

Effects of high-flow nasal cannula with oxygen on self-paced exercise performance in COPD

A randomized cross-over trial

Ke-Yun Chao, RRT, MSc^{a,b} , Wei-Lun Liu, MD^{c,d}, Yasser Nassef, MD, PhD^e, Chi-Wei Tseng, RRT, BS^a, Jong-Shyan Wang, PhD^{f,g,h,*}

Abstract

Introduction: Studies have demonstrated that noninvasive ventilation improves exercise intolerance in patients with chronic obstructive pulmonary disease (COPD). The role of heated humidified high-flow nasal cannula (HFNC) therapy in patients with COPD on self-paced exercise performance remains unclear. Therefore, the purpose of the present study was to determine whether HFNC-aided supplemental oxygen during a 6-minute walk test (6MWT) would change self-paced exercise performance and cardiopulmonary outcomes in patients with stable COPD.

Methods: A single-site, cross-over trial was conducted in a pulmonary rehabilitation outpatient department. This study enrolled 30 stable COPD patients without disability. The participants with and without HFNC performed 6MWTs on 2 consecutive days. Outcomes were the distance walked in the 6MWT, physiological, and cardiopulmonary parameters.

Results: Those performing HFNC-aided walking exhibited a longer walking distance than those performing unaided walking. The mean difference in meters walked between the HFNC-aided and unaided walking scenarios was 27.3 ± 35.6 m (95% CI: 14.4–40.5 m). The energy expenditure index was significantly lower when walking was aided by HHHNFC rather than unaided (median: 1.21 beats/m walked vs median: 1.37 beats/m walked, $P < .001$). However, there were no differences in transcutaneous carbon dioxide tension between HHHNFC and non-HHHNFC patients.

Conclusion: Walking distance and arterial oxygen saturation improved in stable COPD patients receiving HFNC with additional oxygen support. However, HFNC did not affect transcutaneous carbon dioxide tension and the self-reported dyspnea score during the walking test. The present study demonstrated the feasibility and safety of using HFNC in self-paced exercise.

Trial registration: NCT03863821

Abbreviations: 6MWT = 6-minute walk test, 6WMD = 6-minute walk distance, ATS = American Thoracic Society, COPD = chronic obstructive pulmonary disease, EEI = energy expenditure index, HFNC = high-flow nasal cannula, HR = heart rate, NIV = noninvasive ventilation, PtcCO₂ = transcutaneous carbon dioxide tension.

Editor: Maya Saranathan.

Grant number: PL-201808008-M

IRB number: CGHFJCUH107002

ClinicalTrials.gov: NCT03863821

The present study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki. The study was approved by the institutional review board for human studies of Cathay General Hospital Taipei, Taiwan (CGHFJCUH107002). Informed written consent was obtained from all participants.

For access to data, please contact the first author (K-YC: ck_qq@hotmail.com).

This work was supported by a research grant from Fu Jen Catholic University Hospital (PL-201808008-M). This funding source had no role in the design of this study and did not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

^a Department of Respiratory Therapy, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei City, Taiwan, ^b School of Physical Therapy, Graduate Institute of Rehabilitation Sciences, Chang Gung University, Taoyuan, Taiwan, ^c Department of Emergency and Critical Care Medicine, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei City, Taiwan, ^d School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei, Taiwan, ^e Institution of Medicine, Chung Shan Medical University, Taichung, Taiwan, ^f Heart Failure Center, Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Keelung, Taiwan, ^g Healthy Aging Research Center, Graduate Institute of Rehabilitation Science, Medical College, Chang Gung University, Tao-Yuan, Taiwan, ^h Research Center for Chinese Herbal Medicine, College of Human Ecology, Chang Gung University of Science and Technology, Tao-Yuan, Taiwan.

* Correspondence: Jong-Shyan Wang, School of Physical Therapy, Graduate Institute of Rehabilitation Sciences, Chang Gung University, No. 259, Wenhua 1st Rd., Guishan Dist., Taoyuan City 33302, Taiwan (e-mail: s5492@mail.cgu.edu.tw).

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Chao KY, Liu WL, Nassef Y, Tseng CW, Wang JS. Effects of high-flow nasal cannula with oxygen on self-paced exercise performance in COPD: a randomized cross-over trial. *Medicine* 2021;100:51(e28032).

Received: 25 November 2020 / Received in final form: 16 June 2021 / Accepted: 11 November 2021

<http://dx.doi.org/10.1097/MD.00000000000028032>

Keywords: 6-minute walking test, cardiopulmonary outcome, chronic obstructive pulmonary disease, heated humidified high-flow cannula

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation with chronic inflammation of the respiratory system.^[1,2] Patients with COPD often experience exercise limitation and physical inactivity due to muscular weakness and severe dyspnea. Symptoms of COPD may contribute to activity restriction, deconditioning, and exercise intolerance.^[3,4] O'Donnell et al have demonstrated that dynamic hyperinflation can cause dyspnea due to exertion in patients with COPD.^[5-7] Importantly, mismatching of energy demand and supply in ventilatory mechanics may lead to exercise-induced dyspnea.^[8] Growing evidence indicates that pulmonary rehabilitation improves the clinical outcomes, including walking distance in patients with symptomatic COPD.^[8-10] Furthermore, a 5-year observational study revealed that pulmonary rehabilitation coupled with negative pressure ventilation reduced the acute exacerbation rate, medical cost, and improved walking distance in patients with COPD.^[11]

