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Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis

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Abstracts

Background: Although pulmonary rehabilitation (PR) has been reported to improve exercise capacity in patients with idiopathic pulmonary fibrosis (IPF), it is unknown which exercise measurement is the most responsive for evaluation of PR efficacy. The purpose of the present study was to compare the responsiveness of five exercise measurements by evaluating the efficacy of PR in IPF patients.

Methods: We conducted a prospective observational study in which 53 IPF patients were enrolled. The PR group underwent a 10-week out-patient PR program. The control (C) group was observed without any additional intervention including PR. Five exercise measurements (endurance time, peak work rate, VO_{2peak}, six-minute walking distance (6MWD) and incremental shuttle walking distance (ISWD)) were evaluated at baseline and after 10 weeks. The effect size was used for the assessment of responsiveness.

Results: In each group, 24 patients completed the five measurements at baseline and after 10 weeks. The changes in endurance time (PR: 181.6%, C: -8.2%), VO_{2peak} (PR: 7.6%, C: -5.4%), peak work rate (PR: 15.1%, C: -5.1%), 6MWD (PR: 6.0%, C: -3.8%) and ISWD (PR: 9.1%, C: -5.1%) were significantly different between the groups after 10 weeks ($p<0.05$). In the PR group, endurance time showed the most striking improvement among the five measurements ($p<0.05$), and its effect size was as large as 2.96, while the others were all less than 0.5.

Conclusions: Endurance time is the most responsive exercise measurement for evaluating PR efficacy in IPF patients.

238 Words

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Keywords

Endurance time, idiopathic pulmonary fibrosis, pulmonary rehabilitation, exercise capacity, responsiveness

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disorder with significant morbidity and mortality.[1] Several retrospective longitudinal studies suggested a median survival time from 2 to 3 years from the time of diagnosis.[1] Patients with IPF have significantly reduced exercise capacity as manifested by a reduced six-minute walking distance and reduced maximum oxygen uptake.[2, 3]

Exercise capacity is considered to be one of the most important outcome measurements in chronic lung diseases. In patients with IPF, poor exercise capacity indicates a poor prognosis,[4] and a recent study demonstrated that exercise capacity contributes to physiologic function and health-related quality of life.[5] Exercise capacity measurements have been utilized as a primary endpoint in several clinical trials for IPF patients, although most of them failed to show positive results.[6, 7] Only pulmonary rehabilitation (PR) has successfully demonstrated improvement of exercise capacity.[8, 9]

Exercise capacity in general has been evaluated in several ways, including field walking tests such as the six-minute walking test (6MWT) and incremental shuttle walking test (ISWT), and cardiopulmonary exercise tests. In patients with COPD, several studies have reported that endurance time (ET) measured using a cycle ergometer test is reproducible and more responsive to interventions, including drug therapy, than measurements obtained from a maximal test.[10, 11] Moreover a recent study evaluating the synergistic effect of drug and PR successfully demonstrated an improvement of exercise capacity with ET as outcome.[12] However in patients with IPF, the responsiveness of ET as an exercise measurement has not been fully investigated. We hypothesized that ET would also be a more responsive exercise measurement in patients with IPF.

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The purpose of the present study was to compare the responsiveness of five exercise measurements by evaluating the efficacy of PR in IPF patients.

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Methods

Subjects

Subjects were patients referred to the outpatient clinic of Tosei General Hospital between June 2005 and May 2011. Inclusion criteria were as follows: (i) age less than 75 years; (ii) diagnosis of IPF; (iii) shortness of breath on effort; and (iv) stable clinical condition with no infection or exacerbation in the previous three months. Exclusion criteria were severe comorbid illnesses, collagen vascular diseases, and the need for long-term oxygen therapy.

The diagnosis of IPF was made in accordance with the American Thoracic Society and European Respiratory Society statement[13] using the following major criteria: (i) exclusion of other known causes of interstitial lung disease; (ii) abnormal pulmonary function with restriction and impaired gas exchange; (iii) bibasilar reticular abnormalities with minimal ground glass opacities on high-resolution CT; and (iv) transbronchial lung biopsy or bronchoalveolar lavage showing no features to support an alternative diagnosis. Minor criteria included: (i) age >50 years; (ii) insidious onset of otherwise unexplained dyspnea on exercise; (iii) duration of illness >3 months; and (iv) bibasilar inspiratory crackles. All of the major and at least three of the four minor criteria had to be satisfied. For those with a surgical lung biopsy specimen showing usual interstitial pneumonia, only the major criteria were considered relevant.

