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Pulmonary rehabilitation coupled with negative pressure ventilation decreases decline in lung function, hospitalizations, and medical cost in COPD

A 5-year study

Hung-Yu Huang, MD[a], Pai-Chien Chou, MD, PhD[a], Wen-Ching Joa, BScN[a], Li-Fei Chen, BScN[a], Te-Fang Sheng, BScN[a], Horng-Chyuan Lin, MD[a], Lan-Yan Yang, PhD[b], Yu-Bin Pan, MS[b], Fu-Tsai Chung, MD[a], Chun-Hua Wang, MD[a,*], Han-Pin Kuo, MD, PhD[a]

Abstract

Pulmonary rehabilitation (PR) brings benefits to patients with chronic obstructive pulmonary disease (COPD). Negative pressure ventilation (NPV) increases ventilation and decreases hyperinflation as well as breathing work in COPD. We evaluated the long-term effects of a hospital-based PR program coupled with NPV support in patients with COPD on clinical outcomes.

One hundred twenty-nine patients with COPD were followed up for more than 5 years, with the NPV group (n = 63) receiving the support of NPV (20–30 cm H_2O delivery pressure for 60 min) and unsupervised home exercise program of 20 to 30 min daily walk, while the control group (n = 6) only received unsupervised home exercise program. Pulmonary function tests and 6 min walk tests (6MWT) were performed every 3 to 6 months. Emergency room (ER) visits and hospitalization with medical costs were recorded.

A significant time-by-group interaction in the yearly decline of forced expiratory volume in 1 s in the control group analyzed by mixed-model repeated-measure analysis was found ($P = 0.048$). The 6MWT distance of the NPV group was significantly increased during the first 4 years, with the interaction of time and group ($P = 0.003$), the time alone ($P = 0.014$), and the quadratic time ($P < 0.001$) being significant between the 2 groups. ER exacerbations and hospitalizations decreased by 66% ($P < 0.0001$) and 54% ($P < 0.0001$) in the NPV group, respectively. Patients on PR program coupled with NPV had a significant reduction of annual medical costs ($P = 0.022$).

Our hospital-based multidisciplinary PR coupled with NPV reduced yearly decline of lung function, exacerbations, and hospitalization rates, and improved walking distance and medical costs in patients with COPD during a 5-year observation

Abbreviations: 6MWD = 6 min walking distance, 6MWT = 6 min walk test, CI = 95% confidence interval, COPD = chronic obstructive pulmonary disease, ER = emergency room, FEV_1 = forced expiratory volume in 1 s, FVC = forced vital capacity, ICS = inhaled corticosteroid, LABA = long-acting beta-adrenoceptor agonist, LAMA = long-acting muscarinic antagonist, NPV = negative pressure ventilation, OPD = outpatient department, PR = pulmonary rehabilitation, USD = United States dollars.

Keywords: 6 min walk test, chronic obstructive pulmonary disease, hospitalization, lung function, negative pressure ventilation, pulmonary rehabilitation

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Conceived and designed the experiments and wrote the paper: H-YH and C-HW. Performed the experiments: W-CJ, L-FC, T-FS, and H-CL. Analyzed the data: H-YH, C-HW, L-YY, and Y-BP. Contributed reagents/materials/analysis tools: P-CC, F-TC, and H-PK.

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[a] Department of Thoracic Medicine, Chang Gung Memorial Hospital, Taipei, [b] Biostatistics Unit, Clinical Trial Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

[*] Correspondence: Chun-Hua Wang, Department of Thoracic Medicine, Chang Gung Memorial Hospital, 199 Tun-Hwa North Road, Taipei, Taiwan (e-mail: wchunhua@ms7.hinet.net).

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow obstruction with chronic airway inflammation and emphysematous changes in the lung parenchyma.[1] The yearly decline of lung function measured as forced expiratory volume in 1 s (FEV_1) increased in established COPD,[2] with the greatest decline in FEV_1 strongly associated with acute exacerbations and hospitalization.[3] Frequent acute exacerbations in patients with COPD contribute to increasing length of hospitalization,[4] and increased medical costs to healthcare system.[5] Thus, slowing or preventing the accelerated decline in lung function may have a beneficial effect on the clinical outcome of COPD.[6,7]