In 2002, the American Thoracic Society (ATS) published guidelines for the 6-minute walk test (6MWT), standardizing a step-by-step protocol and encouraging further application of the 6MWT. The 6MWT is a self-paced field test that measures the submaximal level of functional capacity and is an ideal examination for patients with chronic respiratory failure who are unable to reach their maximal exercise capacity.^[12] Walking is a submaximal level of exertion that most people can perform during daily activity. Therefore, functional capacity is more easily reflected by the 6MWT than by other examinations.^[12,13] The 6MWT is sensitive for evaluating disease severity and response to treatment for cardiovascular and respiratory diseases.^[14] Decreased distance in the 6MWT is associated with increased risks of morbidity and mortality in patients with pulmonary disorder.^[14-16] Cukier et al^[17] assessed the self-paced exercise capacity with 6MWT in patients with stable COPD. Noninvasive ventilation (NIV) has been demonstrated to improve exercise intolerance and health-related quality of life in patients with severe COPD.^[18,19] NIV can be used by patients with COPD and ventilatory dependence during walking to improve symptoms and increase the walking distance.^[20,21] However, the use of NIV as an adjunct to an exercise program is difficult and labor-intensive, especially in patients who have never experienced NIV or are intolerant to the interface and positive pressure.^[22,23] Studies have reported that the dropout rates from exercise programs with adjunct NIV ranged from 7.1% to 28%.^[24-26] Heated humidified high-flow nasal cannula (HFNC) delivers a flow rate of up to 60 L/min with adequate humidification and prescribed oxygen concentration.^[27-29] Studies have indicated that compared with NIV, HFNC enhances the tolerance because of increased comfort due to warm, and humidified gas inflow that facilitates bronchial hygiene.^[30-32] HFNC can be regarded as appropriate noninvasive respiratory support for patients with COPD during exercise. The use of HFNC has been reported to improve health status and exercise capacity.^[33,34] Suzuki et al^[35] showed HFNC was not superior to conventional oxygen in exercise capacity in patients with fibrotic interstitial lung disease. Cirio et al^[36] demonstrated that HFNC improves the

self-reported dyspnea and fatigue score in patients with severe COPD and ventilatory limitation. Limited evidence is available regarding the application of HFNC in exercise training during pulmonary rehabilitation. Therefore, the purpose of the present study was to determine whether HFNC with additional supplemental oxygen on 6MWT would change the self-paced exercise performance and cardiopulmonary outcomes.

2. Methods

2.1. Participants

This investigation conducted a single-site, cross-over trial at the Pulmonary Rehabilitation Outpatient Department of Fu Jen Catholic University Hospital from August 2018 through November 2019. The study was approved by the institutional review board for human studies of Cathay General Hospital Taipei, Taiwan (CGHFJCUH107002), and was registered with ClinicalTrials.gov (NCT03863821). Informed written consent was obtained from all the participants.

Patients with confirmed diagnosis of COPD and those who underwent the pulmonary rehabilitation program for at least 1 month were eligible for enrollment. COPD was defined using the Global Initiative for Chronic Obstructive Lung Disease definition.^[37] Patients who had left-side heart failure, had COPD acute exacerbation within 3 months, received a diagnosis of neuromuscular disease, had an artificial airway, required mechanical ventilator or NIV support, or were unable to perform the 6MWT were excluded.

2.2. Intervention

Each participant performed 2 6MWTs on 2 consecutive days. On the first day, the participants were randomly assigned to either receive or not receive HHHNFC during the 6MWT. Each participant then repeated the test on the second day but under the opposite condition (Fig. 1). The randomization sequence was performed on the website <http://randomization.com>. In the HHHNFC-aided walking, the participants received supplemental oxygen ($FiO_2 = 0.4$ and flow rate = 40 L/min) during the 6MWT. HFNC was delivered using the Airvo² (Airvo², Fisher & Paykel Healthcare, Auckland, New Zealand). The portable HFNC was powered by an external battery (TS1500C, OPTI-UPS, Taipei, Taiwan) during the 6MWT. The HFNC was provided through 3 sizes of nasal cannula (Optiflow, Fisher & Paykel Healthcare, Auckland, New Zealand). The outer diameter of the nasal cannula ranged from 40 to 70 mm. In the test in which HHHNFC was not received, the participants underwent the 6MWT alone. In accordance with the ATS protocol, an additional oxygen inflow (flow rate = 3 L/min) was delivered through a traditional nasal cannula if the oxygen saturation was < 88%. HFNC was removed immediately at the end of the 6MWT.

2.3. 6MWT

The present study used a checklist for reporting the design of 6MWT in each COPD patient.^[38] The 6MWT was performed in