At the time of the study, none of the subjects were current smokers. Informed consent was obtained from all who participated. This study was approved by the ethics committee of Tosei General Hospital (approval number 213).

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Study design

This was a prospective observational study in which patients consented to being evaluated with pre-determined measurement schedules for the duration of 10 weeks. Fifty-three patients with IPF who had undergone evaluation at diagnosis were included in this study. During their observational periods, 26 patients who also consented to participate in a pulmonary rehabilitation program were regarded as the PR group. The other 27 patients, who were observed without any intervention, including pulmonary rehabilitation or addition of new medicine, were regarded as the control group. Measurements were made at baseline, immediately following the 10-week pulmonary rehabilitation program in the PR group, and 10 weeks after baseline in the control group.

Assessment

All subjects performed four exercise tests including an incremental load ergometry test (ILET), constant load ergometry test (CLET), 6MWT, and ISWT. Through the four exercise tests, five exercise measurements were obtained as described below. Measures of body anthropometry, pulmonary function tests, arterial blood gas tensions, grip strength, quadriceps force and respiratory muscle force were also obtained.

Pulmonary function tests

Spirometry (CHESTAC-55V; Chest, Tokyo, Japan) was performed according to published recommendations.[14] The single-breath diffusion capacity for carbon monoxide was also measured. All values are expressed as a percentage of the predicted values reported by the Japan Society of Respiratory Diseases.[15]

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Muscle strength tests

Quadriceps force was measured using a dynamometer (Cybex II; Lumex, NY, U.S.A.). The peak torque (Newton-meters, Nm) was measured in both legs during a maximal isokinetic knee extension maneuver with the hip in 90° flexion.[16] The highest value from at least four maneuvers for each leg was recorded. Grip strength was measured with a hydraulic hand dynamometer (Smedley's Dynamometer; TTM; Tokyo, Japan). Peak grip strength (newtons, N) was assessed with each hand with the shoulder and wrist in neutral position. The highest value of at least three maneuvers was recorded for each hand. All subjects underwent respiratory muscle testing to determine the maximal inspiratory pressure and maximal expiratory pressure. The former was measured at the residual volume, and the latter was measured at near total lung capacity, according to the method proposed by Black and Hyatt[17] (Vitalopower KH101; Chest, Tokyo, Japan). The highest value from at least three maneuvers was recorded.

Exercise tests

ILET was performed on an electronically braked cycle ergometer (Ergometer 232CXL; Combi, Tokyo, Japan) in accordance with published guidelines[18] to evaluate maximal exercise capacity and to determine the nature of the exercise limitation. Gas exchange and ventilatory variables were collected on a breath by breath basis using eight breath averaging (Centaura-2; Chest, Tokyo, Japan). The protocol required a three-minute unloaded phase followed by a 10-Watt/min-stage at a pedaling rate of 60 rpm, until the subject could no longer continue because of severe dyspnea or leg fatigue. Maximum heart rate (HR_{peak}) was determined using the R-R interval from a 12-lead

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electrocardiogram (CardioStar; Fukuda Denshi, Tokyo, Japan). Peak values were defined as the values averaged during the last 30 seconds of the highest work load achieved. Peak values for oxygen uptake ($\dot{V}O_{2peak}$) and work rate (WR_{peak}) during exercise were recorded. The anaerobic threshold was determined by the V-slope technique. Work efficiency (oxygen consumption during exercise) was determined as the oxygen uptake to work rate ($\Delta\dot{V}O_2/\Delta WR$), which is the increase in oxygen uptake divided by the sum of the workloads (in Watts) during exercise.

CLET was performed to determine ET using the same cycle ergometer as used for the incremental test. The protocol required two minutes of unloaded cycling followed by cycling at 60 rpm with a work rate equivalent to 80% of the WR_{peak} obtained in the incremental test.[10] The patients continued cycling at the constant submaximal workload, they were stopped according to the same criteria as used in ILET, and the ET was measured. The same work rate was used to measure ET at the end of the PR program.

6MWT was measured according to the American Thoracic Society statement.[19] Patients were instructed to walk a 50-m long corridor for as far as possible in six minutes. All patients had performed at least one test prior to study entry for the purpose of excluding training effects. The total distance walked was recorded as 6-minute walking distance (6MWD). After 10 weeks, the number whose distance changed by the minimal important difference (34 m) of 6MWD[20] was counted.