Small airway inflammation-induced air-trapping or atelectasis, and the emphysematous destruction of alveoli and the pulmonary capillary bed, may result in increased dead space and inhomogeneous lung ventilation.[8–10] Hypoxemia on exercise together with muscle wasting is a leading cause for exercise intolerance in patients with COPD, which appears to increase with disease progression.[11,12] Besides, mucus plugging in small airways may cause lung atelectasis and then increase shunting.[13] Dynamic hyperinflation also contributes to exercise limitation in this disease,[14] leading to a decreased pulmonary perfusion[15] and an increase in the work of breathing.[16] Therefore, the reasons for disease progression of COPD are multifactorial, including lack of long-term regular exercise, disease progression and comorbidities, and exacerbations.[17] Therefore, such a multidimensional problem requires a comprehensive pulmonary rehabilitation (PR) to improve the physical status of patients with COPD.

In 2013, the American Thoracic Society and the European Respiratory Society published a statement, in which PR was recognized as an evidence-based, multidisciplinary, and comprehensive intervention, which has positive effects on 6 min walking distance (6MWD), muscle force, cycle exercise endurance time, and quality of life.[18] Comprehensive PR programs may include exercise training, breathing control, mucus clearance, and lung expansion therapy with noninvasive ventilation support.[18] However, so far there has been little study of negative pressure ventilation (NPV) as an adjuvant to PR. NPV on its own has been effective in improving ventilation pattern and arterial blood gases and in unloading inspiratory muscles,[19,20] thus decreasing the work of breathing in patients with COPD.[21] We have demonstrated that exercise training with NPV support is feasible for patients with severe restrictive lung diseases, and improves exercise capacity and health-related quality of life.[22] In patients with COPD, we have shown that home pacing walking exercise can increase exercise capacity and strength of limb muscles, and reduce systemic inflammation.[23] However, it is not known whether long-term PR adjuvant with NPV and exercise training can reduce lung function decline and improve clinical outcomes in patients with COPD.

We have established a hospital-based multidisciplinary PR program, consisting of breathing retraining, NPV support, and an education program (relaxation techniques and home pacing walking exercise) in the daily management of patients with COPD. The aim of this population-based cohort study was to determine the influence of our PR program on lung function and exercise capacity, and to assess its clinical benefit in patients with COPD.

2. Methods

2.1. Study subjects

This was a longitudinal, observational, population-based study performed in our patients with COPD cohort attending the outpatient clinics of Chang Gung Memorial Hospital, a tertiary medical center in Taiwan, during a period of 2008 to 2012. The diagnosis and severity of COPD were confirmed in all patients by spirometry, with a ratio of FEV_1 to forced vital capacity (FVC) <0.7 after bronchodilators.[24] We excluded patients who were younger than 40 years of age, and had symptomatic cardiovascular diseases or severe systemic diseases, such as hematologic disease, malignancy, systemic lupus erythema, end stage of renal disease and severe liver cirrhosis, or musculoskeletal deconditioning with exercise performance limitation.

This study consisted of a pre–post design with outcome measurements and total medical cost to the healthcare system made throughout 5-year follow-up. Comparison was performed in those patients of NPV group who completed multidiscipline PR program (n = 63) (see below) at least 3 times/wk and the control group (n = 66). The study flow-chart is shown in Fig. 1. The study was approved by Chang Gung Memorial Hospital Ethics Committee.

2.2. PR program adjuvant with NPV

All patients were referred to PR Center of Thoracic Department. The hospital-based multidisciplinary PR program is well established in our hospital, including breathing retraining, NPV support, and an educational program (relaxation techniques and home pacing walking exercise). Breathing training consisted of breathing techniques (pursued-lipped, controlled, and diaphragmatic breathing). Patients received NPV with breathing training via the cuirass ventilator settings for 60 min. The ventilator was set to control sign model and delivered by negative pressures ranging -20 to -30 cm H_2O, and +3 cm H_2O base pressure. The frequency was set to 12 cycles/min, and the ratio of inspiratory time to total breathing cycle time (Ti/Ttot) was set to 30%. An unsupervised home endurance exercise program of 20 to 30 min pacing walk, continuously or intermittently (in sessions lasting 10 or more minutes) per day, guided by 40% to 60% of target heart rate or a score of 4 to 6 on the modified Borg scale, with the aim of achieving 3 to 5 exercise sessions per week. A physiotherapist supervised exercise at the first visit. The training was terminated on the basis of the patient's symptoms. Pacing walking was taught to all patients and encouraged to be performed at home by the patients themselves. Supplemental oxygen was given to maintain oxygen saturation, if desaturation (Sat < 90%) was observed. The decision to receive