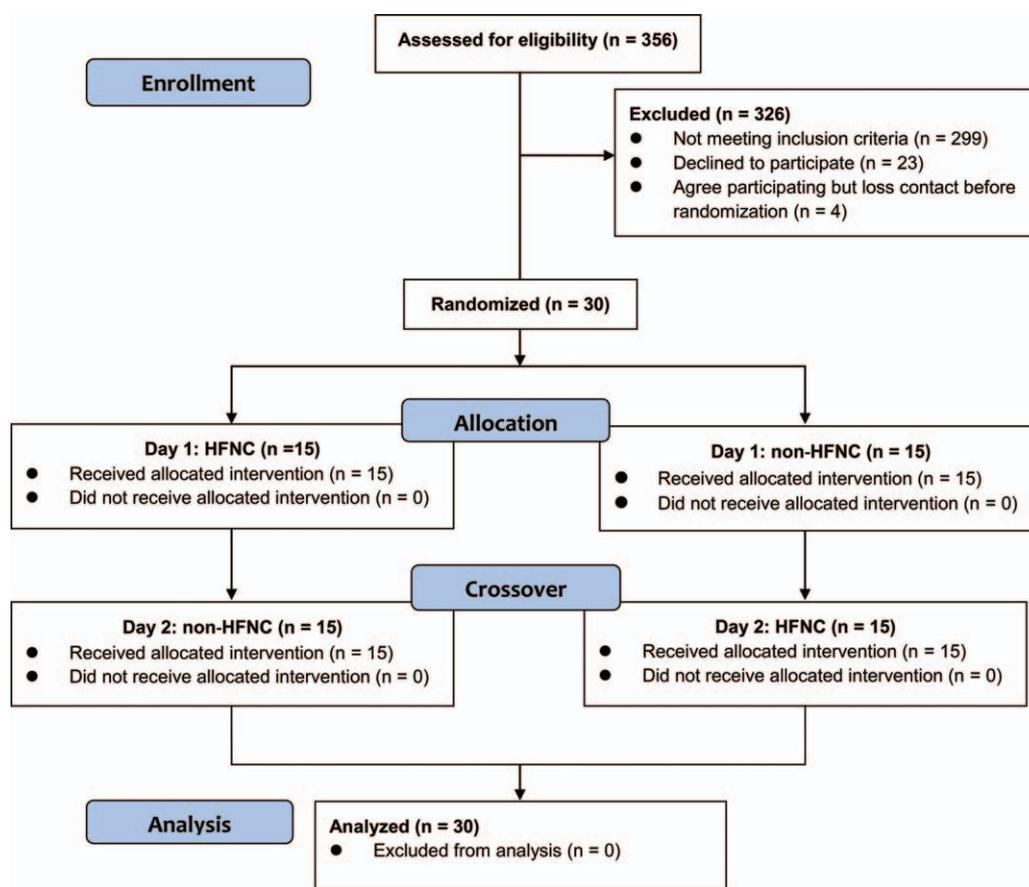


Figure 1. CONSORT diagram. HFNC=heated humidified high-flow nasal cannula.

accordance with the ATS guidelines.^[12] A straight, flat, 20-m-long corridor was used, which is shorter than that which is described in ATS guidelines, because of the site's limitations. Instructions were provided prior to the 6MWT and encouragement was provided during the 6MWT according to the ATS guidelines. All the 6MWTs were conducted by the same investigator. A trolley was used to carry the devices, including the Airvo² with an external battery, oxygen cylinder, and monitors. The same research assistant was responsible for the trolley movement.

2.4. Outcomes measurement

The primary outcome was the 6-minute walk distance (6WMD) with or without HFNC. Heart rate (HR) and SpO₂ were measured continually through a wrist-worn pulse oximeter (WristOx2, Nonin Medical, Plymouth, MN). All data were transferred through Bluetooth transmission, and variables were calculated using computer software (nVision Version 6.4, Nonin Medical, Plymouth, MN). A transcutaneous carbon dioxide tension (PtcCO₂) monitor (TCM4, Radiometer, Medical AsP, Brønshøj, Denmark) that continually measured PtcCO₂ by using an electrochemical transducer was employed. The measurement site on the participants was cleaned using an alcohol pad. Additionally, a noninvasive hemodynamics monitor that obtains measurements using electrical cardiometry was used (ICON, Osypka Medical, Berlin, Germany) before and immediately after the 6MWT. The participants were asked to rate their dyspnea on

a 0 to 10 modified Borg scale, with 0 indicating “none” and 10 indicating “the worst.” Higher scores meant worse dyspnea. Physiological and respiratory parameters were collected 30 minutes before, during, and on completion of the 6MWT. To determine the energy cost of HFNC-aided walking and non-HFNC-aided walking, mean HR and walking speed were employed to calculate the energy expenditure index (EEI). In this research, higher EEI represents poor energy cost of walk.^[39]

2.5. Statistical analysis

To determine the minimal sample size to ensure powerful testing of the intervention, 30 participants were required for the main analysis, as determined using a power of 0.8 with an α error of 0.05 according to previous findings.^[20] Subjects with COPD underwent the 6WMT with and without NIV (O₂: 220 ± 84.8 m vs O₂ + NIV: 260 ± 64.9 m). Statistical analyses were performed using IBM SPSS (version 22.0 for Windows, Chicago, IL). Because the sample size was small, the Wilcoxon signed-rank test was used for analyzing all variables. Statistical significance was indicated by $P < .05$. The results are presented as number (%), mean ± standard deviation, or median (interquartile range).

3. Results

Thirty participants without disability were enrolled in the present study (mean ± standard deviation age, 66.8 ± 8.4 years; forced expiratory volume in 1 s, 72.8 ± 22.2% [predicted]). Description

Table 1
Characteristics of participants.

Subjects	30
Demographic data	
Gender, (male/female)	28/2
Age, yrs	67 (60.8–72)
BMI, kg/m ²	24.2 (21.7–26.7)
Former smoker, (%)	28 (93.3)
Lung function	
FEV ₁ , % predicted	78.5 (57.5–87.8)
FVC, % predicted	91.5 (79.5–104.3)
FEV ₁ /FVC, %	63 (53–67)
RV, % predicted	142 (113–169)
TLC, % predicted	101 (89.3–105)
GOLD stage	
Stage I, (%)	16.0 (53.3)
Stage II, (%)	10.0 (33.3)
Stage III, (%)	4.0 (13.3)

Data are presented as median (IQR) or number (%).

BMI=body mass index, FEV₁=forced expiratory volume in the first second, FVC=forced vital capacity, GOLD=Global Initiative for Chronic Obstructive Lung Disease, RV=residual volume, TLC=total lung capacity.

of the demographic characteristics at baseline is provided in Table 1. All 30 participants completed the 6MWT on 2 consecutive days. During their unaided 6MWT, only 1 participant required additional oxygen support due to low SpO₂. The mean difference in meters walked between the

HFNC-aided and unaided walking scenarios was 27.3±35.6 m (95% CI: 14.4–40.5 m; *P*<.001; Table 2).

The baseline parameters of the participants in the HHHNFC-aided and unaided -walking scenarios were comparable. The difference in SpO₂ between the HFNC-aided and unaided walking scenarios was 2.3%±3.11% (95% CI: 1.14%–3.46%; *P*=.001). The EEI was significantly lower when walking was aided by HHHNFC rather than unaided (median: 1.21 beats/m walked [IQR: 1.13–1.61] beats/m walked vs median: 1.37 beats/m walked [IQR: 1.21–1.57] beats/m walked, *P*<.001). The differences in other parameters did not reach significance (Table 2). The difference in the peak HR during the 6MWT between the HHHNFC-aided and unaided walking scenarios was nonsignificant; however, the SpO₂ nadir was significantly lower when walking was unaided (median: 91.5% [IQR: 87%–94%] vs median: 90.3% [IQR: 90.8%–94%], *P*=.015). A significant difference was observed between the SpO₂ level during the 6MWT. By contrast, the changes in HR and PtcCO₂ did not reach the significance level (Fig. 2 and Table 3). The hemodynamic parameters after the 6MWT performed under and not under HHHNFC were comparable (Table 4). No adverse events related to the present study were noted.