ISWT was performed in a 10-m course identified by two cones placed 0.5 m from each end point.[21] All patients had performed at least one test prior to study entry for the purpose of excluding training effects. The total distance walked was recorded as incremental shuttle walking distance (ISWD).

Patients were asked to rate their dyspnea and leg fatigue at the end of all tests, using

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the modified Borg scale. Transcutaneous oxygen saturation was monitored throughout all tests by pulse oximetry (Pulsox-3Li; Minolta Inc, Tokyo, Japan).

Pulmonary rehabilitation program

The program comprised twice-weekly supervised exercise training for a period of 10 weeks in the Department of Rehabilitation, Tosei General Hospital.[8] The supervised sessions lasted 90 minutes and consisted of respiratory care, subject education, and endurance and strength training. Physical therapists supervised the patients to confirm that they performed the endurance and strength training. Subjects performed supervised endurance training on a braked cycle ergometer, with a target of 20 minutes of continuous cycling. The target intensity was 80% of WR_{peak} obtained from the ILET. Subjects were monitored by pulse oximetry during endurance training. Peripheral muscle strength training included upper and lower limb resistance training with weight machines, hand weights, or elastic bands. The respiratory muscle training was performed using an inspiratory threshold device (Threshold IMT; Respironics, Cedar Grove, NJ, USA). The subjects trained with breathing at a resistance that required 30% of MIP, for 15 minutes. Subjects recorded the number of peripheral muscle strength training and respiratory muscle training sessions in a diary, and the diary was checked at each supervised session. If desaturation was under 80% during the CLET, subjects received oxygen therapy during exercise training. Supplemental oxygen was given in an amount to maintain oxygen saturation above 80% during exercise training.

Statistical analysis

The baseline characteristics between the two groups were compared using unpaired

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t-tests. Differences in the values for each group before and after treatment were evaluated using the paired t-test. The change in the outcome measures was expressed as the percent change before versus after the program. The correlations between the change in the exercise measurements and muscle strength were assessed using Pearson's correlation analysis. The effect size was used widely measure for responsiveness.[22] The effect size represented the mean change in the score divided by the standard deviation of the baseline scores. Cohen suggested that effect sizes of $\geqq 0.2$ to < 0.5 should be regarded as small, $\geqq 0.5$ to < 0.8 as moderate, and $\geqq 0.8$ to be large changes.[23] The significance of the differences in the change observed in the five exercise measurements was determined with a repeated measures analysis of variance. When a significant difference was found, post hoc analysis was performed with the Bonferroni adjustment method to identify which differences were significant. The changes in the outcome measures between the two groups were compared using unpaired t-tests. A p value of less than 0.05 was considered significant. All data are given as mean ± SD. Analyses were performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, USA).

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Results

Fifty-three patients were recruited to the study (Figure 1). Twenty-six patients were entered in the PR group and commenced the pulmonary rehabilitation program, and of them 24 who completed the program underwent the second evaluation. In the control group, 27 patients underwent baseline evaluation, and 24 of them underwent the second evaluation 10 weeks after baseline. In total, 48 IPF patients completed the study protocol and were enrolled in the subsequent analysis. Lung function data, arterial blood gas tensions and exercise capacity at baseline were no different between the two groups (Table 1). In the PR group, six patients received drug treatment during the study period either with prednisolone alone (n=3) or prednisolone combined with cyclosporine (n=3). In the control group, three patients received drug treatment during the study period. Two patients were treated with prednisolone alone. The other patient was treated with sildenafil alone.

Effects of the Rehabilitation Program

In the PR group, 24 patients completed 20 training sessions in the PR program. All patients showed good adherence. The baseline characteristics of the two groups together with their lung function data measured at baseline and after 10 weeks are summarized in Table 1. Lung function and arterial blood gas tensions were not changed after 10 weeks in either group. Table 2 shows the muscle strength and exercise test data at baseline and after 10-weeks. In the PR group, the grip strength, quadriceps force, maximal expiratory pressure and maximal inspiratory pressure improved significantly after 10 weeks. In the control group, measurements of muscle strength remained unchanged after 10 weeks. In the PR group, ET, WR_{peak}, anaerobic threshold, work efficiency, 6-minute walking

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distance (6MWD) and incremental shuttle walking distance (ISWD) were improved significantly after 10 weeks ($p<0.05$), whereas $\dot{V}O_{2peak}$ was not improved ($p=0.19$). In the control group, anaerobic threshold and work efficiency were decreased significantly after 10 weeks ($p<0.05$). In the PR group, 10 patients improved greater than the minimal important difference of 6MWD. In the control group, 8 patients' results worsened more than the minimal important difference of 6MWD.

