



Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: <http://www.elsevier.com/locate/rmcr>

Comprehensive pulmonary rehabilitation in patients with bronchiolitis obliterans syndrome: A case series

Hee Eun Choi^{a,*}, Sung-Nam Lim^b, Jae Ha Lee^c, Se-Heum Park^a

^a Department of Physical Medicine and Rehabilitation, Haeundae Paik Hospital, Inje University College of Medicine, Busan, North Korea

^b Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, North Korea

^c Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, North Korea

ARTICLE INFO

Keywords:

Pulmonary rehabilitation
Bronchiolitis obliterans
Graft versus host disease

ABSTRACT

Chronic graft-versus-host disease (GVHD) is a significant complication of allogeneic hematopoietic stem cell transplantation, affecting 30%–70% of transplant recipients. One of the most challenging manifestations of chronic pulmonary GVHD is bronchiolitis obliterans syndrome (BOS), a rare and difficult-to-diagnose disease associated with a high mortality rate. BOS results in progressive circumferential fibrosis and, ultimately, cicatrization of the small terminal airways, manifesting as new fixed airflow obstruction. Although BOS patients are typically treated with immunosuppressive agents, there is no strong evidence that any specific therapies are effective in improving long-term outcomes. Thus, the mortality rate remains high. Therefore, there is an increasing need for additional therapies, including pulmonary rehabilitation (PR), in patients with BOS. PR is an evidence-based and comprehensive intervention for patients with chronic obstructive lung disease aimed at alleviating respiratory symptoms and optimizing functional capacity. This present case series demonstrates that comprehensive PR may also improve exercise tolerance and dyspnea in patients with BOS.

1. Introduction

Bronchiolitis obliterans syndrome (BOS) is the most serious form of pulmonary graft-versus-host disease (GVHD) and is clinically characterized by obstructive airflow disease and pathologically by circumferential fibrous scar tissue targeting the small airways [1,2]. The prevalence of BOS is estimated to be 2–3% in allogeneic hematopoietic stem cell transplantation (Allo-HSCT) recipients and 6% in chronic GVHD patients [2]. Although BOS patients are typically treated with immunosuppressive agents, there is no strong evidence that any specific therapies are effective in improving long-term outcomes. As such, the mortality rate remains high [2]. Exercise capacity outcomes, such as 6 min walk distance (6MWD) and peak oxygen consumption (VO_{2peak}), are strong prognostic indicators for mortality in chronic lung disease [3]. Therefore, we attempted to implement a pulmonary rehabilitation (PR) program in patients with BOS to observe its effectiveness and safety.

2. Case description

Outpatient-based PR, consisting of breathing retraining, inspiratory and expiratory muscle strengthening, and aerobic and resistance exercise, was prescribed. To strengthen the respiratory muscle, POWERbreathe® K5 (POWERbreathe International Ltd., Warwickshire, United Kingdom) and Threshold IMT®/PEP® (Philips Respironics, Monroeville, PA, USA) were used. Patients performed the aerobic exercise program on a treadmill, which consisted of a 5-min warm-up at 50% of heart rate reserve (HRR), followed by four of 3-min intervals at 60–85% of HRR, with three recovery periods of 3 min at 50% of HRR and a 5 min cool-down at 50% of HRR. The intensity of the interval began at 60% of HRR and gradually increased with improvements in the patients' exercise capacity. In all training sessions, a telemetry monitoring system (Central Nursing Station CNS-6201, Nihon Kohden, Tokyo, Japan) was used to monitor the patients' electrocardiograms, heart rate (HR), and oxygen saturation. Furthermore, medical staff checked each patient's subjective rate of perceived exertion. To evaluate the outcomes after PR, each patient underwent a cardiopulmonary exercise test (CPET), pulmonary function test (PFT), 6 MWD test, and their modified Medical

* Corresponding author. Department of Physical Medicine and Rehabilitation, Haeundae Paik Hospital, Inje University College of Medicine, 875, Haeun-daero, Haeundae-gu, Busan, 48108, North Korea.