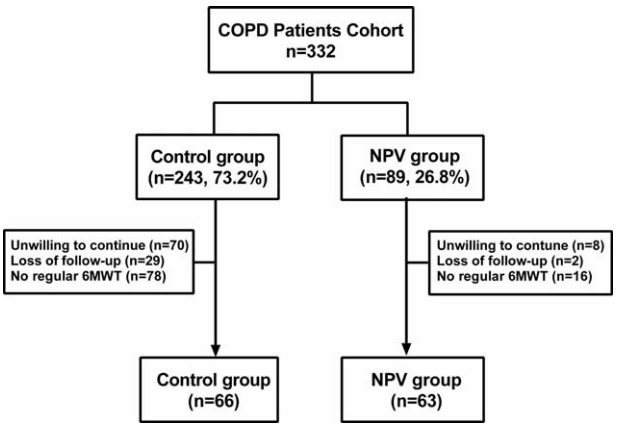

Figure 1. The study flow chart.

multidisciplinary PR program was made by the pulmonary physician after discussing the program with the patients and their family. If they did not agree the hospital-based PR program, they were asked to perform unsupervised home walking exercise as much as possible and this was considered as the control group. In the control group, they were reminded of breathing training and relaxation techniques, and home pacing walking exercise, when they went back to outpatient clinics or performed 6 MWT. In the NPV group, patients underwent a comprehensive hospital-based PR program once every week. PR intensity and duration was individualized based on clinical status and estimated exercise capabilities.

3. Outcome measures

3.1. 6 Min walk test

All subjects performed 6 min walk test (6MWT) every 3 to 6 months in order to monitor the effect of training, according to our previously published paper.[25] The participants were instructed to walk back and forth in a 35 m corridor. Our clinical staff educated patients before the test. The modified Borg dyspnea score was evaluated before and after walking. At each minute, a therapist reminded participant the remaining time and gave encouragement for walking as the participant could do as possible. The participants stopped walking at the end of 6 min, and walking distance was recorded. Pulmonary function test including FVC, FEV_1, and FEV_1/FVC ratio was recorded before and after walking. Heart rate and oxygen saturation were measured during the procedure.

3.2. Exacerbation rates

A mild exacerbation was defined as worsening respiratory symptoms that required oral antibiotics and/or prednisone in OPD.[26] The definition of a severe exacerbation included emergency room (ER) visit and time spent in the ER stay for <18 h due to respiratory symptoms.[27] The exacerbations were recorded and classified as mild or severe in intensity. Hospitalization was defined as a primary discharge diagnosis of COPD.[28] The number of exacerbation and hospitalization rates per year was then calculated. Time to the first severe exacerbation or hospitalization was also recorded.

3.3. Healthcare cost

Annual medical cost of all the patients was calculated according to the perspective of medical expenses paid by the National Health Insurance scheme. The medical cost of healthcare system included COPD maintenance medication, clinic visits, ER visits, and hospitalization. The outpatient clinic (OPD) costs consisted of maintenance medication and the expense of PR, clinical visits, and diagnostic tests. Maintenance medication was defined as the drugs prescribed at discharge or taken by patients prior to any exacerbation.[29] We counted the total medical cost for each episode of ER visit or hospitalization based on the database from National Health Insurance scheme. In Taiwan, the National Health Insurance scheme provides compulsory health insurance and pays the complete reimbursement of healthcare costs for almost every citizen. We recorded the expenditure in New Taiwan dollars and converted to United States dollars (USD) by the current exchange rate of 1:32.

3.4. Statistical analysis

We reported means and standard deviations for the continuous variables and frequency/percentage was reported for the categorical variables. We used a Kolmogorov–Smirnov test to determine normality of the variables within groups. For data with an even or uneven distribution, continuous variables were compared between groups using the Student t test or the Mann–Whitney test. In this study, because the lung function and 6MWD measurements were not taken at regular time points, a mixed-model repeated-measure analysis was used for subjects with repeated scheduled measurements to examine changes in pulmonary function and walked distance in 6MWT and to compare the differences between groups. A baseline measurement was obtained at time = 0 for each individual. The Kaplan–Meier estimates of the time to first exacerbation and hospitalization were tested for significance by using the log-rank test. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC). A P value < 0.05 was considered statistically significant.

