise intolerance due to training interruption improves again when training is resumed5). Considering these previous studies, the frequency of participation in outpatient CR and the amount of physical activity recovered in study participants after lifting the emergency declaration improved. As a result, exercise tolerance improved again.

The presence of ≥3 comorbidities increased the risk of declined exercise tolerance for 3 months after lifting the emergency declaration. A previous study has reported that patients with heart disease and lifestyle-related diseases are at a high risk of serious injury due to COVID-1917). Furthermore, Japanese information media has reported the risk of severe COVID-19 infection to be higher in patients with underlying diseases. These factors may have influenced those with more comorbidities to refrain excessively from going out and engaging in activities. As a result, the amount of physical activity is more likely to decrease, which may have led to a decreased peak $\dot{V}O_2$.

Previous studies on community-dwelling elderly people have reported that grip strength and gait speed are both predictors of peak $\dot{V}O_2$18). However, the results of the present study suggested that people with a slow gait speed before the emergency declaration had a high risk of a declined peak $\dot{V}O_2$ 12 months after lifting the emergency declaration. Previous studies have shown that gait speed predicts the subsequent activities of daily living decline19) and that those with a gait speed of <1.0 m/s have difficulty walking at crosswalks20); therefore, gait speed can have a direct impact on daily life. Furthermore, the study participants lived in the metropolitan area, which tended to have a particularly poor COVID-19 infection rate in Japan21), and were asked to refrain from leaving the home unnecessarily for a long time even after lifting of the first emergency declaration. Therefore, slow gait speed may have limited the amount of activity for a longer time, resulting in lesser improved peak $\dot{V}O_2$. Thus, it may be necessary to recommend more aggressive self-training to maintain activity levels in those with slower gait speed.

This study has the strengths of using longitudinal data to investigate exercise tolerance in patients on phase III CR before and after the emergency declaration due to the COVID-19 epidemic. Conversely, some limitations should still be considered. First, the amount of physical activity during the study period is inadequately investigated. Therefore, whether the study results reduce the physical activity associated with the emergency declaration or normal aging-related changes remains controversial. Second, although the study was conducted in a multicenter setting, the number of patients was less. Third, patients usually participated in the outpatient CR and performed CPET. Therefore, it is possible that those with relatively good physical function and a high motivation to exercise are included in the population. Therefore, physical function was relatively maintained and was biased toward those who were highly motivated to exercise. Sampling biases may have occurred and influenced the results. Fourth, although we have described background factors that make peak $\dot{V}O_2$ more likely to decline and less likely to improve, these subjects are generally a difficult population to recover from, and it is not possible to confirm whether the differences observed are the result of the emergency declaration or not.

Conclusion

Before and after the first emergency declaration, exercise tolerance of patients on phase III CR declined; however, after 1 year, it improved to the level as before the declaration. However, those with ≥3 comorbidities before the declaration declined to 3 months after lifting and those with a gait speed of <1.0 m/s had low peak $\dot{V}O_2$ until 12 months after lifting the emergency declaration. This study suggests that increasing physical activity and providing an intervention program for patients with such characteristics should be promoted.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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Supplementary Material (Appendices)

Appendix 1. Clinical characteristics in 56 participants

Appendix 2. Exercise tolerance and body composition of 56 participants before the emergency declaration, 3 months after lifting, and 12 months after lifting

PHYSICAL
THERAPY
RESEARCH

ORIGINAL ARTICLE

Effect of 8-week Shoulder External Rotation Exercise with Low Intensity and Slow Movement on Infraspinatus

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ABSTRACT. Objective: Generally, low-intensity training is recommended as selective training of the infraspinatus muscle. This study aimed to investigate whether an 8-week intervention of low-intensity, slow-movement, external rotation exercise of the shoulder led to an increase in muscle strength with shoulder external rotation and cross-sectional area (CSA) infraspinatus muscle. Methods: Sixteen healthy male volunteers were randomly assigned to the low-intensity and slow-movement (LS) group (N = 8) or the normal-intensity and normal-speed (NN) group (N = 8). The LS and NN groups performed shoulder external rotation exercises with low intensity and slow movement, and normal intensity and normal speed, respectively. The exercise session consisted of three sets of 10 repetitions, which were performed three times per week for 8 weeks. We measured the CSA of the infraspinatus and muscle strength of the shoulder external rotation before and after the 8-week intervention. Results: A significant increase in infraspinatus CSA from baseline to 8 weeks was found in the LS group (7.3% of baseline) but not in the NN group. No significant differences were found in the muscle strength of shoulder external rotation. Conclusion: Our results suggest that low-intensity exercise of the infraspinatus is effective for muscle hypertrophy when performed with slow movement. This finding may help patients who should avoid excessive stress in the early phase of rehabilitation.

Key words: Rotator cuff, Infraspinatus, Low intensity, Slow movement, Hypertrophy

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Two stability mechanisms in shoulder function are identified: static and dynamic. Static stabilizers consist of anatomical structures such as the capsules, ligaments, and labrums, whereas dynamic stabilizers consist of rotator cuff and periscapular muscles[1,2]. Given their functions as dynamic stabilizers, the coordinated movement of the deltoid and rotator cuff muscles is essential for smooth shoulder joint movement. Specifically, the infraspinatus, subscapularis, and teres minor muscles stabilize the humeral head against the glenoid and provide a fulcrum for the actions of the deltoid and supraspinatus muscles[3]. In the transverse plane, the balance of the infraspinatus and subscapularis controls the anteroposterior movement of the humeral head[4]. Infraspinatus dysfunction is known to decrease the stability of the humeral head, causing superior migration and impingement of the subacromial structures. A previous study reported that a patient with subacromial impingement also had infraspinatus dysfunction[5].

Previous studies have investigated the activity of the infraspinatus during shoulder exercises using electromyography (EMG)[6–9]. Bitter et al. reported that low-intensity shoulder external rotation was appropriate to optimize the relative contribution of the infraspinatus while minimizing deltoid activity[7]. Moreover, several studies have investigated the effect of low-intensity exercise on the infraspinatus (full can, empty can, shoulder external rotation, etc., with an elastic band or lightweight dumbbell) and found no significant and/or a very small increase in shoulder external rotator muscle strength[10–12]. However, none of these studies have

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investigated the effect of low-intensity exercise on infraspinatus cross-sectional area (CSA). Therefore, although low-intensity training is frequently recommended for selective infraspinatus training, the effect of this training on increasing infraspinatus muscle strength and CSA remains unclear.