We further analyzed effect sizes of each metric for assessing their responsiveness. In the PR group, a large effect size (2.96) was observed for ET, while effect sizes observed for WR_{peak}, 6MWD and ISWD were small (less than 0.5). In the control group, all five measurements remained unchanged after 10 weeks.

The changes in $VO_{2\ peak}$ (PR group: 7.6 ± 22.7%, control group: -5.4 ± 16.5%; $p<0.05$), peak work rate (PR: 15.1 ± 35.4%, control: -5.1 ± 16.7%; $p<0.05$), ET (PR: 181.6 ± 195.1%, control: -8.2 ± 49.7%; $p<0.01$), 6MWD (PR: 6.0 ± 7.3%, control: -3.8 ± 12.9%; $p<0.01$) and ISWD (PR: 9.1 ± 15.7%, control: -5.1 ± 21.6%; $p<0.05$) were significantly different between the PR group and the control group after 10 weeks (Figure 2). In the PR group, ET showed the most striking improvement among the five exercise measurements, increasing by 181.6% ($p<0.01$).

For all 48 patients, the changes in ET were significantly correlated with change in the anaerobic threshold ($r=0.50$, $p = 0.0004$), and marginally significantly correlated with changes in work efficiency ($r=0.28$, $p = 0.06$). The changes in ET were not correlated with change in muscle strength, including quadriceps force.

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Discussion

The present study is the first to compare the responsiveness of five different exercise measurements in evaluating the effects of PR in patients with IPF. We demonstrated that ET is the most responsive exercise measurement in IPF patients as well as in COPD patients. The effect size of ET following PR was observed to be large compared with other exercise measurements. ET indicates submaximal exercise capacity.[10] $VO_{2\ peak}$ is the golden standard for exercise capacity.[18] WR_{peak} and ISWD indicate performance measurements of maximal exercise capacity.[21] 6MWD is a popular exercise measurement.[19] The superiority of ET as a measurement of treatment efficacy has been studied in COPD. O'Donnell et al. reported that ET is both reproducible and responsive in evaluation of the efficacy of pharmacological therapy in COPD.[11] Oga et al. found that ET was the most responsive test in detecting the effects of inhaled anticholinergic agents on exercise performance in patients with stable COPD.[10] We also recently reported that ET is the most responsive test for detecting the effects of PR in COPD patients.[24] Considering the superiority of ET as shown in COPD, evaluation of ET in IPF in future trials may be able to detect the favorable effects of intervention more effectively.

In the present study, PR demonstrated the largest increase in ET and moderate significant increases in WR_{peak}, 6MWD and ISWD, but no significant change in $\dot{V}O_{2\ peak}$. Two recent randomized controlled trials in subjects with IPF[8] and ILD[9] provide support for the benefits of PR. They measured exercise capacity by 6MWD for the benefits of PR, and the observed modest benefits. Kozu et al. reported that PR produced smaller 6MWD improvements in IPF patients than in COPD patients.[25] 6MWD may reflect the maximal exercise capacity, as does WR_{peak} and ISWD.[26, 27] On the other

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hand, ET measures the ability to sustain a submaximal exercise capacity.[10] ET can improve even when there is no significant increase in the maximal exercise capacity.[10, 28]

In the current study, ET and anaerobic threshold were improved significantly after PR in IPF patients. The changes in ET were significantly correlated with change in the anaerobic threshold. It is possible that in IPF patients the PR also reduced exercise-induced lactic acidosis and increased oxidative enzymes in the peripheral muscles, which would have contributed to the improvement in ET. Work efficiency was improved significantly after PR in IPF patients. There was a weak association between the change in work efficiency and the change in ET. Low work efficiency often indicates inadequate oxygen transport during exercise, and contributes to exercise intolerance in pulmonary diseases.[18, 29] PR may improve inadequate oxygen transport in IPF patients. Improvement in oxygen transport may be related to improvement in ET in IPF patients as well as in COPD patients.[24] The improvement of ET was not influenced by the improvement of muscle strength, such as quadriceps force. In IPF patients, the mechanism of the improvement in ET and muscle strength may be different from that in COPD patients

There are several limitations to the present study. First, it remains uncertain whether the difference in responsiveness observed in this study is also true against other intervention such as medication. We believe that several metrics should be assessed simultaneously in future trials which aim to improve exercise capacity. Second, this study was not randomized to assign IPF patients to the PR group and the control group. Selection bias may be present between treatment groups. However the main results that ET was the most responsive metric would not seem to be seriously influenced by this.