4. Results

Of the 332 patients, 89 (26.8%) agreed to receive a hospital-based multidisciplinary PR program, defined as NPV group, and 243 (73.2%) refused the PR program and enrolled into unsupervised pacing walking at home, considered as control group. Twenty-six patients in the NPV group were excluded because of unwilling to continue program (n = 8), loss of follow-up (n = 2), and no regular recording of 6MWT (n = 16), while 177 patients in the control group had 70 unwilling to continuing program, 29 lost to follow-up, and 98 with no regular records of 6MWT during a period of 5 years (Fig. 1). In the end, the study population included 66 in the control group and 63 in the NPV group. The characteristics of patients with COPD according to acceptance or refusal of a hospital-based multidisciplinary PR program were summarized in Table 1. There was no difference in terms of age, gender, severity of GOLD, lung functions, 6MWD, and medication between these 2 groups.

4.1. Yearly decline in FEV_1

Based on the mixed-model repeated-measure models with quadratic effect of time (Fig. 2), it depicted the yearly decline in FEV_1 over time especially for the control group. The effects of interaction of time and group were significant ($P = 0.048$ in Fig. 2A and $P = 0.0002$ in Fig. 2B). The means estimated FEV_1 from baseline to the 5th year were 1136 to 1056 and 1093 to 905 mL for the NPV and the control groups, respectively (Fig. 2A). In the NPV group, the FEV_1 was reduced by 16.1 mL/y during the 5-year study, whereas the yearly decline in FEV_1 was 37.6 mL in the control group. The multidisciplinary PR program slowed down the yearly decline in lung function. On the other hand, the estimated changes in percent predicted value of FEV_1 from baseline to the 5th year were 49.4 to 49.1 and 50.8 to 38.1 for the NPV and the control groups, respectively (Fig. 2B). The estimated β parameter and model fitness were shown in Supplement Table S1A and B, http://links.lww.com/MD/B351.

4.2. Walking distance

The model of walking distance with quadratic effect of time showed that the groups were changing over time and they were changing in different ways (Fig. 3). In the NPV group, there was an improvement in walking distance at 1 year (340.9 m), 2 years

Table 1

Characteristics of patients with chronic obstructive pulmonary disease.

	Control (n = 66)	NPV (n = 63)	P*
Age, y	71.1 ± 7.3	72.9 ± 7.2	0.061
Gender, male	66	63	0.976
Smoking, pack per y	40.0 ± 33.4	33.7 ± 38.1	0.122
Body mass index, kg/m^2	22.7 ± 3.7	23.0 ± 3.8	0.578
Gold stage			0.427
Stage I, n (%)	4 (6.0)	7 (11.1)	
Stage II, n (%)	18 (27.3)	22 (34.9)	
Stage III, n (%)	30 (45.5)	21 (33.3)	
Stage IV, n (%)	14 (21.2)	13 (20.6)	
6MWD, m	339.1 ± 13.3	323.4 ± 12.9	0.815
FVC, L	1.8 ± 0.5	1.8 ± 0.6	0.603
FVC, % pred.	58.0 ± 2.4	57.0 ± 2.2	0.994
FEV_1, L	1.0 ± 0.5	1.1 ± 0.5	0.226
FEV_1, % pred.	50.8 ± 3.2	49.4 ± 3.8	0.554
FEV_1/FVC, %	56.3 ± 14.5	60.5 ± 11.2	0.201
O_2 saturation			
Pre-exercise, %	94.4 ± 2.6	94.4 ± 2.6	0.847
Postexercise, %	85.4 ± 7.7	85.2 ± 8.7	0.834
Medication over previous year			0.771
None inhaled medicine	12	7	
LABA + ICS	7	10	
LAMA alone	5	5	
LABA + ICS +LAMA	42	41	
Oral corticosteroid	9	8	

Data expressed as mean ± standard deviation.

6MWD = 6 min walking distance, FEV_1 = forced expiratory volume in 1 s, FVC = forced vital capacity, ICS = inhaled corticosteroid, LABA = long-acting beta-adrenergic agonist, LAMA = long-acting muscarinic antagonist, NPV = negative pressure ventilation.

* Analysis was used by Mann–Whitney test for continuous variables and Chi-squared test for categorical variables.