E-mail address: solideogloria@paik.ac.kr (H.E. Choi).

<https://doi.org/10.1016/j.rmcr.2020.101161>

Received 27 March 2020; Accepted 4 July 2020

Available online 9 July 2020

2213-0071/© 2020 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Research Council (mMRC) dyspnea scale score was checked.

Demographic data for 4 cases are summarized in Table 1. Changes in exercise capacity and pulmonary function are summarized in Table 2. Written informed consent for publication of the clinical data was obtained from all patients.

2.1. Case 1

This patient underwent Allo-HSCT for acute myeloid leukemia. She was diagnosed with BOS using high-resolution computed tomography (Fig. 1) 14 months after HSCT and was referred to the PR clinic with complaints of dyspnea. This patient was using a portable oxygen concentrator and her mMRC scale score was 3. She used inhaled corticosteroids, long-acting beta agonists (LABA) and long-acting anticholinergic agents (LAAC). She underwent comprehensive PR three times per week for 12 weeks at the PR clinic. After 12 weeks in the PR program, her mMRC scale score decreased from 3 to 2, and she was able to discontinue the use of the oxygen concentrator during the daytime. Her VO_{2peak} increased from 15.7 to 18.4 ml/kg/min, and 6MWD also improved from 215 m to 297 m. Moreover, her resting HR decreased from 116 to 95 beats/min. For her PFT results, forced vital capacity (FVC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) increased after PR. However, forced expiratory volume in 1 s (FEV_1) demonstrated no significant changes.

2.2. Case 2

This patient was also diagnosed with acute myeloid leukemia and underwent Allo-HSCT. He visited the PR clinic 1 year after being diagnosed with BOS. He complained of dyspnea on exertion, with an mMRC scale score of 2. Inhaled LAAC was used to control his BOS. He participated in a PR program two times per week for 8 weeks, after which his exercise capacity significantly improved and he was able to return to school. His resting HR decreased from 112 to 97 beats/min. FVC, MIP, and MEP were also increased, while FEV_1 remained unchanged.

2.3. Case 3

This patient was referred to the PR clinic for worsening PFT results. He was enrolled in the PR program immediately after being diagnosed with BOS. He had been diagnosed with severe aplastic anemia. Although he underwent Allo-HSCT, he experienced secondary haploidentical HSCT due to engraftment failure. He was prescribed an inhaled corticosteroid, LABA, LAAC and a leukotriene receptor antagonist. When he first visited the PR clinic, his mMRC scale score was 2. He participated in a PR program two times per week for 12 weeks at the PR clinic. However, his attendance rate in the PR program was low. Multiple comorbidities, including pneumonia, chest wall pain and depression,

Table 1

Demographic and medical records of 4 cases.

	Case 1	Case 2	Case 3	Case 4
Age	42	19	28	55
Sex	Female	Male	Male	Male
BMI	15.1	17.8	18.5	21.7
Cause of HSCT	AML	AML	AA	MDS
BOS onset time after HSCT	14 months	8 months	6 months	20 months
The period between BOS diagnosed and PR starting	5 years	1 year	7 days	2 years
PR duration	3 month	2 month	3 month	2 month
mMRC ^a	3	2	2	2

BMI = body mass index, HSCT = hematopoietic stem cell transplantation, AML = acute myeloid leukemia, AA = aplastic anemia, MDS = myelodysplastic syndrome, mMRC = modified medical research council dyspnea scale.

^a mMRC scale, when first visited PR clinic.

Table 2

Changes of exercise capacity and pulmonary function, before and after PR.