4. Discussion

In patients with stable COPD, the use of HFNC with additional oxygen support during the walking test resulted in significantly increased walking distance. Reports on the 6MWT indicated that

Table 2
Physiological parameters and walking distance before and after the 6MWT.

	HFNC (n=30)	Non-HFNC (n=30)	Mean change (HFNC minus non-HFNC)		P value
				95% CI	
6MWT outcome					
6WMD, m	454 (360–515)	430 (320–494)	27.3±35.6	14.1–40.5	<.001 [‡]
Walking speed, m/min	75.7 (59.9–85.8)	71.6 (53.3–82.4)	4.54±5.89	2.34–6.74	<.001 [‡]
HR peak, b/m	109 (96–122.5)	112 (105.8–124.5)	−3.9±12.6	−8.61 to 0.81	.072
SpO ₂ nadir, %	93 (90.8–94)	91.5 (87–94)	1.8±3.65	0.47–3.2	.015*
EEI, beats/meter walked	1.21 (1.13–1.61)	1.37 (1.21–1.57)	−0.13±0.18	−0.19 to −0.06	<.001 [‡]
Before 6MWT					
HR, b/m	78.7 (67.8–87.8)	77.2 (66.9–91)	1.12±6.2	−1.20 to 3.43	.411
SpO ₂ , %	94.9 (93.5–96.4)	95.0 (93.3–96.2)	0.19±1.37	−0.33 to 0.7	.566
RR, b/m	17.5 (16.2–20)	17.5 (15.7–20)	0.21±2.02	−0.55 to 0.96	.755
Borg-D	1 (0–2)	1.5 (0–2)		.658	
sBP, mm Hg	123 (118–138)	126 (117–139)	−4.35±23.3	−13.1 to 4.36	.658
dBp, mm Hg	76 (70–84)	78 (69–86)	0.9±7.08	−1.75 to 3.55	.416
MAP, mm Hg	92 (86–102)	95 (84–101)	−0.85±9.68	−4.46 to 2.76	.805
PtcCO ₂ , mmHg	40.5 (36.7–43.7)	39.7 (36.1–44)	0.55±5.62	−1.55 to 2.65	.741
After 6MWT					
HR, b/m	93.5 (80–105)	92 (81.8–110)	0.07±11.6	−4.28 to 4.41	.9
SpO ₂ , %	97 (95–98)	95 (92.8–97)	2.3±3.11	1.14–3.46	.001 [†]
RR, b/m	23 (21–25.3)	25 (21.8–25)	−0.4±3.3	−1.63 to 0.83	.574
Borg-D	5 (3–6.25)	5.5 (3–6)		.257	
sBP, mm Hg	138 (128–161)	145 (130–160)	−1.9±18.4	−8.76 to 4.96	.354
dBp, mm Hg	82 (72–93)	83 (72–91)	0.28±8.85	−3.03 to 3.58	.714
MAP, mm Hg	104 (91–115)	101 (93–113)	−0.45±9.59	−4.03 to 3.13	.551
PtcCO ₂ , mmHg	41.5 (36–46.3)	41.5 (36.8–45.3)	−0.16±5.7	−2.29 to 1.97	.596

Data are presented as mean±SD or median (IQR).

6MWT=six-minute walking test, 6WMD=six-minute walking distance, Borg-D=Borg dyspnea score, dBp=diastolic blood pressure, EEI=energy expenditure index, HFNC=high-flow nasal cannula, HR=heart beat, MAP=mean arterial pressure, PtcCO₂=transcutaneous carbon dioxide tension, RR=respiratory rate, sBP=systolic blood pressure, SpO₂=oxygen saturation.

* *P*<.05.

† *P*<.01.

‡ *P*<.001.