(347.7 m), 3 years (344.1 m), and a slight decrease at 4 years (305.1 m) compared to the baseline (323.4 m) (Fig. 3). However, in the control group, estimated walking distance (339.1 m, baseline) fell rapidly over time (277.5 and 235.7 m at 4 and 5 years, respectively) (Fig. 3). The slope of the walking distances over time in the NPV group was significantly higher compared to the control group ($P < 0.0001$) (Fig. 3). The effects of interaction of time and group ($P = 0.003$), time ($P = 0.014$), and the quadratic time ($P < 0.001$) were significant between 2 groups. The estimated β parameter and model fitness were indicated in Supplement Table S2, http://links.lww.com/MD/B351.

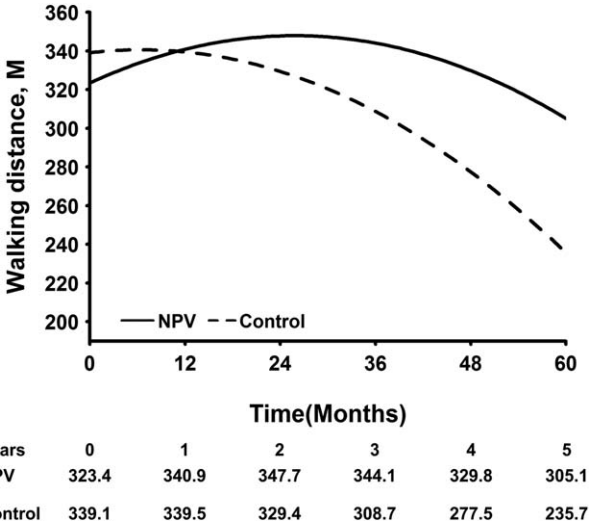

Figure 3. Modeled 6 min walking distance (meter, M) over time of the negative pressure and control groups.

4.3. Exacerbations per patient-year

The mean number of mild COPD exacerbation per person-year of observation did not show any difference between the 2 groups (Table 2). Patients who received a comprehensive PR program experienced significantly less exacerbations of 0.37 (CI: 0.25–0.49, $P < 0.0001$) ER visit per patient-year of 5-year follow-up compared with 1.03 (CI: 0.69–1.36) exacerbations of ER visit per patient-year in the control group. The mean hospitalizations for the control group of 0.67 per person-year

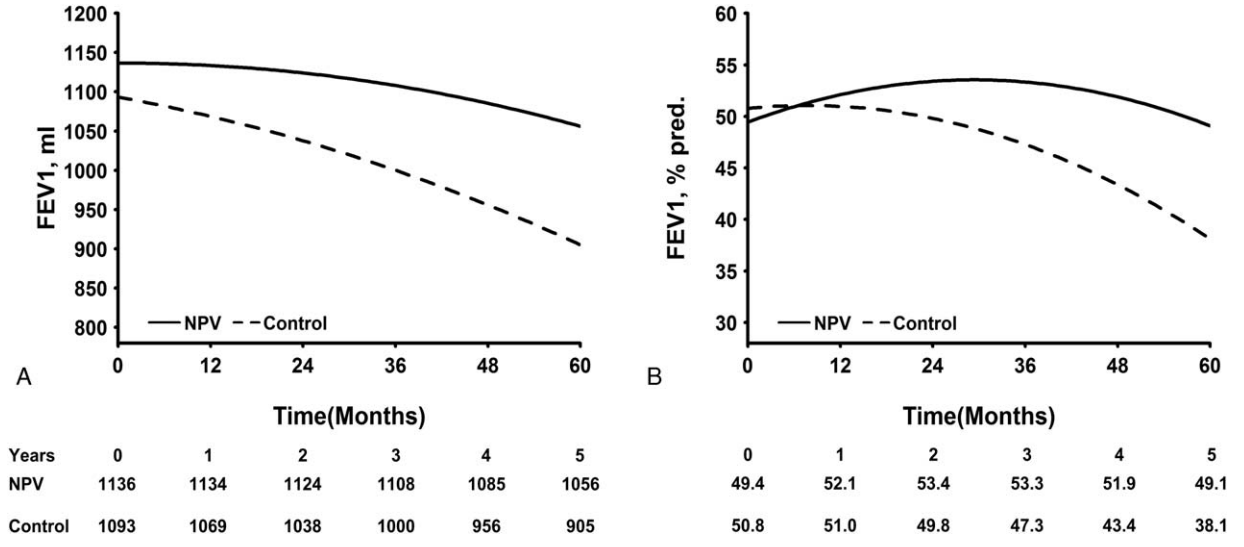

Figure 2. Modeled forced expiratory volume in 1 s (FEV_1) over time of the negative pressure ventilation and control groups (A) in volume of FEV_1 (mL) (B) in predicted value of FEV_1 (predicted %).