Variables	Case 1	Case 2	Case 3	Case 4
VO_{2peak} (ml/kg/min)				
Baseline	15.7	18.4	22.7	20.0
After PR	18.4	22.8	26.6	25.7
Change rate (%)	+17.2	+23.9	+17.2	+28.5
6 MWT (m)				
Baseline	215	450	456	480
After PR	297	534	558	582
Change rate (%)	+38.1	+18.7	+22.4	+21.2
Resting heart rate				
Baseline	116	112	103	89
After PR	95	97	86	78
Change rate (%)	-18.1	-13.4	-16.5	-12.4
Maximal heart rate				
Baseline	130	167	136	137
After PR	135	161	134	151
Change rate (%)	+3.9	-3.6	-1.5	+10.2
mMRC				
Baseline	3	2	2	2
After PR	2	2	1	1
FVC (%)				
Baseline	44	55	76	74
After PR	71	71	87	80
Change rate (%p)	+27	+16	+11.8	+8.1
MIP (cmH₂O)				
Baseline	70	71	45	101
After PR	104	91	69	107
Change rate (%)	+48.6	+28.2	+53.3	+5.9
MEP (cmH₂O)				
Baseline	83	51	68	93
After PR	89	89	81	102
Change rate (%)	+7.2	+74.5	+11.8	+9.7
FEV_1 (%)				
Baseline	26	41	46	37
After PR	27	42	44	37.8
Change rate (%p)	+1	+1	-2	+2.1

6MWT = 6 minute walk test, FVC = forced vital capacity, FEV_1 = forced expiratory volume in the first second of expiration, mMRC = modified medical research council dyspnea scale, MIP = maximal inspiratory pressure, MEP = maximal expiratory pressure.



Fig. 1. High-resolution computed tomography image of patient 1. Multifocal ground-glass opacities with multifocal bronchial wall thickening, mild bronchial wall dilatation, and suspicious mosaic attenuation areas in both lungs.

prevented his participation in PR. After 16 sessions of PR were completed in a 12-week period, his VO_{2peak} improved by 17%. However, his FEV_1 was not markedly altered.

2.4. Case 4

This patient underwent HSCT due to myelodysplastic syndrome. He was referred to the PR clinic with complaints of dyspnea on exertion. His

mMRC scale score was 2. An inhaled corticosteroid, LABA, LAAC, and leukotriene receptor antagonist were prescribed. He underwent comprehensive PR three times per week for 8 weeks, after which his mMRC scale score improved from 2 to 1. His VO_{2peak} increased from 20.0 to 25.7 ml/kg/min. His resting HR decreased from 89 to 78 beats/min. Moreover, his FEV_1 was slightly increased.

3. Discussion

Most PR strategies and research have focused on patients with chronic obstructive pulmonary disease (COPD). However, more recent studies have demonstrated the effectiveness of PR for other chronic respiratory diseases [4,5], although the effect of PR in patients with BOS has not been extensively studied [1].

BOS and COPD share similarities in pathophysiology and symptoms, although the causes of both differ [6]. BOS affects the small airways and is characterized by progressive fixed air flow obstruction [7]. Individuals with COPD also exhibit airway obstruction with hyperinflation of the lung affecting the small airways. Furthermore, patients with BOS and COPD exhibit respiratory and skeletal muscle weakness, which is associated with pulmonary function and exercise intolerance [2,6,7]. Based on these similarities, we investigated the effects of PR in patients with BOS.

To our knowledge, this was the first study to directly evaluate measures of exercise capacity in BOS patients through CPETs. PR objectively improved the VO_{2peak} in BOS patients by 17%–28%. Moreover, 6MWD showed improvement of more than 54 m in all 4 patients. The 6MWD is widely used to measure the functional status of patients with cardiopulmonary diseases and the minimal clinically important difference is estimated to be 54 m. [8] Increased 6MWD after PR could be interpreted as objectively showing the efficacy of PR in patients with BOS. Considering that VO_{2peak} is a strong predictor of mortality in chronic lung disease, it will be necessary to recommend PR for patients with BOS.

However, improvement of pulmonary function after PR remains controversial [9]. In particular, FEV_1 is used as marker for pathophysiological changes in chronic lung disease because it reflects airway resistance and elastic recoil [10]. In our cases, we found no remarkable changes in FEV_1 compared with increases in FVC, MIP, and MEP. We speculate that the efficacy of PR arises from a peripheral training effect, thus relieving symptoms and improving exercise capacity. However, it may be difficult to alter the progression and pathophysiology of BOS through PR.