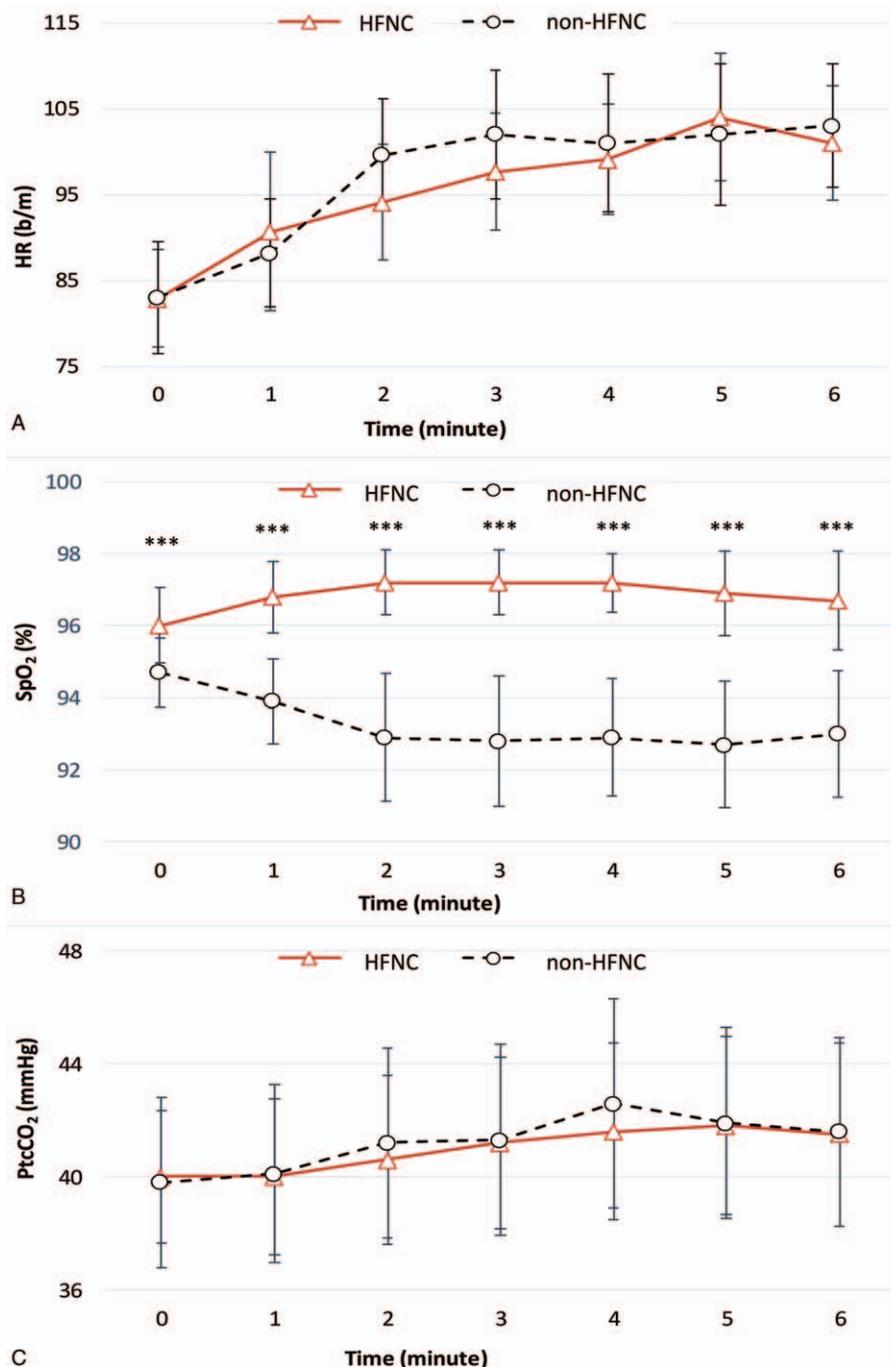


Figure 2. The physiological trend for (A) heart rate (HR), (B) oxygen saturation (SpO₂), and (C) transcutaneous carbon dioxide tension (PtcCO₂) during the 6MWT. ****P* < .001. 6MWT=six-minute walking test, HFNC=heated humidified high-flow nasal cannula.

the minimal clinically important change in distance was > 30 m in patient response to pulmonary rehabilitation^[40] and ranged from 14 to 30.5 m across multiple patient groups.^[41] The difference of 6WMD caused by HFNC was 27.3 m (95% CI: 14.1–40.5 m) in the present study. HFNC patients had significantly higher arterial oxygen saturation with additional oxygen support during the 6MWT than non-HFNC patients. Additionally, EEI is used to evaluate the economy of walking at different speeds based on heart rate and oxygen intake. In this study, HFNC lowered EEI in patients with stable COPD.

On the other hand, no significant difference in PtcCO₂ and breathing frequency was observed between HFNC and non-HFNC patients in this investigation, which may have indicated rapid washout of CO₂. PtcCO₂ was suggested in 1 report to be highly heterogeneous among patients with severe COPD during the 6MWT.^[42] Mauri et al demonstrated that HFNC enhanced CO₂ clearance by reducing the respiratory rate and minute ventilation at similar arterial CO₂ tension and pH level compared with conventional oxygen therapy in critically ill hypoxemic patients.^[43,44]

Table 3
Changes of HR, SpO₂, and PtcCO₂ during 6MWT.

	HFNC (n = 30)	Non-HFNC (n = 30)	Mean change (HFNC minus non-HFNC)		P value
				95% CI	
Change of HR					
HR at begging, b/min	80.5 (73.3–96)	82.5 (72–92.3)	0.03 ± 8.02	–2.96 to 3.03	.703
HR at 1-min, b/min	93.5 (79.3–102)	92 (79–99.3)	2.4 ± 22.7	–6.08 to 10.9	.734
HR at 2-min, b/min	97.5 (83.3–105)	102 (89–109)	–5.5 ± 15.5	–11.3 to 0.29	.045
HR at 3-min, b/min	98 (86.8–108)	103 (90.8–111)	–4.4 ± 13.5	–9.42 to 0.62	.07
HR at 4-min, b/min	97 (82.8–114)	101 (90.5–112)	–2.2 ± 16.1	–8.29 to 3.76	.432
HR at 5-min, b/min	103 (89.3–114)	105 (87–112)	1.7 ± 18.6	–5.25 to 8.65	.936
HR at 6-min, b/min	103 (87.5–112)	107 (92.5–112)	–1.9 ± 13.4	–6.88 to 3.14	.35
Change of SpO ₂					
SpO ₂ at begging, %	96 (94–98)	95 (93–96)	1.37 ± 1.54	0.79–1.94	< .001*
SpO ₂ at 1-min, %	97 (95–98)	94 (91.8–96)	2.87 ± 2.18	2.05–3.68	< .001*
SpO ₂ at 2-min, %	98 (96–98.3)	94 (89.8–96)	4.37 ± 3.25	3.15–5.58	< .001*
SpO ₂ at 3-min, %	98 (96–98)	94 (89.8–96)	4.43 ± 3.39	3.17–5.7	< .001*
SpO ₂ at 4-min, %	98 (96.8–98)	94 (90–95.3)	4.27 ± 3.35	3.01–5.52	< .001*
SpO ₂ at 5-min, %	98 (96–98)	94 (89.8–96)	4.20 ± 3.52	2.89–5.51	< .001*
SpO ₂ at 6-min, %	98 (95.8–98)	94 (90–96)	3.73 ± 3.82	2.31–5.16	< .001*
Change of PtcCO ₂					
PtcCO ₂ at begging, mm Hg	40 (36.8–43)	40 (36–45.3)	0.27 ± 5.55	–1.80 to 2.34	.698
PtcCO ₂ at 1-min, mm Hg	41 (36.8–43.3)	40 (36.8–46)	0.1 ± 5.59	–1.99 to 2.19	.596
PtcCO ₂ at 2-min, mm Hg	42 (36–45)	41 (37.8–47.5)	–0.67 ± 6.44	–3.07 to 1.74	.321
PtcCO ₂ at 3-min, mm Hg	42.5 (36–46)	41 (37.8–47)	–0.13 ± 6.26	–2.47 to 2.2	.501
PtcCO ₂ at 4-min, mm Hg	45 (37–47)	42.5 (37.8–50.3)	–0.93 ± 7.65	–3.79 to 1.92	.366
PtcCO ₂ at 5-min, mm Hg	43.5 (37.8–47)	42 (37.8–47)	–0.17 ± 6.28	–2.51 to 2.18	.523
PtcCO ₂ at 6-min, mm Hg	42.5 (37–47.3)	42 (37–44.3)	–0.13 ± 6.20	–2.45 to 2.18	.555

Data are presented as mean ± SD or median (IQR).