Table 2

Exacerbations, hospitalizations, and mortality during 5 years.

	Control group (n=66)	NPV group (n=63)	P
Mean exacerbations per person-year			
Mild exacerbation, n (CI)	1.35±1.62 (0.95–1.75)	1.54±1.38 (1.19–1.89)	0.174*
Severe exacerbations of ER visit, n (CI)	1.03±1.35 (0.69–1.36)	0.37±0.48 (0.25–0.49)	<0.001*
Hospitalizations, n (CI)	0.67±0.80 (0.48–0.87)	0.31±0.45 (0.20–0.42)	<0.001*
Mortality, n (%)	14 (21.21)	6 (9.52)	0.067†

Data expressed as mean ± standard deviation.

CI = 95% confidence interval, ER = emergency room, NPV = negative pressure ventilation.

* Mann–Whitney test

† Chi-squared test.

(CI, 0.48–0.87) were significantly higher than 0.31 per person-year (CI: 0.20–0.42) for the NPV group ($P < 0.0001$) (Table 2). In addition, our multidisciplinary PR program reduced the risk of severe exacerbations requiring an ER visit by 66% and requiring hospitalization by 54% of 5-year follow-up. However, the mortality of the control group was increased compared to the NPV group, but no significance was achieved (Table 2).

4.4. Time to first severe exacerbations and hospitalization

The Kaplan–Meier plots for the time to first severe exacerbation and hospitalization are shown in Fig. 4A and B. The median free time to first ER visit was 200.1 weeks (hazard ratio: 0.51; 95% CI: 0.34–0.78) of the NPV group compared with 153.9 weeks (hazard ratio: 1.94; 95% CI: 1.28–2.96) of the control group ($P = 0.002$) (Fig. 4A). The median free time to first hospitalization of 260.0 weeks (hazard ratio: 0.38; 95% CI: 0.24–0.60) for the NPV group was significantly longer than 148.7 weeks (hazard ratio: 2.67; 95% CI: 1.68–4.24) for the control group ($P < 0.0001$) (Fig. 4B).

4.5. Medical cost of healthcare system

The annual OPD medical costs per person of the NPV group (2163±862 USD, CI: 1945–2380) was higher than that of the control group (1826±939 USD, CI: 1595–2056, $P = 0.004$), because of the PR payment (Table 3). In contrast, patients with COPD who were on PR program had spent significantly less medical cost per person-year in ER visits and hospitalization (1111±1458 USD, CI: 744–1478) compared to those of the control group (2510±2925 USD, CI: 1790–3229, $P < 0.001$). Therefore, the control group had used more annual medical cost of healthcare system per person (4335±3269 USD, CI: 3525–5139) compared with the NPV group (3274±1604 USD, CI: 2870–3678, $P = 0.022$) (Table 3).

5. Discussion

This is the first report to demonstrate that a long-term PR program coupled with noninvasive NPV support may slow down the yearly decline in FEV_1 and improve walking distance in patients with COPD. Our cohort study showed that during a period of 5 years, the multidisciplinary PR program significantly reduced severe exacerbation rates and hospitalization, time to first severe acute exacerbation and hospitalization, and decreased the medical cost of healthcare system in patients with COPD. PR in the management of COPD can increase exercise performance, and slow the yearly decline in lung function, thus relating to a reduction in exacerbations and hospitalization observed in our patients. Furthermore, our report is compatible with an emerging literature that well-organized PR leads to a reduction in healthcare costs.[30]

Although our study did not show an improvement in FEV_1 during the PR program, we found that a significant reduction of the progression of airways obstruction (FEV_1/FVC %) occurring after the 5 years of treatment. Thus, participating in the PR