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Third, ventilatory gas analysis such as oxygen consumption during CLET was not performed. Fourth, the number of subjects was small for a comparison of the responsiveness of five exercise measurements. Finally, we did not evaluate the longer-term effects of PR in IPF patients.

In conclusion, our study showed that the five metrics obtained by four different exercise tests had different capacities to detect changes produced by PR in exercise performance in IPF patients. ET assessed by CLET showed the largest increase after PR, and it was considered to be the most responsive exercise measurement for evaluating PR efficacy in IPF patients.

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Figure legend

Figure 1. Participant flow diagram.

In the PR group, *other reason* is that one patient received long term oxygen therapy because of severe hypoxia at rest. In the control group, *other reason* is that one patient received long term oxygen therapy and one patient participated in another clinical trial study.

Figure 2. Changes in various measures of exercise capacity on four exercise tests after 10 weeks.

†: $p<0.05$, compared with control group, ‡: $p<0.01$, compared with control group, *: $p < 0.01$ compared with all measures in PR group

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Table 1 Lung function data and arterial blood gas tension data at baseline and after 10 weeks

	PR group		control group	
	baseline	10-weeks	baseline	10-weeks
Male / Female (n)	16 / 8		16 / 8	
Age (yrs)	69.4 ± 7.4		69.4 ± 6.6	
VC (L)	2.08 ± 0.75	2.01 ± 0.71	2.22 ± 0.68	2.17 ± 0.72
VC (% predicted)	70.8 ± 18.1	71.5 ± 16.4	75.7 ± 16.0	74.2 ± 17.1
FEV_1 (L)	1.70 ± 0.55	1.72 ± 0.53	1.75 ± 0.43	1.73 ± 0.48
FEV_1 (% predicted)	82.9 ± 19.5	82.4 ± 18.8	85.5 ± 18.2	82.1 ± 18.4
FEV_1/FVC (%)	84.3 ± 8.4	82.4 ± 9.5	82.4 ± 9.5	82.1 ± 8.6
DLco (ml/min/mmHg)	7.92 ± 2.88	7.98 ± 2.93	7.69 ± 2.82	7.67 ± 2.77
DLco (% predicted)	49.7 ± 15.9	49.8 ± 18.4	47.7 ± 17.4	47.4 ± 16.5
$PaCO_2$	41.3 ± 4.0	41.0 ± 4.4	40.7 ± 4.5	41.7 ± 5.6
PaO_2	79.6 ± 9.9	81.7 ± 13.4	78.6 ± 15.1	78.5 ± 11.2

Data are presented as mean ± SD, PR, pulmonary rehabilitation; VC, vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; $PaCO_2$, partial arterial carbon dioxide concentration; PaO_2, partial arterial oxygen concentration.

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Table 2 Muscle strength and exercise test data at baseline and immediately following pulmonary rehabilitation

	PR group			control group		
	baseline	10 weeks	ES	baseline	10 weeks	ES
Muscle strength						
Grip strength (N)	270.7 ± 94.2	293.0 ± 100.6 ‡	0.24	277.3 ± 88.2	263.7 ± 83.8	-0.15
Quadriceps force (Nm)	83.1 ± 30.3	92.0 ± 33.2 ‡	0.29	82.6 ± 25.3	85.9 ± 28.5	0.13
MEP (cmH_2O)	141.1 ± 53.3	156.4 ± 55.2 ‡	0.29	139.0 ± 42.8	144.6 ± 45.5	0.13
MIP (cmH_2O)	111.5 ± 36.8	129.1 ± 45.7 ‡	0.48	92.1 ± 41.1	101.5 ± 29.7	0.23
ILET						
$\dot{V}O_{2\ peak}$ (ml/min)	651.7 ± 294.2	694.5 ± 284.0	0.12	743.1 ± 255.0	703.7 ± 237.3	-0.20
WR_{peak} (w)	60.8 ± 24.4	66.7 ± 26.2 ‡	0.24	65.9 ± 17.1	62.4 ± 19.3	-0.21
AT (ml/min)	479.7 ± 207.0	585.4 ±277.5 ‡	0.51	613.3 ± 165.8	520.0 ± 149.0 ‡	-0.52
Work efficiency	5.8 ± 2.1	6.4 ± 2.7 †	0.29	6.9 ± 2.0	5.8 ± 2.6 †	-0.55
CLET						
ET (min)	5.7 ± 3.1	15.0 ± 10.7 ‡	2.96	6.5 ± 5.5	5.4 ± 4.9	-0.16
6MWT						
6MWD (m)	477.7 ± 91.0	504.4 ± 96.8 ‡	0.29	499.4 ± 66.6	478.8 ± 78.7	-0.31
ISWT						
ISWD (m)	365.6 ± 119.7	393.3 ± 139.6 ‡	0.26	393.5 ± 116.3	363.8 ± 116.3	-0.20

