High Flow Nasal Oxygen at Home to Prevent Chronic Obstructive Pulmonary Disease Exacerbations?

The natural history of chronic obstructive pulmonary disease (COPD) is characterized by recurrent exacerbations leading to lung function decline and reducing quality of life with an increased risk of early death (1). Even though there is no strong evidence that long-term oxygen using conventional oxygen therapy is beneficial to reduce mortality and need for hospital admission (2), a new approach using high-flow nasal cannula oxygen therapy (HFNC) as long-term treatment at home could be beneficial.

Although HFNC is widely used in intensive care units for management of acute hypoxemic respiratory failure and is now recommended in most recent clinical practice guidelines (3, 4), few clinical trials have assessed HFNC for acute exacerbation of COPD or as long-term treatment at home.

However, several physiological studies have shown beneficial effects of HFNC in hypercapnic patients, as a flow-dependent clearance of carbon dioxide of the upper airways, contributing to the reduction of anatomical dead space ventilation and carbon dioxide rebreathing (5, 6). Breathing pattern is improved with increased V_Ts and decreased respiratory rate, resulting in increased alveolar ventilation and reduced neuro-ventilatory drive and work of breathing (5, 7). HFNC also helps to generate positive end-expiratory pressure effect, thereby counterbalancing flow-limited intrinsic positive end-expiratory pressure and further decreasing work of breathing (8). All of these physiological effects suggest potential benefits of HFNC in patients with acute moderate exacerbation of COPD, and several studies have shown that it may reverse respiratory acidosis and improve prognosis (9, 10). In addition, HFNC may have long-term effects promoting respiratory muscle recovery and through the conditioning of inspired gas, i.e., humidification and heating of the inhaled air, which could facilitate mucociliary clearance and potentially decrease chronic airway inflammation (11).

Two previous trials have reported benefits of HFNC at home in patients with COPD (12, 13). In the first study (conducted in a single-center), 108 patients with COPD or bronchiectasis at risk of exacerbation were randomized to receive HFNC (1.6 h/d in mean ± SD 0.67) in addition to conventional long-term oxygen or conventional long-term oxygen alone during a 1-year follow-up (12). Despite a trend, the number of exacerbations did not significantly differ between groups (3 exacerbations per patient per year versus 3.6; odds ratio, 0.82 [95% confidence interval (CI), 0.66–1.01]). However, time to first exacerbation was significantly delayed in patients treated with HFNC.

In the second study (multicenter randomized controlled trial), 200 hypoxemic patients with COPD received HFNC (7 h/d in mean at a flow rate of 20 L/min) in addition to conventional long-term oxygen or conventional long-term oxygen alone during a one-year follow-up. Patients treated with HFNC had lower rates of exacerbation as compared with conventional long-term oxygen alone (3.1 exacerbations per patient versus 4.9; $P < 0.001$) (13). In both studies, patients receiving HFNC had a better lung function test than those receiving conventional long-term oxygen alone. Therefore, a thorough approach could suggest that long-term HFNC treatment decelerates disease progression.

In the current issue of the *Journal*, Nagata and colleagues (14) (pp. 1326–1335) assessed the effects of long-term HFNC at home in hypercapnic patients treated with long-term oxygen therapy (at least 16 h/d) for moderate-to-severe COPD. In this multicenter randomized controlled trial, 99 patients received HFNC in addition to conventional long-term oxygen or conventional long-term oxygen alone, with the hypothesis that HFNC may decrease the number of moderate-to-severe exacerbations (primary outcome) and improve quality of life at 1-year follow-up. HFNC was applied at a flow rate of around 30 L/min for 7 hours per day (mainly during the night), while patients were instructed to use HFNC for a minimum of 4 hours while sleeping. The main finding is that the number of moderate or severe exacerbations during the 1-year follow-up significantly decreased with HFNC as compared with conventional long-term oxygen alone (1 exacerbation per patient per year versus 2.5, adjusted ratio 2.85 [95% CI, 1.48–5.47]). However, quality of life, sleep quality, and dyspnea did not significantly differ between groups at 1 year. Patients did not show sustained improvement in lung function tests (forced vital capacity or forced expiratory volume in 1 s) beyond 6 months, probably owing to their having more severe disease. However, patients had fewer exacerbations and one strength of the study is that exacerbations were established from a committee of adjudication for reviewing and qualifying levels of exacerbation (mild, moderate and severe) through a daily diary recording any worsening symptoms, and the control of changes in medications (commencement of rehabilitation or use of noninvasive ventilation). Unlike previous studies, HFNC was applied for a long time per day at a high level of gas flow (30 L/min versus 20 to 25 L/min in the two previous trials) with good adherence, owing to the incentive of application during the night. On the other hand, there were some limitations. By necessity, the trial could not be blinded, but the allocated treatment in each group was well-followed and only a few patients changed their treatments for escalation to long-term noninvasive ventilation during the study. Although the total number of patients enrolled was modest, they represented a homogeneous population of patients with severe COPD, all of whom suffered from chronic hypoxemia and hypercapnia.