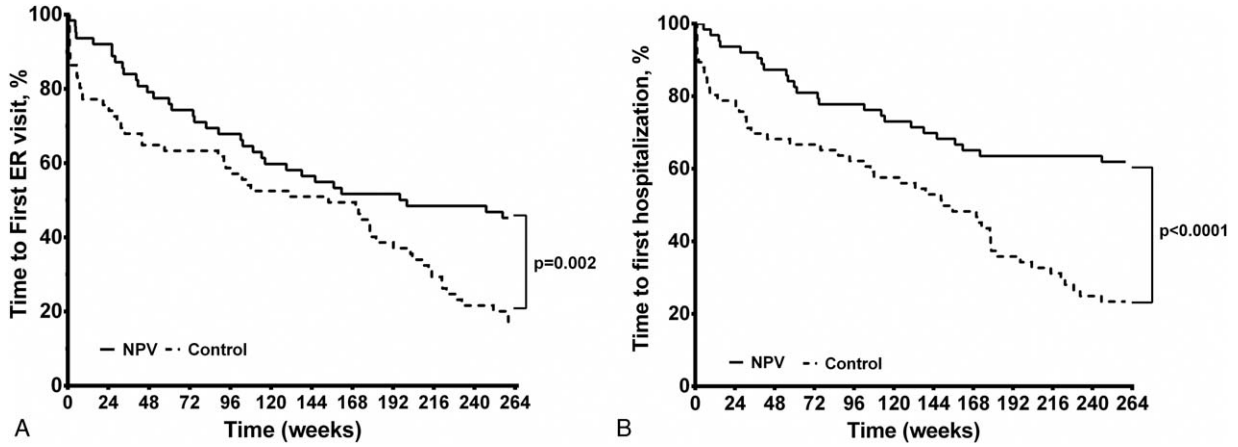

Figure 4. The Kaplan–Meier plots for the time to a first severe exacerbation (A) and hospitalization (B). The solid line represents the negative pressure ventilation group and dashed line is shown the control group. Significance is indicated by using the log-rank test.

Table 3

Medical cost of healthcare system per person-year.

	Control group (n = 66)	NPV group (n = 63)	P^*
OPD cost, USD	1826 ± 939 (1595–2056)	2163 ± 862 (1945–2380)	0.036
ER and hospitalization cost, USD	2510 ± 2925 (1790–3229)	1111 ± 1458 (744–1478)	0.0009
Total direct cost, USD	4335 ± 3269 (3532–5139)	3274 ± 1604 (2870–3678)	0.022

Data express as mean ± standard deviation (95% confidence interval).

ER = emergency room, NPV = negative pressure ventilation, OPD = outpatient department, USD = United States dollars.

* Analysis was used by Student *t* test.

program coupled with NPV support improved small airways function and/or recruitment in accordance with previous studies[6,7] that showed beneficial improvements in the progressive decline in lung function. The progressive deterioration of lung function was multifactorial, including factors such as small airway inflammation, dynamic hyperinflation, inhomogeneous lung ventilation, hypoxemia, oxidative stress, muscle dysfunction, mucus plugging, or combinations.[1,9,11–13] The mechanism by which NPV leads to a reduction of lung function decline was not determined in our study. However, 1 possibility is that NPV may improve ventilation pattern and arterial blood gas exchange and unloading of inspiratory muscles,[19,20] thus reducing the work of breathing in patients with COPD.[21] Another possible benefit of NPV is an improvement in clearing of secretions which can lead to a reduction in airways infections and inflammation and decrease COPD exacerbations. In fact, our patients with COPD on PR program showed a mean 16.1 mL yearly decline in FEV_1, a value similar to that reported in a previous study of patients undergoing PR program.[7,31] Our patients with COPD showed more impairment of FEV_1 (1136 mL) than that study (1620 mL) at baseline.[31] A mean of 37.6 mL yearly decline in FEV_1 was observed in our control group, which has been reported in some studies,[7,32] while being less than others.[33,34] Taken together, we show that our regular multidisciplinary PR program coupled with NPV may protect against the effects of chronic systemic inflammation,[23,35] which may play an important pathogenetic factor in COPD. The reduced yearly decline may be related to the reduction in number of exacerbations.

The 6MWT has been used as an outcome measure in patients with COPD,[36] and is a submaximal exercise test, that correlates well with maximal cardiopulmonary exercise test.[37,38] The 6MWD is a potentially useful biomarker of disease severity and considered as an important prognostic factor for outcome independent of FEV_1.[39,40] The decline rate in 6MWD is related to severity of COPD and to acute exacerbations and comorbidities.[40,41] The annual decline in 6MWD was around 12.5 to 26 m/y in patients with COPD.[39,41] The mean yearly decline in 6MWD was 20.7 m/y in our control group, which was comparable with previous study.[39] The present results showed that the annual decline in 6MWD was relatively small in the NPV group at 8.1 m/y. The 6MWD was significantly increased at the first 3 years in the NPV group. The interaction of time and group ($P = 0.003$), time ($P = 0.014$), and the quadratic time ($P < 0.001$) were significant between the NPV and control groups. This means that the PR program had a more beneficial effect on exercise capacity in the long term. A previous study had proposed that a reduction in the 6MWD of 30 m or more was associated with increased risk of death and worse clinical status in patients with COPD.[40] In our control group, the changes in 6MWD decline became greater (31 m at 4th year and 42 m at the end of 5th year) and steeper after a 3-year follow-up that could have contributed to increased incidence of severe exacerbations and hospitalization.