Recent studies have suggested that low-intensity resistance exercises with slow movement and tonic force generation can increase muscle strength and CSA, which have mainly been investigated in the lower extremity[13–15]. This low-intensity exercise is a safe training method because of less stress on the joints[14]. Low-intensity exercises are recommended for selective infraspinatus activation and avoidance of overloading the glenohumeral joint; therefore, we hypothesized that low-intensity exercises performed with slow movement can increase muscle strength and CSA of the infraspinatus.

This study aimed to investigate whether 8 weeks of low-intensity shoulder external rotation exercises, performed with slow movement, would lead to an increase in the CSA and muscle strength of the infraspinatus. Previously, we have shown that low-intensity and slow-movement external rotation exercise caused greater stress on the infraspinatus compared to the stress caused by normal-intensity and normal-speed condition[16]. In addition, low-intensity and normal-speed condition did not cause the stress on infraspinatus. Therefore, we selected low-intensity and slow-movement condition and normal-intensity and normal-speed condition, which are expected to have training effects on the infraspinatus in this study.

Methods

Study design

This randomized controlled study examined the effects of low-intensity exercises with slow movement performed for 8 weeks and was conducted in accordance with the CONSORT (Consolidated Standards of Reporting Trial) statement[17]. Figure 1 shows the experimental protocol.

As baseline evaluation, we measured infraspinatus CSA using ultrasonography, isometric shoulder external rotation strength using a handheld dynamometer, and isokinetic external rotation strength using a dynamometer. Then, the participants were randomly assigned to one of the two experimental groups. The exercise session consisted of three sets of 10 repetitions, which were performed three times per week for 8 weeks. Researchers supervised the participants for the initial 4 weeks. After 4 weeks of evaluation, the participants performed the exercises on their own. The infraspinatus CSA and muscle strength of the shoulder external rotation were measured after 4 and 8 weeks of exercise. To avoid the acute effects of exercise, all measurements were performed at least 48 h after the most recent exercise session. Additionally, an EMG surface electrode was used to record the activities of the infraspinatus and posterior deltoid muscles in the first exercise session.

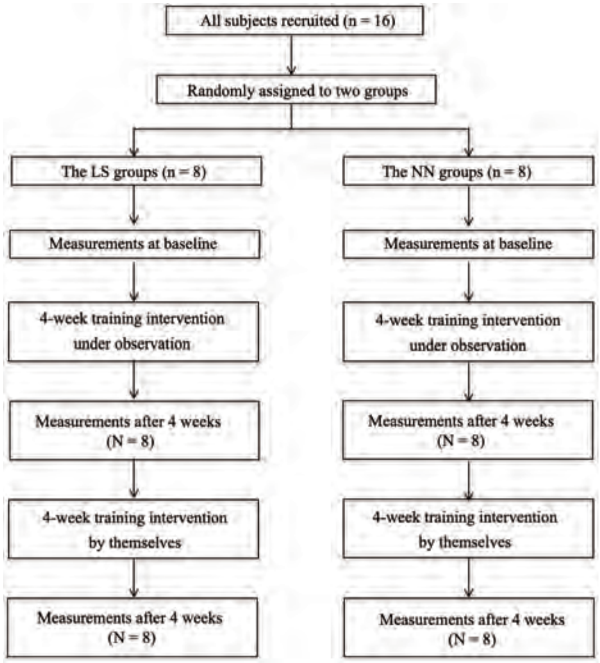

Fig. 1. Flow chart of the experimental protocol

LS, low intensity and slow movement; NN, normal intensity and normal speed

Participants

Sixteen healthy male volunteers, aged 22–32 years, participated in this study and were not involved in any upper extremity strength training or any kind of regular overhead sports during the study. Participants with a history of musculoskeletal injury or neuromuscular disease involving their upper arms were excluded. A power of 0.80, alpha level of 0.05, effect size F of 0.4 (large), and number of measurements of 3 were assumed for the analysis of variance for the split-plot factorial design, which determined the sample size of 12 in total. All participants were fully informed of the procedures and purpose of this study, and they provided written informed consent. Additionally, the Ethical Review Board of Kyoto University Graduate School of Medicine approved this research (E1407).

Procedures

Measurement of infraspinatus CSA

B-mode ultrasonography (LOGIQ Book XP; GE Healthcare Japan, Tokyo, Japan) with an 8-MHz linear probe was used to obtain images of the infraspinatus and measure CSA. The infraspinatus CSA was measured as described in a previous study[18]. Briefly, the participants lay prone on the treatment table, with their arms on their sides. To determine the standardized location for the ultrasound, the acromial angle, trigonum spinae, and inferior angle of the scapula were identified through palpation and marked with a marker. After the landmarks were identified, an investigator drew a line connecting the acromial and inferior angles and a second line perpendicular to the first line, intersecting the trigonum spinae (Fig. 2). Hypoechoic markers were placed along the second line. We constructed the full image of the infraspinatus from a series of overlapping images guided by the hypoechoic markers using Adobe Photoshop (Adobe, San Jose, CA, USA) (Fig. 3). Then, the CSA was measured by tracing the inside of the epimysium of the infraspinatus using ImageJ software (National Institutes of Health, Bethesda, MD, USA)[18]. The average of three measurements of the infraspinatus CSA was calculated to express the values for each participant in each session, in which the experimenter was blinded for the group allocation and timing of measurement. We also calculated the percentage of change in the infraspinatus CSA using the following equation:

Percentage of change (%) = (value at 8 weeks − value at baseline)/value at baseline × 100.

Measurement of muscle strength

Isometric and isokinetic strength of the shoulder external rotator muscles was assessed. The maximal isometric shoulder external rotation torque was measured using a handheld dynamometer (PowerTrack II MMT Commander; JTECH Medical, Midvale, USA). The participants sat on a chair, with their back upright, arms by their side in shoulder neutral rotation position, and elbows flexed to 90. The dynamometer was placed distal to the radius. Each subject made two times of maximal efforts during muscle strength tests, and we used the greater value for analysis. Strong verbal encouragement was provided during every contraction to promote maximal effort.