High resting HR in COPD patients is known to be caused by hypoxia, autonomic dysfunction, decreased stroke volume, and left ventricular size [11]. Many recent studies have investigated the relationship between mortality in COPD and resting HR. Although we found a high resting HR in our 4 BOS patients, they experienced a decrease in resting HR after the PR sessions. One aspect of the PR program, aerobic exercise, appeared to play a major role in decreasing resting HR in BOS patients. Similar to COPD, by correcting autonomic dysfunction, hypoxia, and increasing oxygen utilization in the peripheral muscles, PR may help reduce resting HR in patients with BOS.

These cases showed progressively decreased pulmonary function and daily activities after BOS diagnosed. Moreover, PR began more than a

year after the BOS diagnosis in 3 out of 4 of our cases. However, through more than 2 months of PR, these cases showed improvements in FVC, MIP, MEP and peak oxygen uptake. PR should be considered as a treatment option for BOS patients earlier in clinical practice.

In conclusion, our case series demonstrated that PR could be beneficial for BOS patients by improving subjective symptoms, lung capacity, respiratory muscle strength, and exercise capacity. However, more research is required to accumulate further evidence that supports the efficacy of PR as well as to investigate the long term effects with additional patients.

Funding

This work was supported by the 2018 Inje University research grant.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Hee Eun Choi: Conceptualization, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Sung-Nam Lim:** Data curation, Writing - review & editing. **Jae Ha Lee:** Data curation, Writing - review & editing. **Se-Heum Park:** Investigation, Writing - original draft.

References

- [1] J. Tran, E.E. Norder, P.T. Diaz, G.S. Phillips, P. Elder, S.M. Devine, et al., Pulmonary rehabilitation for bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation, *Biol. Blood Marrow Transplant.* 18 (8) (2012) 1250–1254.
- [2] B.K. Au, M.A. Au, J.W. Chien, Bronchiolitis obliterans syndrome epidemiology after allogeneic hematopoietic cell transplantation, *Biol. Blood Marrow Transplant.* 17 (7) (2011) 1072–1078.
- [3] C.E. Berry, R.A. Wise, Mortality in COPD: causes, risk factors, and prevention, *COPD* 7 (5) (2010) 375–382.
- [4] A.L. Ries, G.S. Bauldoff, B.W. Carlin, R. Casaburi, C.F. Emery, D.A. Mahler, et al., Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines, *Chest* 131 (5 Suppl) (2007) 4S–42S.
- [5] A. Ferreira, C. Garvey, G.L. Connors, L. Hilling, J. Rigler, S. Farrell, et al., Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response, *Chest* 135 (2) (2009) 442–447.
- [6] A. Bergeron, C. Godet, S. Chevreton, G. Lorillon, R. Peffault de Latour, T. de Revel, et al., Bronchiolitis obliterans syndrome after allogeneic hematopoietic SCT: phenotypes and prognosis, *Bone Marrow Transplant.* 48 (6) (2013) 819–824.
- [7] P.R. Burgel, A. Bergeron, J. de Blic, P. Bonniaud, A. Bourdin, P. Chanez, et al., Small airways diseases, excluding asthma and COPD: an overview, *Eur. Respir. Rev.* 22 (128) (2013) 131–147.
- [8] R.A. Wise, C.D. Brown, Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test, *COPD* 2 (1) (2005) 125–129.
- [9] N.B. Elkhateeb, A.A. Elhadidi, H.H. Masood, A.R. Mohammed, Pulmonary rehabilitation in chronic obstructive pulmonary disease, *Egypt. J. Chest Dis. Tuberc.* 64 (2) (2015) 359–369.
- [10] P.W. Jones, A.G. Agusti, Outcomes and markers in the assessment of chronic obstructive pulmonary disease, *Eur. Respir. J.* 27 (4) (2006) 822–832.
- [11] M.T. Jensen, J.L. Marott, P. Lange, J. Vestbo, P. Schnohr, O.W. Nielsen, et al., Resting heart rate is a predictor of mortality in COPD, *Eur. Respir. J.* 42 (2) (2013) 341–349.