Data are presented as mean ± SD. ES, effect size, † $p<0.05$, ‡: $p<0.01$, compared with baseline, MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; ILET, incremental load ergometry test; $\dot{V}O_{2\ peak}$, peak oxygen uptake; WR_{peak}, peak work rate; AT, anaerobic threshold; CLET, constant load ergometry test; ET, endurance time; 6MWT, six-minute walking test; 6MWD, six-minute walking distance; ISWT, incremental shuttle walking test; ISWD, incremental shuttle walking distance.

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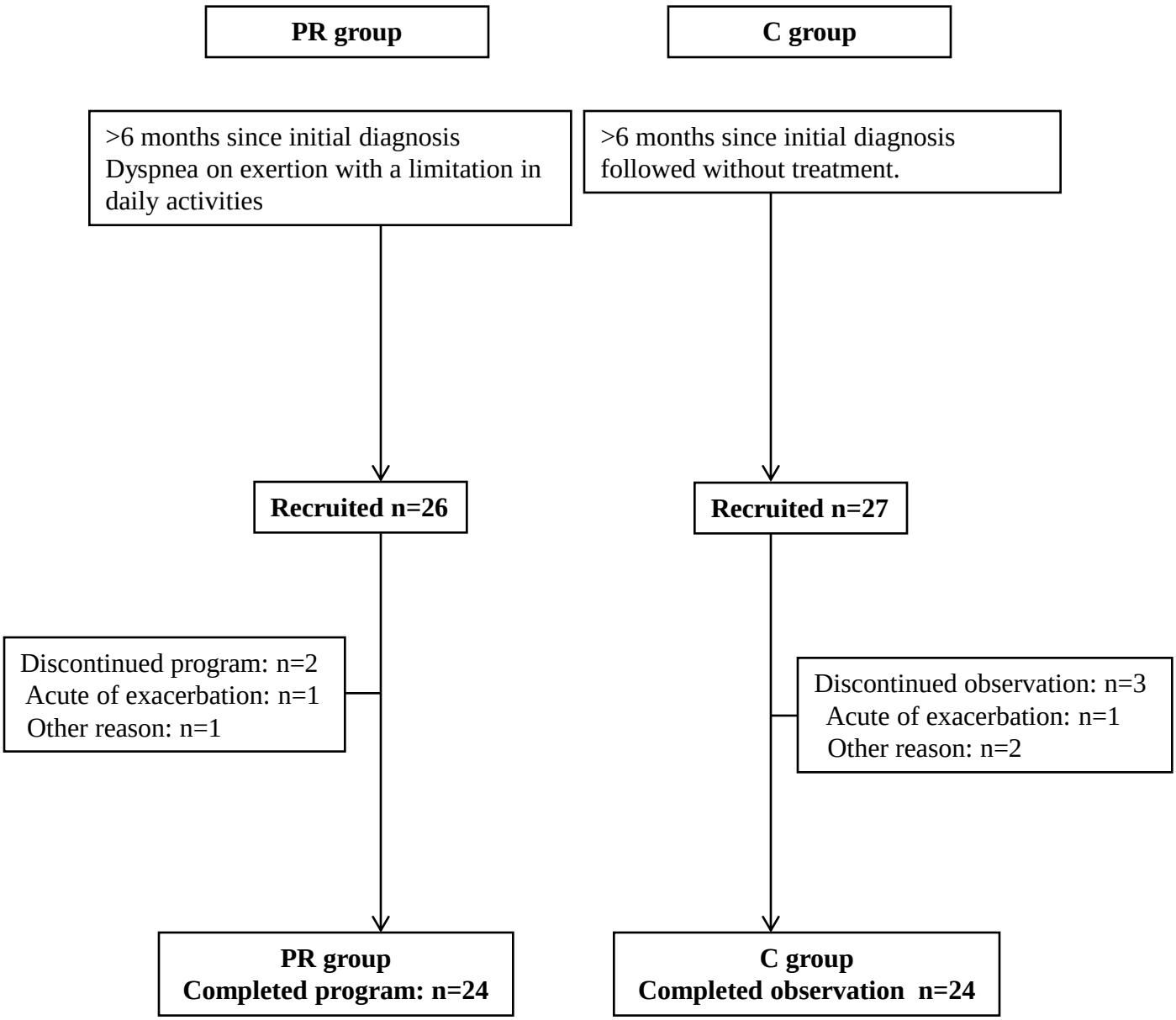