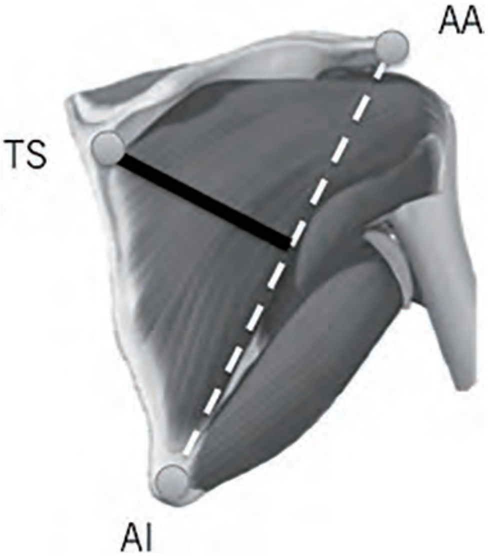

Fig. 2. Measuring place of infraspinatus CSA

TS, trignum spinae; AA, acromial angle; AI, inferior angle; CSA, cross-sectional area

The maximal isokinetic shoulder external rotation torque was measured using a dynamometer (MYORET RZ-450; Kawasaki Heavy Industries, Kobe, Japan). The participants lay in the supine position with the shoulder abducted 90° and the elbow flexed 90°. The shoulder joint was aligned with the axis of rotation of the dynamometer shaft, and the external rotation ranged 0°–90°. The torso and upper arms were fastened with a belt to avoid shoulder flexion or abduction. Then, both the concentric and eccentric maximal torques in shoulder external rotation were evaluated. After five practice repetitions, a test of two consecutive maximal efforts was conducted at 60°/s. After adequate rest, participants performed two consecutive maximal efforts at 120°/s. We used the greater peak torque in the test session for the analysis.

EMG

During the first session of exercise, an EMG (TeleMyo 2400; Noraxon USA, Scottsdale, AZ, USA) surface electrode (BlueSensor M; Ambu, Copenhagen, Denmark) was used to record muscle activity from the infraspinatus and posterior deltoid. Before the surface electrodes were applied, the participant's skin was prepared to reduce skin impedance. The surface electrode for the infraspinatus was positioned at the point halfway along the scapular spine and halfway down toward the inferior apex of the scapula, parallel to the muscle fibers[19]. Maximal voluntary isometric contractions (MVCs) were performed for 3 s to normalize EMG data, as previously described for manual muscle testing[7]. We provided strong verbal encouragement during every contraction to promote maximal effort.

The EMG data were sampled at 1500 Hz. Raw EMG signals were digitally filtered (band-pass filtered at 20–500 Hz) and were smoothed using a moving root mean square with a window of 50 ms. These EMG data were normalized and expressed as a percentage of their MVC. EMG values for

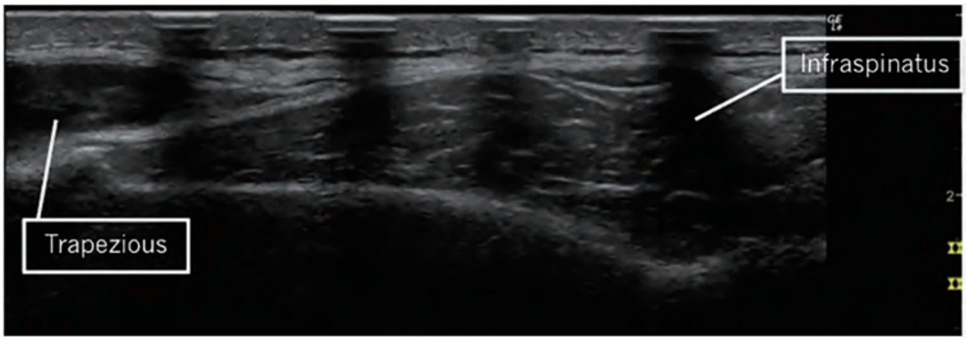

Fig. 3. Ultrasound image of the infraspinatus muscle constructed from the series of overlapping images

Fig. 4. Exercise task

each muscle were averaged across the eight intermediate repetitions of the 10 repetitions completed (% MVC). We also calculated an integrated EMG value for each muscle in the set of exercises and calculated the average of the three sets in the first exercise session (% MVC·s).

Exercise task

Previous studies examining the effects of low-intensity with slow-movement exercise in lower extremity muscles used 50% of the 1 repetition maximum (RM) as the low intensity. To prevent overstressing the joints, low-intensity exercise is generally considered more appropriate for rotator cuff muscles in rehabilitation[20,21]. In previous studies examining the effects of low load exercise for rotator cuff muscles, elastic band and 3-kg dumbbell were used[10–12]. However, even these loadings are considered too high for patients with shoulder disorders in the early phase of rehabilitation. Therefore, we used a 500-g dumbbell as low intensity in this study.

Between the two experimental groups, one group (low intensity and slow movement: LS) exercised with low intensity (dumbbell of 500 g) and slow movement (5 s of external rotation, 5 s of internal rotation, and 1 s of isometric actions with no rest between each repetition). The other group (normal intensity and normal speed: NN) exercised with normal intensity (dumbbell of 2.5 kg) and normal speed (1 s of external rotation and 1 s of internal rotation with 1 s of rest on a table between each repetition). The exercises targeted shoulder external rotation and were performed with the arm by the side and the elbow flexed 90° while lying on the side (Fig. 4). Participants held a towel under their arms to avoid trick motion. The range of shoulder joint motion for shoulder external rotation exercise was set from 45° internal rotation to 45° external rotation. Both groups repeated the movements at approximately constant speed and frequency by following a metronome.

Statistical analysis

All statistical analyses were performed with SPSS Statistics version 17.0 (SPSS, Chicago, USA). Differences between the LS and NN groups, including participant characteristics and all variables at baseline, were assessed using an independent t-test. For the measurements of the CSA and muscle strength, split-plot analyses of variance using two factors (groups × test time) were used to analyze the interaction and main effects. When we obtained a significant interaction, we used a paired t-test with the Holm method correction to determine the differences between the variables at baseline and after 4 and 8 weeks within the groups. Additionally, we used the Mann–Whitney U test to compare EMG values. Significance was accepted at $p < 0.05$.

Table 1. Characteristics of participants (mean ± SD)

	LS group (N = 8)	NN group (N = 8)
Age (y/o)	25.8 (±4.6)	23.0 (±1.1)
Height (cm)	177.2 (±5.2)	169.1 (±3.4)
Weight (kg)	65.5 (±7.7)	63.9 (±10.1)
External rotation muscle strength (Nm)	33.5 (±5.7)	32.0 (±4.0)
Infraspinatus CSA (cm^2)	13.4 (±1.9)	12.5 (±1.4)

SD, standard deviation; LS, low intensity and slow movement; NN, normal intensity and normal speed; y/o, years old; CSA, cross-sectional area

Table 2. Infraspinatus CSA (mean ± SD)

CSA (cm^2)	Baseline	4 weeks	8 weeks
LS	13.4 (±1.9)	13.7 (±2.2)	14.4 (±2.5)*
NN	12.5 (±1.4)	12.5 (±1.5)	12.5 (±1.3)

*: significant difference compared with baseline ($p < 0.05$)

CSA, cross-sectional area; SD, standard deviation; LS, low intensity and slow movement; NN, normal intensity and normal speed

Results

Sixteen participants were recruited from July 30 to September 20, 2012. No participants were excluded from the study, and all participants completed the exercise program. Therefore, all data of the LS (N = 8) and NN (N = 8) groups were used for statistical analysis. The participants performed the exercises >80% of the time during the intervention period based on the recording sheet. Table 1 shows the characteristics of the participants. The only significant difference between the groups was height.