Although additional trials are needed to determine the effect of HFNC on hospital admissions and mortality, this trial as the previous

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ones showed that long-term HFNC at home was feasible and safe with benefits in terms of reduction of exacerbation, leading to consideration of HFNC at home as a supplement to long-term oxygen therapy in the management of patients with severe COPD. ■

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References

1. Whittaker H, Rubino A, Müllerová H, Morris T, Varghese P, Xu Y, *et al.* Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. *Int J Chron Obstruct Pulmon Dis* 2022;17:427–437.
2. Albert RK, Au DH, Blackford AL, Casaburi R, Cooper JA Jr, Criner GJ, *et al.*; Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med* 2016;375:1617–1627.
3. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, *et al.*; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185–2196.
4. Oczkowski S, Ergan B, Bos L, Chatwin M, Ferrer M, Gregoretti C, *et al.* ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. *Eur Respir J* 2022;59:2101574.
5. Pisani L, Fasano L, Corcione N, Comellini V, Musti MA, Brandao M, *et al.* Change in pulmonary mechanics and the effect on breathing pattern of high flow oxygen therapy in stable hypercapnic COPD. *Thorax* 2017;72:373–375.
6. Möller W, Feng S, Domanski U, Franke KJ, Celik G, Bartenstein P, *et al.* Nasal high flow reduces dead space. *J Appl Physiol* 2017;122:191–197.
7. Di Mussi R, Spadaro S, Stripoli T, Volta CA, Trerotoli P, Pierucci P, *et al.* High-flow nasal cannula oxygen therapy decreases postextubation neuroventilatory drive and work of breathing in patients with chronic obstructive pulmonary disease. *Crit Care* 2018;22:180.
8. Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, *et al.* Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2017;195:1207–1215.
9. Cortegiani A, Longhini F, Madotto F, Groff P, Scala R, Crimi C, *et al.*; H. F.-AECOPD study investigators. High flow nasal therapy versus noninvasive ventilation as initial ventilatory strategy in COPD exacerbation: a multicenter non-inferiority randomized trial. *Crit Care* 2020;24:692.
10. Li XY, Tang X, Wang R, Yuan X, Zhao Y, Wang L, *et al.* High-flow nasal cannula for chronic obstructive pulmonary disease with acute compensated hypercapnic respiratory failure: a randomized, controlled trial. *Int J Chron Obstruct Pulmon Dis* 2020;15:3051–3061.
11. Williams R, Rankin N, Smith T, Galler D, Seakins P. Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. *Crit Care Med* 1996;24:1920–1929.
12. Rea H, McAuley S, Jayaram L, Garrett J, Hockey H, Storey L, *et al.* The clinical utility of long-term humidification therapy in chronic airway disease. *Respir Med* 2010;104:525–533.
13. 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;13:1195–1205.
14. Nagata K, Horie T, Chohnabayashi N, Jinta T, Tsugitomi R, Shiraki A, *et al.*; FLOCOP study investigators. Home high-flow nasal cannula oxygen therapy for stable hypercapnic COPD: a randomized trial. *Am J Respir Crit Care Med* 2022;206:1326–1335.

Airway Mucus Dysfunction in COVID-19

Several anecdotal reports suggested the occurrence of excessive mucus production in coronavirus disease (COVID-19), but no systematic analysis had been published until the article by Kato and colleagues (pp. 1336–1352) in this issue of the *Journal* (1). In autopsy specimens, they found high degrees of production of the secreted airway mucin MUC5B and moderate amounts of MUC5AC. Strikingly, they also found occlusion of ∼50% of the small airways by mucus, as well as widespread aberrant expression of MUC5B within microcysts in damaged alveolar parenchyma. These findings have implications for understanding the pathophysiology and treatment of COVID-19 in particular and of viral pneumonia in general. Here, we address these implications in three sections.

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Airway Mucus Occlusion

The first important finding is widespread small airway occlusion by mucus. This is somewhat surprising because the cough that accompanies SARS-CoV-2 infection of the lower respiratory tract has generally been reported to be nonproductive (2, 3). However, mucus