Figure 1

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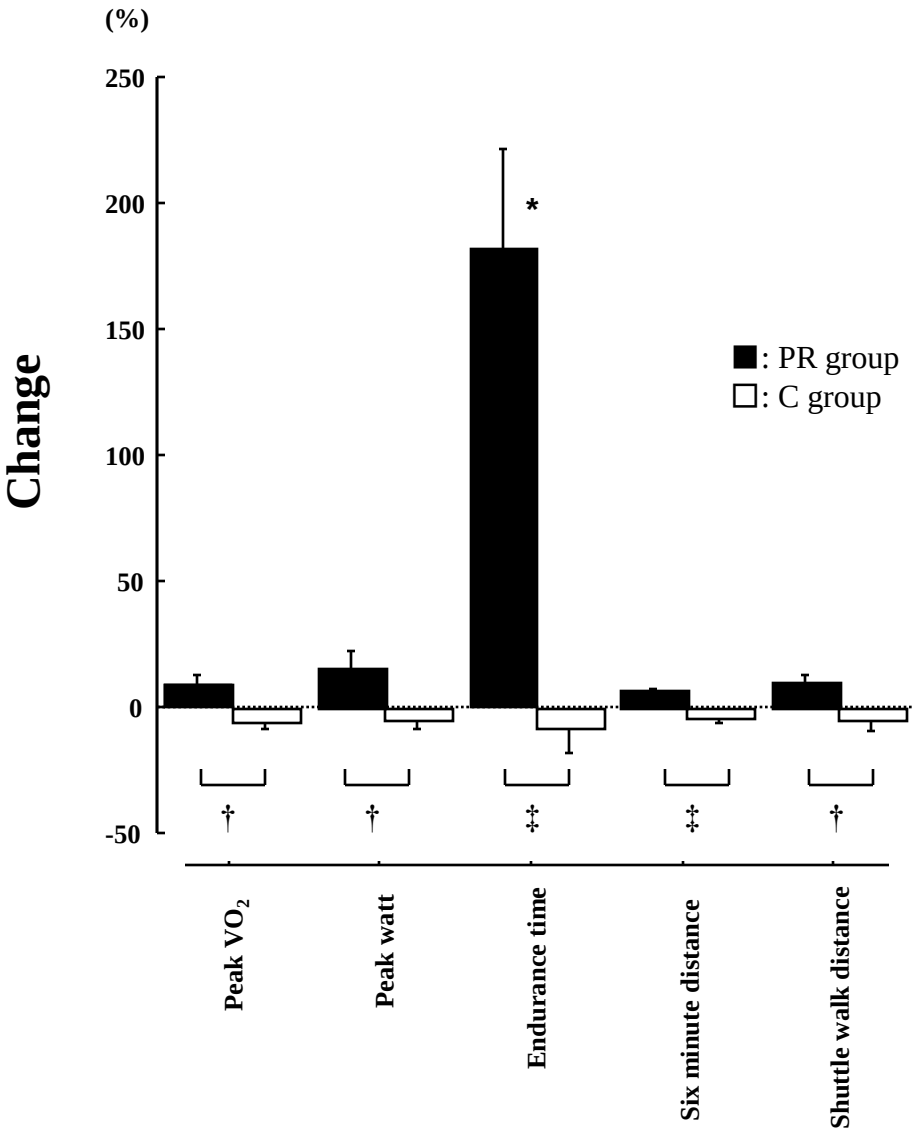

Figure 2