Infraspinatus CSA

Table 2 shows the infraspinatus CSA. The significant main effect was presented between factors of time ($F = 7.19$, $p < 0.01$), and a significant interaction effect between groups and time was also found ($F = 7.84$, $p < 0.01$). The post-hoc test indicated that the infraspinatus CSA significantly increased in the LS group between baseline and 8 weeks. In the NN group, no significant changes were found in the infraspinatus CSA. The percentage of change in the infraspinatus was significantly greater in the LS group (7.3% ± 0.1%) than in the NN group (−0.1% ± 0.0%).

Table 3. External rotation muscle strength (mean ± SD)

Isometric (Nm)	Baseline	4 weeks	8 weeks
LS	33.5 (±5.7)	34.8 (±6.5)	35.5 (±6.3)
NN	31.6 (±3.9)	35.1 (±4.1)	33.8 (±5.6)
60°/s concentric (Nm)			
LS	21.8 (±8.8)	22.8 (±6.0)	22.5 (±3.9)
NN	25.6 (±4.0)	24.6 (±2.9)	25.1 (±4.1)
120°/s concentric (Nm)			
LS	21.0 (±7.4)	21.5 (±6.3)	21.9 (±6.2)
NN	23.0 (±4.6)	23.5 (±3.1)	24.0 (±4.0)
60°/s eccentric (Nm)			
LS	28.8 (±7.6)	30.4 (±6.7)	29.9 (±8.2)
NN	30.6 (±3.9)	32.1 (±4.3)	33.6 (±6.8)
120°/s eccentric (Nm)			
LS	28.8 (±9.5)	29.4 (±8.5)	29.0 (±8.7)
NN	32.8 (±4.0)	30.4 (±4.0)	33.9 (±8.5)

There were no significant differences in any values.

SD, standard deviation; LS, low intensity and slow movement; NN, normal intensity and normal speed

Table 4. Infraspinatus EMG (mean ± SD)

	LS	NN	
Averaged EMG (% MVC)	14.5 (±4.6)	22.1 (±8.0)	p = 0.12
Integrated EMG (% MVCs)	1,243.6 (±533.2)	533.0 (±241.2)	p <0.01

EMG, electromyography; SD, standard deviation; LS, low intensity and slow movement; NN, normal intensity and normal speed; MVC, maximal voluntary isometric contraction

Muscle strength of the external rotator

Table 3 shows the muscle strength values. No significant main or interaction effects were found in either isometric or isokinetic muscle strength.

Infraspinatus EMG

Table 4 shows the EMG values of the infraspinatus. No significant differences in averaged EMG activity were found between the two groups. However, the LS group had significantly greater integrated EMG activity than the NN group.

Discussion

This study investigated whether an 8-week intervention of low-intensity shoulder external rotation exercises with slow movement increases the muscle strength and CSA of the infraspinatus. We hypothesized that infraspinatus CSA would significantly increase following low-intensity exercises with slow movement after 8 weeks. To our knowledge, this study is the first to report the effect of LS exercise on the CSA of infraspinatus hypertrophy.

No significant difference in the averaged infraspinatus EMG activity, measured during one repetition of shoulder external rotation exercises, was found between the two groups. Bitter et al. investigated infraspinatus EMG activity with various intensities and reported that infraspinatus activity did not increase even when the intensity was increased from 10% to 70% of shoulder isometric external rotation strength7). Additionally, Cools et al. noted that high middle part of trapezius EMG activity occurred during shoulder external rotation, with the arms at the side22). Therefore, in the NN group, the infraspinatus EMG activity did not increase with the increase in exercise load because of the compensation by the middle part of trapezius muscle. By contrast, the LS group had significantly greater infraspinatus integrated EMG activity, measured during one set of exercises, than the NN group. This finding indicated that the infraspinatus had a greater workload during exercise in the LS group than that in the NN group. Infraspinatus hypertrophy was observed only in the LS group because the workload of the infraspinatus contributes to muscle hypertrophy. Burd et al. investigated whether the time in which the muscle was under loaded tension during low-intensity resistance exercises affects the synthesis of muscle proteins in the quadriceps muscles of healthy male participants23). They observed significant protein synthesis after slow-movement exercises. They concluded that the time the muscle was under tension during exercise was important in increasing protein synthesis and optimizing muscle growth. As known, eccentric contraction exercises have greater effects on muscle hypertrophy and muscle strength than concentric contraction exercises24). However, Moore et al. reported contradictory results25). They investigated whether training-induced increase in the size and strength of the elbow flexor muscles differed between muscle contraction types (eccentric or concentric) when the total external workload was the same. They found no significant differences in the increases in muscle size and strength between the two groups after 9 weeks, so they concluded that increases in muscle size and strength with short-term resistance training were unrelated to the muscle contraction type when matched for both exercise intensity and total external workload. In the present study, the mechanical stress on the infraspinatus was larger in the LS group than in the NN group because of the longer contraction times caused by slow movement, which contributed to the increase in the workload of the infraspinatus throughout the exercise. These results, taken together with those of previous studies, suggest that the larger mechanical stress on the infraspinatus caused infraspinatus hypertrophy and therefore was observed only in the LS group.