6MWT = six-minute walking test, HFNC = high-flow nasal cannula, HR = Heart rate, PtcCO₂ = transcutaneous carbon dioxide tension, SpO₂ = oxygen saturation.

* P < .001.

Table 4
Hemodynamics outcomes.

	HFNC (n = 30)	Non-HFNC (n = 30)	Mean change (HFNC minus non-HFNC)		P value
				95% CI	
Before 6MWT					
SV, mL	48.7 (42.9–55.8)	49.6 (45.5–54.6)	0.86 ± 8.32	–2.25 to 3.97	.666
CO, L/min	3.94 (3.36–5.18)	3.99 (3.26–4.73)	0.2 ± 0.89	–0.13 to 0.53	.381
TFC, unit	16 (14.0–17.3)	16 (14.8–18)	–0.77 ± 3.04	–1.90 to 0.37	.22
ICON, unit	28.4 (22.5–39.9)	27.8 (23.8–37.2)	1.53 ± 10.7	–2.45 to 5.51	.399
FTC, ms	323 (316–331)	320 (316–329)	–1.53 ± 17.09	–7.91 to 4.85	.813
SVV, %	18 (13.8–21)	16.5 (13.0–22.5)	–0.4 ± 7.87	–3.34 to 2.54	.618
SVR, dynes · sec/cm ⁵ /m ²	1744 (1334–2280)	1952 (1476–2430)	–95.2 ± 429	–256 to 65.1	.206
SVRI, unit	2775 (2331–4099)	3388 (2594–3985)	–145 ± 758	–429 to 138	.245
STR, unit	0.49 (0.44–0.53)	0.47 (0.41–0.5)	0.02 ± 0.08	–0.01 to 0.05	.265
PEP, ms	130 (119–138)	130 (117–138)	0.17 ± 17.3	–6.27 to 6.61	.861
LVET, ms	279 (252–301)	282 (259–304)	–3.47 ± 27.6	–13.8 to 6.85	.649
After 6MWT					
SV, mL	59.1 (49.9–68.7)	54.2 (52.3–62.4)	1.67 ± 12.3	–2.91 to 6.26	.622
CO, L/min	5.07 (3.86–6.86)	5.36 (4–6.39)	0.09 ± 1.98	–0.65 to 0.83	.886
TFC, unit	16 (14–18.3)	16 (14.8–18)	–0.27 ± 2.8	–1.31 to 0.78	.623
ICON, unit	44.2 (28.1–59.4)	39 (30–54)	–0.03 ± 23.2	–8.68 to 8.62	.758
FTC, ms	326 (314–330)	324 (312–330)	0.83 ± 17.01	–5.52 to 7.18	.967
SVV, %	22 (17.8–25.3)	20.5 (16–25.3)	0.1 ± 11.1	–4.04 to 4.24	.51
SVR, dynes · sec/cm ⁵ /m ²	1487 (1046–1759)	1460 (1200–1777)	–36 ± 434	–198 to 126	.75
SVRI, unit	2596 (2014–2950)	2526 (2005–3169)	–80 ± 720	–349 to 189	.688
STR, unit	0.44 (0.41–0.52)	0.43 (0.36–0.5)	0.02 ± 0.08	–0.01 to 0.05	.235
PEP, ms	114 (100–129)	112 (102–131)	1.13 ± 16.4	–4.99 to 7.26	.75
LVET, ms	277 (240–291)	260 (233–291)	6.23 ± 28.7	–4.49 to 17	.233

Data are presented as mean ± SD or median (IQR).

6MWT = six-minute walking test, CO = cardiac output, FTC = correct flow time, HFNC = high-flow nasal cannula, ICON = index of contractility, LVET = left ventricular ejection time, PEP = pre-ejection period, STR = systolic time ratio, SV = stroke volume, SVV = stroke volume variation, TFC = thoracic fluid content.

Menadue et al^[45] reported that NIV during exercise training improves the percentage change in the peak, endurance exercise capacity and improves the physiological training effect. NIV during lower limb exercise training may help patients with COPD to exercise at a higher training intensity.^[45] However, to maintain the treatment pressure level of NIV, the mask must be tight-fitting, which may lead to intolerance of NIV. Two studies reported a 25% to 28% dropout rate due to NIV intolerance.^[24,46] HFNC causes less discomfort and irritation than NIV,^[30,31] improving adherence during exercise training. Similar to the observations of Cirio et al,^[36] no participants dropped out due to intolerance of HFNC in the present study. The 6MWT is a self-paced examination through which it is difficult to assess the outcomes of higher strength level exercises. Therefore, no significant change was observed in the hemodynamic parameter. Dreher et al^[20] used NIV during the walking test and asked participants to self-move the rollator. A report indicated that use of a rollator improves walking distance even without ventilatory support in patients with COPD.^[47] By contrast, the 6WMD was decreased by 14% to 22% when patients with severe respiratory disability carried an air container.^[48] The trolley used in this work was moved by the research assistant, thus diminishing its influence on results.