Patients with COPD show a progressive deterioration in exercise capacity over time, which was strongly correlated with dynamic hyperinflation and airflow limitation.[42] NPV used as an adjunct to exercise-based PR may augment the effects of an exercise program, probably by allowing increased breathing work load or unloading the respiratory muscles, and improved gas exchange associated with acute reductions in dyspnea,[43,44] thus increasing exercise capacity. The benefit appeared to be most marked in severe COPD, and higher positive pressures (if tolerated) may lead to greater improvements. As a result, NPV may be useful as an adjunctive therapy to PR.

There are 2 types of negative pressure ventilators. One is tank ventilation that provides intermittent subatmospheric pressure around the whole body.[45] The other one is cuirass ventilator that provides negative pressure around the chest only and may create a pressure gradient between thorax and lower body, which would increase intrathoracic venous return, increase right cardiac output, and improve lung perfusion.[45] Breathing pattern undergoing cuirass NPV is a real approximation of normal physiological breathing, with more natural distribution of air in the lungs. Thus, NPV does not restrict the activities of patients, and patients can be more comfortable.

A significant reduction in exacerbations and hospitalizations has been demonstrated in our study. The relationships between exacerbations and longitudinal changes in pulmonary function or health status have been discussed in other studies.[46,47] It is possible that our PR program augmented regular physical activity associated with a reduced lung function decline in patients with COPD, thus decreasing the risk of acute exacerbations and hospitalization. However, the mortality was increased in the control group, but this did not achieved significance.

COPD places a major economic burden on healthcare systems and there is a relationship between costs and diseases severity previously reported.[48,49] In a tertiary center in Taiwan, the total costs of patients with severe COPD were twice higher than those with moderate COPD.[29] Previous studies in many countries have confirmed that hospitalization is the major cost component.[29,49,50] Our healthcare system pays around 11,000 USD for each hospitalization, which was much higher than the cost of acute exacerbation or outpatient medical care. The present study showed that patients with COPD receiving multidisciplinary PR program had a reduced risk of severe exacerbations needing ER visit by 66% and hospitalization by 54%. Though the NPV group had higher OPD cost including maintenance medicine and PR costs, the total medical cost was significantly lower compared with the control group. Therefore, a therapeutic strategy leading to a significant reduction in exacerbation-related hospitalization frequency in patients with COPD has the potential to decrease healthcare costs dramatically.

6. Limitations of findings

Our study has some limitations. Firstly, the sample size is small, with a lack of female population, and comes from only 1 tertiary medical center. The generalization of the results might therefore be limited. Secondly, the study design is less than ideal being only an observational study based on our daily clinical practice for patients with COPD in our department. A randomized, controlled, and matched study would be preferable for evaluation of additional effects of NPV in PR. In a matched study, the control subjects are "matched" with the treated subjects over background covariates that the investigator believes need to be controlled. Thirdly, we have not collected information on subjective responses. Since this study included control patients, the long duration of 5 years to complete the study may have contributed to the relatively high number of dropouts (including death), which may be related to deterioration of patients with COPD in the control group. Finally, the prognostic influence of acute exacerbations of COPD requiring hospital management was only analyzed and it is not clear whether other less severe exacerbation episodes could also exert a prognostic influence. We lack detailed data on the acute exacerbations such as clinical etiology and treatment, so no in-depth evaluation of NPV support can be made of the causes underlying their long-term course. Further studies designed specifically to address these issues are needed.

7. Conclusion

In summary, we showed that maintenance PR coupled with NPV could reduce the yearly decline of lung function, improve walking distance, and reduce exacerbation and hospitalization rates and medical costs in patients with COPD during a 5-year observation. This therapeutic strategy could lead to the prevention of yearly decline in pulmonary function or exercise capacity with a reduction on total healthcare costs.

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