In the LS and NN groups, no significant increase in shoulder external rotation strength was found. The absence of an increase in muscle strength in both groups can be explained by the principle of resistance training, that is, "principle of specificity." In this principle, the maximal benefit may be derived from exercise styles that closely simulate those used in the specific activities. Regarding movement speed, muscle strength increased most at the speed same as that used during training[26)]. In the present study, we evaluated isometric and isokinetic muscle strength. These evaluated values possibly did not reflect the effect of the intervention because the contraction style and movement speed differed from exercises in the actual intervention. Neural adaptation is another factor that contributes to muscle strength and hypertrophy. A previous study reported that at least 80% of maximal muscle strength is needed for neural adaptation[27)]. Moreover, a meta-analysis that investigated which load was the most effective for muscle strengthening reported that 60% of maximal muscle strength had the largest effect size in participants without training experience compared with 80% in participants with training experience[28)]. Another meta-analysis study noted that 85% of maximal strength had the largest effect size in athletes[29)]. In view of these studies, it appears necessary that training would start from at least 60% of maximal strength and gradually increase up to approximately 85% to achieve muscle strengthening. Additionally, no previous study has reported an increase in muscle strength because of low-intensity training for the infraspinatus[10,12)], which is consistent with our results. Because the averaged infraspinatus EMG activity was approximately 20% MVC in both groups in this study, it appears that the load used was insufficient for muscle strengthening. Therefore, the evaluated muscle strength was different from the principle of specificity of training, and the intensity was too low to cause neural adaptation of the infraspinatus; thus, the effect of the exercise possibly did not influence the shoulder external rotation strength despite the increase in the CSA. Previous studies reported that low-intensity and slow-movement exercises improved muscle strength as well as the CSA and muscle thickness of lower limb muscles[13–15)]. In this study, LS condition significantly increased the CSA of the infraspinatus; however, there was no significant increase in shoulder external rotation strength. These differences may result from very light load (500 g) of the LS group. Previous studies used 50% of 1RM as the low-intensity condition. In this study, a very light load was used in the LS group in order to prevent compensation by the deltoid muscles and to examine the effects of clinically used loads. In the LS group, 500 g was equivalent to 4% of the maximum isokinetic muscle strength and a very low load compared to previous studies of the lower limb muscles. Therefore, the results of muscle strength may differ from those of previous studies.

Clinically, atrophy of the rotator cuff muscles is observed frequently in participants with shoulder disorders. To solve this problem, low-intensity exercise is generally considered more appropriate for rotator cuff muscles[20,21)]. Although a few reports have indicated that low-intensity exercises caused muscle strengthening, no studies have indicated muscle hypertrophy[10–12)]. Additionally, because these studies involved the use of a 3-kg dumbbell, elastic band, or isokinetic dynamometer, the load appears to be too high for a patient who is sensitive to excessive stress, even using these loads. In this study, we used a 500-g dumbbell, which was much lighter than that in previous studies, and we observed infraspinatus hypertrophy by adjusting the movement speed. Therefore, it may be an effective training method for developing infraspinatus hypertrophy in patients who should avoid excessive stress in the early phase of rehabilitation.

This study has some limitations. First, the study participants were healthy young men and the sample size was small; thus, it is unknown whether the training protocol used could be effective for patients with shoulder disorders. Since weakness of rotator cuff muscle strength may exist in patients with shoulder disorder, the effect of muscle strengthening may be more likely to occur. Further interventional study is needed to solve this limitation. Second, although significant differences in muscle CSA were observed, no significant differences were found in isometric and isokinetic muscle strength. Because it is possible that the angular velocity for evaluating isokinetic muscle strength in this study was too fast for the exercise conditions and muscle function also includes muscle power and endurance, further study is needed to clarify the effects on muscle strength and functions by comparing these factors.

Conclusion

In this study, we investigated the effect of an 8-week low-intensity shoulder external rotation exercise with slow movement. Our results suggest that low-intensity exercises with slow movement significantly increased the CSA of the infraspinatus compared with normal-intensity exercises with normal speed.

Conflict of Interest: None. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this article.

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PHYSICAL
THERAPY
RESEARCH

ORIGINAL ARTICLE

Leg Cycling Leads to Improvement of Spasticity by Enhancement of Presynaptic Inhibition in Patients with Cerebral Palsy

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ABSTRACT. Objective: The purpose of this study was to investigate if leg cycling could reduce lower extremity spasticity in patients with cerebral palsy (CP). In addition, we investigated whether the intervention could cause changes in the modulation of presynaptic inhibition. Methods: This study was a quasi-experimental study, with pretest–posttest for 1 group. Participants in this experiment were eight adult patients with CP with lower extremity spasticity. Spasticity parameters assessed were the amplitude of soleus maximum Hoffmann's reflex (H_{max}) and maximum angular velocity (MAV) of knee flexion measured using the pendulum test. D1 inhibition, which seems to be related to the presynaptic inhibition, was recorded by measuring soleus Hoffmann's reflex (H-reflex) with conditioned electric stimuli to the common peroneal nerve. Results: D1 inhibition was significantly enhanced immediately by the cycling intervention. The amplitude of the soleus H_{max} was significantly depressed, and there was significant difference in H_{max}/maximum M-wave. The MAV was increased due to inhibition of the stretch reflex. Conclusion: Leg cycling suppressed stretch reflex and H-reflex, and caused plasticity of inhibitory circuits in patients with CP with lower extremity spasticity. These findings strongly suggest that lower extremity spasticity can be improved by cycling movements.

Key words: Cerebral palsy, Spasticity, Pendulum test, Cycling, Presynaptic inhibition

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Cerebral palsy (CP) includes a group of permanent disorders of movement and postural development that cause activity limitations and can be attributed to non-progressive disturbances in the developing fetal or infant brain[1]. The motor disorders associated with CP are often accompanied by secondary musculoskeletal problems[2]. Spasticity is defined as a motor disorder characterized by velocity-dependent stretch reflexes with exaggerated tendon jerks, which is a symptom of upper motor neuron syndrome[3]. Spastic CP accounts for approximately 80%–90% of all patients with CP[4]; they suffer from symptoms such as muscle stiffness[5], shortening, and increase risk for falls[6]. Moreover, the contracture responsible for stiffness causes further muscle overactivity, including spasticity[7]. Although spasticity has been attributed to lesions of the pyramidal tract, in animals, isolated lesions of the primary motor cortex (Broadman area 4) have been shown to decrease muscle tone and tendon reflexes instead of causing spasticity. Moreover, lesions of the premotor cortex and supplementary motor cortex (Broadman area 6) have been often shown to induce spasticity[8,9]. Even though pathophysiological mechanisms underlying spasticity in humans are not completely understood, the evidence suggests that an indirect descending pathway modulating the stretch reflex circuit from the motor cortex, such as the vestibulospinal tract, and presynaptic Ia inhibition is one of the spinal inhibitory interneuron systems involved in stretch reflex modulation[10,11].

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D1 inhibition[12)], which seems to be related to the excitability of primary afferent depolarization interneurons mediating presynaptic inhibition of Ia terminals, deteriorates in CP[13)]. In addition, several studies have reported that patients with stroke[14)] and multiple sclerosis[15)] show increased Hoffmann's reflex (H-reflex) amplitude and impaired presynaptic Ia inhibition in the lower limbs in comparison with healthy controls.