The present study had limitations in several aspects. First, the use of additional oxygen support may have affected the outcomes. Oxygen is an independent variable affecting the 6MWT results of patients with COPD or interstitial lung disease.^[48–50] The 6MWD may have been increased by acute administration of oxygen.^[14] In the present study, none of the participants had received long-term oxygen therapy in their daily life. Second, we recruited patients with mild to moderate COPD; the results of the present study cannot be directly transferred to patients with severe COPD. Third, the 6MWT only reflects functional capacity; it cannot measure exercise capacity.^[51] Exercise capacity tests were conducted using a cycle ergometer.^[52,53] or treadmill.^[54,55] Fourth, HFNC is an open system, and it is difficult to simultaneously use pneumotachographs and plethysmography due to the device's limitations. Neither minute volume nor respiratory system pressure was measured in the present study. Therefore, information regarding CO₂ clearance was not obtained. Transcutaneous O₂ and CO₂ monitoring presented a decent signal quality index, whereas noninvasive cardiometry was unable to obtain data during the exercise movement. The sensor lines of the monitors and HFNC circuit may have caused interference for participants during the walking test. The wrist-worn pulse oximeter was the only device with Bluetooth transmission in the present study. Fifth, the present study demonstrated the short-term effect of HFNC on cardiopulmonary exercise performance in patients with COPD. However, the long-term effect remains unclear.

5. Conclusion

Application of HFNC with additional oxygen support improved the self-paced exercise performance by increasing walking distance and arterial oxygen saturation with unaltered PtcCO₂ during the 6MWT in COPD patients. A lower energy cost was also observed in those performing HFNC-aided walking. Therefore, these findings suggest that the use of HFNC makes it feasible and safe to perform physical activity in patients with COPD. However, the application of HFNC in pulmonary rehabilitation warrants further research with

long-term follow-up to determine the effects of regular exercise training with HFNC.

Acknowledgments

This manuscript was edited by Wallace Academic Editing. This work was supported by a research grant from Fu Jen Catholic University Hospital (PL-201808008-M). This funding source had no role in the design of this study and did not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Author contributions

Conceptualization: Ke-Yun Chao, Wei-Lun Liu, Jong-Shyan Wang.

Data curation: Ke-Yun Chao, Chi-Wei Tseng.

Formal analysis: Ke-Yun Chao, Yasser Nassef, Chi-Wei Tseng.

Funding acquisition: Ke-Yun Chao.

Investigation: Ke-Yun Chao, Wei-Lun Liu.

Methodology: Ke-Yun Chao, Wei-Lun Liu, Yasser Nassef, Jong-Shyan Wang.

Project administration: Ke-Yun Chao, Chi-Wei Tseng.

Supervision: Wei-Lun Liu, Jong-Shyan Wang.

Validation: Ke-Yun Chao, Wei-Lun Liu, Yasser Nassef, Jong-Shyan Wang.

Writing – original draft: Ke-Yun Chao.

Writing – review & editing: Ke-Yun Chao, Yasser Nassef, Jong-Shyan Wang.

References

- [1] Maltais F, Decramer M, Casaburi R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014;189:e15–62.
- [2] Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;176:532–55.
- [3] Killian KJ, Leblanc P, Martin DH, et al. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis* 1992;146:935–40.
- [4] O'Donnell DE, Gebke KB. Activity restriction in mild COPD: a challenging clinical problem. *Int J Chron Obstruct Pulmon Dis* 2014;9:577–88.
- [5] O'Donnell DE, Reville SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:770–7.
- [6] O'Donnell DE, Banzett RB, Carrieri-Kohlman V, et al. Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. *Proc Am Thorac Soc* 2007;4:145–68.
- [7] Casaburi R, Rennard SI. Exercise limitation in chronic obstructive pulmonary disease. The O'Donnell threshold. *Am J Respir Crit Care Med* 2015;191:873–5.
- [8] Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:19–38.
- [9] Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44:1428–46.
- [10] Carone M, Patessio A, Ambrosino N, et al. Efficacy of pulmonary rehabilitation in chronic respiratory failure (CRF) due to chronic obstructive pulmonary disease (COPD): the Maugeri Study. *Respir Med* 2007;101:2447–53.
- [11] Huang HY, Chou PC, Joa WC, et al. Pulmonary rehabilitation coupled with negative pressure ventilation decreases decline in lung function, hospitalizations, and medical cost in COPD: a 5-year study. *Medicine (Baltimore)* 2016;95:e5119.