Considering these findings, appropriate interventions for spasticity are extremely important, and its management is currently achieved through various therapeutic exercises, pharmacotherapy, and orthopedic surgery. In a recent systematic review on the evidence for interventions for CP, botulinum toxin, diazepam, intrathecal baclofen, and selective dorsal rhizotomy were recommended for reducing muscle spasticity[16)], while no established evidence could be identified for therapeutic exercise. Nevertheless, we have experienced decreased muscle tone in patients with CP after cycling exercise in our daily clinical practice. Recent investigations have demonstrated that cycling movements induce a reduction in spasticity variables such as the H-reflex amplitude and Modified Ashworth Scale (MAS) scores[17)] and enhance inhibitory spinal pathways such as those mediating presynaptic inhibition in patients with diseases of the central nervous system other than CP[18–21)]. In contrast, only a few studies have focused on the combination of electrophysiological measurements and use of this therapeutic intervention for spasticity in CP, and its effects on the modulation of spinal inhibitory interneuron systems in patients with spastic CP.

Rhythmic movements such as cycling and walking have different neural controls than normal voluntary movements[22,23)]. The common core hypothesis suggests the existence of central pattern generators (CPGs) and regulatory systems that modulate reflex output within the spinal cord. The reason for focusing on D1 inhibition is that presynaptic inhibition may contribute to inputs from higher centers, CPGs, and even peripheral sensory receptors to modulate reflex outputs in the spinal cord.

Moreover, the spasticity in CP was often evaluated using the MAS according to published literature and in clinical practice, although some studies have questioned the reliability and validity of this evaluation[24–26)], and little evidence is available for the quantitative evaluation of spasticity. In this regard, the pendulum test[27)], which is performed by freely dropping the lower leg from knee extension in a relaxed state, has proven to be a reliable and objective method to assess various aspects of spasticity in CP[28,29)].

This study aimed to investigate if leg cycling could reduce lower extremity spasticity in patients with CP. In addition, we investigated whether the modulation of presynaptic inhibition (i.e., D1 inhibition) changed after this intervention.

Methods

Study design

This study was a non-randomized, quasi-experimental study, with pretest–posttest for 1 group.

Participants

Fourteen adult patients with CP were recruited from Sapporo Medical University Hospital. Six of them were unable to start the electrophysiological measurement protocol because of discomfort and excessive involuntary movements in response to the slight stimulus. The remaining eight patients (mean age, 33.4 years; standard deviation, 11.3 years; range 19–45 years; seven males and one female in each year) finally participated in this study. The functional level of participants was classified according to the Gross Motor Function Classification System[30)] (GMFCS). Six patients with CP were classified as level I and two were classified as level III. CP subtypes were also assigned by classifying four patients with spastic diplegia, one with hemiplegia, and three with mixed CP. While kinematic measurement was feasible for all participants, electrophysiological measurements showed that so while D1 inhibition was evaluable in seven patients, the maximum M wave (M_{max}) in the soleus muscle was obtained from five participants because three of them could not tolerate the maximal supra-stimulus intensity to the nerve. The study protocol was approved by Sapporo Medical University Hospital Institutional Review Board (Permit Number: 282-32) and was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013. Written informed consent was obtained from patients who participated in this study.

Inclusion criteria were: (1) adults with CP and lower extremity spasticity (quadriceps and soleus muscle MAS score ≥1), (2) ability to comply with simple verbal directions, (3) GMFCS levels I to III, (4) ability to pedal the ergometer, and (5) knee extension range of motion ≥–30°.

Exclusion criteria were: (1) orthopedic surgery within six months preceding the experiment, (2) a history of botulinum injections or other medications used in the treatment of spasticity within three months preceding the experiment, and (3) difficulty in cycling without orthoses.

Electrophysiological and kinematic measurements were obtained using the H-reflex method and pendulum test, respectively. Each measurement was obtained only for the more affected spastic lower extremity.

Electrophysiological measurements

The participants were required to take a break of 10 min before the experiment, subsequently seated comfortably in a wheelchair with the knees flexed approximately 70° and the ankle joint fixed in the mid position. Electromyographic (EMG) activities were recorded using bipolar surface electrodes (NM-317Y3; Nihon Kohden, Tokyo, Japan) placed 2 cm apart over the muscle bellies of the soleus and tibialis anterior (two-thirds of the distance between the medial condyle of the femur and the medial malleolus, and the proximal one-third of the distance between the caput fibulae and the medial malleolus).

The EMG signals were amplified and sampled at 2000 Hz, and band-pass filtered at 10–1000 Hz, capable of making measurements across a ±5 mV range (10 mV span) using an

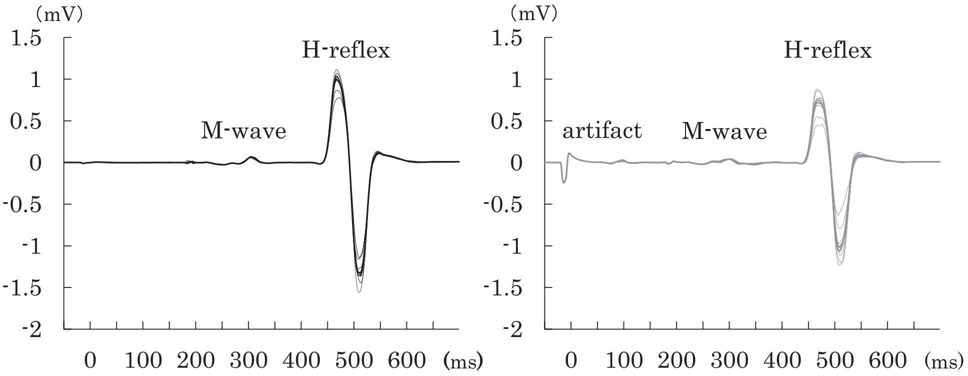

Fig. 1. The control H-reflex (black line) is adjusted to 50% of H_{max}

The conditioned H-reflex (gray line) is expressed as suppression of the soleus H-reflex with conditioning stimulus. Depicted waveforms are superimposed (thin line) and average (bold line) waves of 10 sweeps for each of the reflexes.

H-reflex, Hoffmann's reflex; H_{max}, maximum H-reflex

16-bit A/D converter connected to a computer (Neuropack MEB-2306; Nihon Kohden). Soleus H-reflexes were elicited by percutaneous stimulation (rectangular pulse of 1 ms duration, 0.33 Hz) of the posterior tibial nerve in the popliteal fossa through the bipolar stimulating electrode. D1 inhibition was evoked by soleus H-reflex induced with an electrical stimulus applied to the common peroneal nerve (CPN)[12].

The conditioning stimulus was generated at the dorsolateral aspect of the caput fibulae with a rectangular pulse of 1 ms duration and an intensity that was 1.2 fold the motor threshold, and it preceded the test stimulus with a 20-ms interstimulus interval (ISI). The control H-reflex intensity was adjusted at 50% of the ipsilateral soleus maximum H-reflex (H_{max}), and both conditioned and control H-reflexes were recorded in 10 sweeps each (Fig. 1). Conditioning stimulation to the CPN was performed while monitoring tibialis anterior EMG and H-reflex to ensure consistency of stimulation. D1 inhibition was indicated by the following formula: D1 inhibition (%) = (conditioned-H reflex amplitude/control-H reflex amplitude) × 100; a decrease in this value indicates suppression conditioned H-reflex due to the potentiation of presynaptic Ia inhibition. The H-reflexes and M-waves were expressed as peak-to-peak amplitudes, and the ratio of the H_{max} to M_{max} (H_{max}/M_{max}) was determined in the recruitment curve of each participant.

Kinematic measurements

The pendulum test was performed with the patient semi-reclined comfortably on the medical bed with legs hanging freely over the edge. A wireless gyro sensor (WAA-006; Wireless Technology, Tokyo, Japan) was attached to the front of lower leg distal to the side tested, and the swinging motion with angular velocity of the rotation around the X axis was recorded and sampled at 250 Hz. The examiner passively lifted the lower limb to full extension and held the leg position until the state of complete relaxation for 5 s or more, as indicated by palpation and inspection of quadriceps contraction and spasm. Subsequently, the relaxed limb was released to swing freely and allowed to oscillate until it stopped at a resting position. The maximum angular velocity (MAV) during the first swing, which was obtained using the gyro sensor, was stored on a computer for subsequent offline analysis. As for data processing, zero point correction was performed on angular velocity from data in which the sensor was stationary for 3 s for each patient.

Interventions

All participants performed a 20-min exercise at a 20-W constant work rate on the ergometer. Adjustable foot straps and magic tape were used to hold the participants' feet and prevent slipping. The saddle height was adjusted so that the knee flexion angle was approximately 20°–30° at the bottom dead center of the pedal. The participants were instructed to cycle at a comfortable rate with smooth movements without clonus and stretch reflexes. Therefore, we did not control the rotation speed for each participant, although made sure that it was not less than approximately 20 rpm. The positions of the surface electrodes and accelerometer were ensured to remain constant during the intervention.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences version 21 (IBM, Armonk, NY, USA). The results were expressed as mean ± standard error of the mean. Differences between the measurements before and after the intervention were calculated with a paired two-tailed t-test. The effect size was calculated by Cohen's d[31] for only parametric tests (Cohen's operational definitions; $d \geq 0.20$, $d \geq 0.50$, and $d \geq 0.80$ for small, medium, and large effect sizes, respectively). Statistical significance was determined by a p-value of 0.05.

Results

The results are shown in Table 1. D1 inhibition was significantly enhanced after the cycling intervention (pre:

Table 1. Descriptive statistics of all variables calculated from soleus H-reflex and the pendulum test

	Pre	Post	Effect size	p-value
D1 inhibition (%)	85.51 ± 5.45	75.72 ± 5.86	d = 0.654	p = 0.041*
H_{max} (mV)	2.58 ± 0.49	2.05 ± 0.53	d = 0.465	p = 0.001*
M_{max} (mV)	6.83 ± 1.10	7.03 ± 1.12	d = 0.080	p = 0.428
H_{max}/M_{max}	0.385 ± 0.065	0.282 ± 0.050	d = 0.792	p = 0.016*
MAV (deg/s)	204.1 ± 21.3	250.3 ± 18.7	d = 0.815	p = 0.001*

Data are expressed as mean ± standard error of the mean. Asterisks indicate significant differences ($p < 0.05$).

H-reflex, Hoffmann's reflex; H_{max}, maximum H-reflex; M_{max}, maximum M-wave; MAV, maximum angular velocity

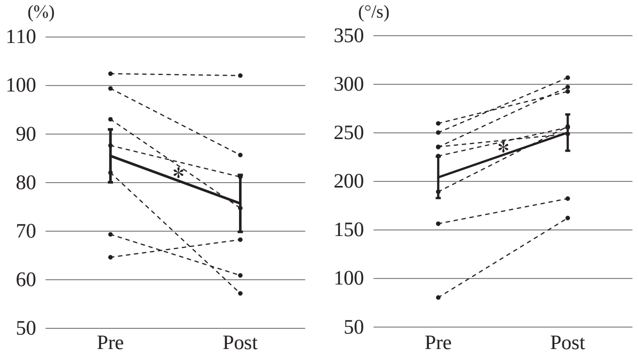

Fig. 2. Changes in D1 inhibition (left figure) and MAV of knee flexion (right figure) in the pendulum test

The mean and standard error of the mean values are presented in bold lines and circles, and the dashed lines indicate changes in the values of each individual. Asterisks indicate significant differences ($p < 0.05$).

MAV, maximum angular velocity

85.51 ± 5.45%, post: 75.72 ± 5.86%, t = 2.602, p = 0.041; Fig. 2, left). The amplitudes of the soleus H_{max} were significantly depressed (pre: 2.58 ± 0.49 mV, post: 2.05 ± 0.53 mV, t = 8.454, p = 0.001), but no significant differences were observed in M_{max} before and after the intervention (pre: 6.83 ± 1.10 mV, post: 7.03 ± 1.12 mV, t = 0.881, p = 0.428), and so there was a significant reduction in H_{max}/M_{max} ratio (pre: 0.385 ± 0.065, post: 0.282 ± 0.050, t = 4.008, p = 0.016). In addition, the MAV values significantly increased after the intervention (pre: 204.1 ± 21.3°/s, post: 250.3 ± 18.7°/s, t = 5.445, p = 0.001; Fig. 2, right).

Discussion

In a series of experiments in patients with CP, the present study showed that leg cycling caused (i) enhancement of D1 inhibition, (ii) suppression of H-reflex amplitude, and (iii) increase in MAV.