- [12] ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–7.
- [13] Balke B. A Simple field test for the assessment of physical fitness. *Rep Civ Aeromed Res Inst US* 1963;1–8.
- [14] Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. *Intern Med J* 2009;39:495–501.
- [15] Alameri H, Al-Majed S, Al-Howaikan A. Six-min walk test in a healthy adult Arab population. *Respir Med* 2009;103:1041–6.
- [16] Ghofraniha L, Dalir Sani Z, Vakilian F, Khajedalooyi M, Arabshahi ZJ. The six-minute walk test (6MWT) for the evaluation of pulmonary diseases. *J Cardiothorac Med* 2015;3:284–7.
- [17] Cukier A, Ferreira CA, Stelmach R, Ribeiro M, Cortopassi F, Calverley PM. The effect of bronchodilators and oxygen alone and in combination on self-paced exercise performance in stable COPD. *Respir Med* 2007;101:746–53.
- [18] Köhnlein T, Schönheit-Kenn U, Winterkamp S, Welte T, Kenn K. Noninvasive ventilation in pulmonary rehabilitation of COPD patients. *Respir Med* 2009;103:1329–36.
- [19] Ambrosino N, Cigni P. Non invasive ventilation as an additional tool for exercise training. *Multidiscip Respir Med* 2015;10:14.
- [20] Dreher M, Storre JH, Windisch W. Noninvasive ventilation during walking in patients with severe COPD: a randomised cross-over trial. *Eur Respir J* 2007;29:930–6.
- [21] Menadue C, Alison JA, Piper AJ, Flunt D, Ellis ER. Non-invasive ventilation during arm exercise and ground walking in patients with chronic hypercapnic respiratory failure. *Respirology* 2009;14:251–9.
- [22] Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188:e13–64.
- [23] Hess DR. The growing role of noninvasive ventilation in patients requiring prolonged mechanical ventilation. *Respir Care* 2012;57:900–18.
- [24] Bianchi L, Foglio K, Porta R, Baiardi P, Vitacca M, Ambrosino N. Lack of additional effect of adjunct of assisted ventilation to pulmonary rehabilitation in mild COPD patients. *Respir Med* 2002;96:359–67.
- [25] Borghi-Silva A, Oliveira CC, Carrascosa C, et al. Respiratory muscle unloading improves leg muscle oxygenation during exercise in patients with COPD. *Thorax* 2008;63:910–5.
- [26] Vitacca M, Kaymaz D, Lanini B, et al. Non-invasive ventilation during cycle exercise training in patients with chronic respiratory failure on long-term ventilatory support: a randomized controlled trial. *Respirology* 2018;23:182–9.
- [27] Chao KY, Chen YL, Tsai LY, Chien YH, Mu SC. The role of heated humidified high-flow nasal cannula as noninvasive respiratory support in neonates. *Pediatr Neonatol* 2017;58:295–302.
- [28] Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults. *Chest* 2015;148:253–61.
- [29] Nishimura M. High-flow nasal cannula oxygen therapy in adults. *J Intensive Care* 2015;3:15.
- [30] Gotera C, Diaz Lobato S, Pinto T, Winck JC. Clinical evidence on high flow oxygen therapy and active humidification in adults. *Rev Port Pneumol* 2013;19:217–27.
- [31] Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. *Respir Med* 2009;103:1400–5.
- [32] Frat JP, Brugiere B, Ragot S, et al. Sequential application of oxygen therapy via high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: an observational pilot study. *Respir Care* 2015;60:170–8.
- [33] Nagata K, Kikuchi T, Horie T, et al. Domiciliary high-flow nasal cannula oxygen therapy for patients with stable hypercapnic chronic obstructive pulmonary disease. A multicenter randomized crossover trial. *Ann Am Thorac Soc* 2018;15:432–9.
- [34] Storgaard LH, Hockey HU, Laursen BS, Weinreich UM. Long-term effects of oxygen-enriched high-flow nasal cannula treatment in COPD patients with chronic hypoxemic respiratory failure. *Int J Chron Obstruct Pulmon Dis* 2018;13:1195–205.
- [35] Suzuki A, Ando M, Kimura T, et al. The impact of high-flow nasal cannula oxygen therapy on exercise capacity in fibrotic interstitial lung disease: a proof-of-concept randomized controlled crossover trial. *BMC Pulm Med* 2020;20:51.
- [36] Cirio S, Piran M, Vitacca M, et al. Effects of heated and humidified high flow gases during high-intensity constant-load exercise on severe COPD patients with ventilatory limitation. *Respir Med* 2016;118:128–32.
- [37] Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: 2019 report. Global initiative for chronic obstructive lung disease (GOLD); 2019 [cited 2019]; Available from: www.goldcopd.org.
- [38] Dunn A, Marsden DL, Nugent E, et al. Protocol variations and six-minute walk test performance in stroke survivors: a systematic review with meta-analysis. *Stroke Res Treat* 2015;2015:484813.
- [39] Rose J, Gamble JG, Lee J, Lee R, Haskell WL. The energy expenditure index: a method to quantitate and compare walking energy expenditure for children and adolescents. *J Pediatr Orthop* 1991;11:571–8.
- [40] Polkey MI, Spruit MA, Edwards LD, et al. Six-minute-walk test in chronic obstructive pulmonary disease: minimal clinically important difference for death or hospitalization. *Am J Respir Crit Care Med* 2013;187:382–6.
- [41] Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract* 2017;23:377–81.
- [42] Andrianopoulos V, Vanfleteren LE, Jarosch I, et al. Transcutaneous carbon-dioxide partial pressure trends during six-minute walk test in patients with very severe COPD. *Respir Physiol Neurobiol* 2016;233:52–9.
- [43] Mauri T, Eronia N, Turrini C, Grasselli G, Bellani G, Pesenti A. High flow nasal cannula Improves lung aeration and enhances CO2 removal in hypoxemic critically ill patients. *Intensive Care Med Exp* 2015;3:A176.
- [44] Mauri T, Turrini C, Eronia N, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2017;195:1207–15.
- [45] Menadue C, Piper AJ, van 't Hul AJ, Wong KK. Non-invasive ventilation during exercise training for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014.
- [46] Reuveny R, Ben-Dov I, Gaides M, Reichert N. Ventilatory support during training improves training benefit in severe chronic airway obstruction. *J Cardiopulm Rehabil Prev* 2005;25:236–7.
- [47] Probst VS, Troosters T, Coosemans I, et al. Mechanisms of improvement in exercise capacity using a rollator in patients with COPD. *Chest* 2004;126:1102–7.
- [48] Leach RM, Davidson AC, Chinn S, Twort CH, Cameron IR, Bateman NT. Portable liquid oxygen and exercise ability in severe respiratory disability. *Thorax* 1992;47:781–9.
- [49] Grove A, Lipworth BJ, Reid P, et al. Effects of regular salmeterol on lung function and exercise capacity in patients with chronic obstructive airways disease. *Thorax* 1996;51:689–93.
- [50] Roberts CM, Bell J, Wedzicha JA. Comparison of the efficacy of a demand oxygen delivery system with continuous low flow oxygen in subjects with stable COPD and severe oxygen desaturation on walking. *Thorax* 1996;51:831–4.
- [51] Pitta F, Troosters T, Spruit MA, Decramer M, Gosselink R. Activity monitoring for assessment of physical activities in daily life in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2005;86:1979–85.
- [52] van't HA, Gosselink R, Hollander P, Postmus P, Kwakkel G. Acute effects of inspiratory pressure support during exercise in patients with COPD. *Eur Respir J* 2004;23:34.
- [53] van't HA, Gosselink R, Hollander P, Postmus P, Kwakkel G. Training with inspiratory pressure support in patients with severe COPD. *Eur Respir J* 2006;27:65.
- [54] Johnson JE, Gavin DJ, Adams-Dramiga S. Effects of training with heliox and noninvasive positive pressure ventilation on exercise ability in patients with severe COPD. *Chest* 2002;122:464–72.
- [55] Keilty SE, Ponte J, Fleming TA, Moxham J. Effect of inspiratory pressure support on exercise tolerance and breathlessness in patients with severe stable chronic obstructive pulmonary disease. *Thorax* 1994;49:990–4.