The currently accepted hypothesis of spasticity focuses on inhibitory rather than excitatory mechanisms in the spinal circuit[10]. An increase in D1 inhibition reflects the enhancement of presynaptic Ia inhibition, which is one of the inhibitory mechanisms in spinal neural circuits that are impaired in patients with spasticity[13–15]. In a previous study, the mean suppression of the H-reflex by D1 inhibition was 86.19% on the paralyzed side and 77.64% on the non-paralyzed side in stroke patients with spasticity (n = 29)[13], 87.56% in children with CP (n = 21), and 69.56% (n = 21) in non-disabled children[14]. These findings are similar to the pre- and post-intervention suppression in the present study. Long-term cycling exercises in patients with spinocerebellar ataxia causing coordination defects have been shown to enhance D1 inhibition concurrently with improvements in ataxia score[32]. Thus, the enhancement of D1 inhibition may be related to agonist and antagonist control in the cycling task. Spastic CP is characterized by impairments in coordination and selective motor control in the lower extremities, particularly the distal joints[1,33]. Patients with spastic CP show high co-contraction ratios for the lower limb muscles during a single cycling session compared with healthy participants[34]. Whether an improvement in selective motor control of the lower extremities leads to enhanced D1 inhibition is a topic for future studies.

Another possibility is that increases in presynaptic inhibition by rhythmic and reciprocal movements influence several spinal pathways and afferent fibers. Numerous studies have demonstrated that the H-reflex of the lower limb changes during and after lower extremity cycling exercise in a task-dependent manner[18,19,35,36]. Furthermore, other studies have reported that the soleus H-reflex decreases after arm cycling exercise[19]. When it was conditioned with CPN stimulation during arm cycling[37], a greater reduction than that in static control was observed. These findings support the role of excitability of presynaptic inhibition in the activation of supraspinal and propriospinal pathways and the CPGs in cyclic arm movement. Neural mechanisms such as the CPGs and peripheral feedback during rhythmic movement have specific modulatory effects on reflex inhibition[38]. The increased presynaptic inhibition in cycling probably contributed to the degradation of the input of Ia afferent fibers and suppressed the soleus H-reflex; additionally, D1 inhibition was enhanced in this study. Previous studies have shown that the soleus H-reflex is depressed by continuous passive and active cycling for at least 30 min. Since passive cycling involves almost no muscle contraction, afferent input from types III and IV afferent mechanoreceptors may be associated with presynaptic inhibition of Ia afferent terminals and contributes to reflex control[35,39)].

These findings suggest that downregulation of the H-reflex is less related to descending motor pathways such as corticospinal or corticobulbar tracts and is more associated with increased fusimotor drive, Ia activity, and primary afferent depolarization[40)]. Post-activation depression[41)], one of the presynaptic mechanisms underlying spasticity, is related to muscle spasticity[13,14)]. However, a previous study has reported that inhibition of spasticity is not explained by its depression since cycling training decreased the soleus H-reflex and MAS score for calf muscle in contrast to the sustained post-activation depression observed in patients with multiple sclerosis[19)]. Thus, H-reflex suppression after cycling exercise in patients with CP may have been caused by the modulation of presynaptic inhibition rather than post-activation depression.

The increased MAV indicated that the velocity-dependent stretch reflex in the quadriceps was inhibited by this intervention. The MAV (mean ± standard deviation) for children with (n = 10) and without (n = 10) CP in a previous report was 201.82 ± 67.96°/s and 292.51 ± 35.93°/s, respectively, suggesting that MAV is significantly lower in children with CP[28)]. Another study found that among 20 children with CP, the mean MAV improved from 244°/s to 364°/s after selective dorsal rhizotomy to control spasticity[29)]. In our study, the increase in the MAV was statistically significant, although it was not close to this value.

Suppression of the soleus H-reflex and enhancement of D1 inhibition may be the result of a specific effect of pedaling exercise. Previous studies have described task-dependent changes in the soleus H-reflex during and after pedaling in able-bodied people[35,36)]. In the present study, the stretch reflex of the quadriceps was suppressed. While there are no studies assessing quadriceps stretch reflexes after pedaling, studies report decreased hamstring MAS[42)]. Since pedaling generates muscle activity in the quadriceps, hamstrings, and lower leg in CP[34)], it is possible that the suppression of the reflex occurred in a task-dependent manner not only in the soleus muscle but also in the quadriceps.

The suppressed H-reflex in D1 inhibition could not be confirmed in the hemiplegic patient (pre: 102.4%, post: 102.1% of control H-reflex). Strongly impaired D1 inhibition in spastic hemiplegic CP has been previously reported, but the number of participants was small[13)] (N = 3, 99.14 ± 6.58% of control H-reflex). In contrast, another study found that spastic stroke patients have impaired D1 inhibition compared to healthy participants[14)]. Regarding the amount of H-reflex suppression, it is possible that stroke patients have a smaller degree of D1 inhibition of the damage despite the shorter time from onset than hemiplegic CP.

We hypothesized that impaired H-reflex inhibition in hemiplegic patients with CP may be related to the timing of brain damage in infancy or fetal life because GABAergic neurons in the central nervous system have been shown to change from excitatory to inhibitory synapses during early neuronal development in animal testing[43,44)]. In the participants with hemiplegia in our study, D1 inhibition was not modified, whereas the reflex (i.e., H-reflex and MAV) was inhibited. Hence, the exaggerated reflex in hemiplegic CP must be affected by mechanisms other than presynaptic inhibition, but further data accumulation is necessary.

The clinical significance of these results is that the enhancement of the spinal inhibitory interneuron is a result of reciprocal movement. Moreover, the cycling task is easy to use in clinical practice and can be recommended as an exercise therapy. For future studies, the effect on motor functions such as walking speed and endurance, as well as the long-term effects and required duration of intervention need to be further examined. The intervention time in this study was within the same time frame as that of several previous studies, and similar results were obtained. However, there are reports of changes in spasticity scores in even shorter time periods.

The present study has some limitations. The ISI required to obtain maximum suppression of the H-reflex in D1 inhibition is approximately 20 ms, and many studies have used 20 or 21 ms[13,14,32)]. However, it is important to note that this value may vary among individuals[12)]. Moreover, this experiment was performed with participants showing several types of CP (e.g., hemiplegia, diplegia, and mixed), a wide range of ages, and a relatively small sample size, which could limit the interpretation of the results. Nevertheless, we anticipate that cycling movements will become an effective intervention for the treatment of spasticity in patients with CP.

Conclusion

The findings of the present study suggest that cycling intervention in adults with CP can induce suppression of H-reflex and stretch reflex in the leg, and activation of presynaptic inhibitory networks within the spinal cord. Therefore, leg cycling may reduce spasticity in the lower extremities of patients with CP.

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