In COPD, Nocturnal Noninvasive Ventilation Reduces the F_{IO_2} Delivered Compared With Long-Term Oxygen Therapy at the Same Flow

Michael Cardinale, Pierre-Julien Cungi, Pierre Esnault, Olivier Castagna, Cédric Nguyen, Erwan Daranda, Julien Bordes, Jean-Michel Arnal, Eric Meaudre, and Philippe Goutorbe

BACKGROUND: Nocturnal noninvasive ventilation is recommended for patients with hypercapnic COPD. Long-term oxygen therapy improves survival in patients with hypoxemic disease. However, leaks during noninvasive ventilation are likely to reduce the fraction of inspired oxygen. OBJECTIVES: To compare nocturnal inspired O_2 fractions during noninvasive ventilation with daytime pharyngeal inspired O_2 fractions during nasal cannula oxygen therapy (with the same O_2 flow) in patients with COPD at home (ie, real-life conditions). METHODS: This single-center prospective observational study included 14 subjects with COPD who received long-term O_2 therapy. We analyzed pharyngeal inspired O_2 fractions in the evening, with a nasopharyngeal probe (sidestream gas analyzer). The O_2 flow was measured with a precision flow meter, at the usual flow. Then, the same O_2 flow was implemented for noninvasive ventilation with a study's home ventilator. The all-night noninvasive ventilation parameters were delivered in pressure mode with a single-limb leaking circuit. Daytime and nighttime inspired O_2 fractions were compared. RESULTS: The mean ± SD daytime pharyngeal inspired O_2 fraction, measured with normobaric basal O_2 flow, 0.308 ± 0.026%, was significantly higher than the mean ± SD nighttime inspired O_2 fraction, measured during noninvasive ventilation (0.251 ± 0.011; $P < .001$). CONCLUSIONS: The nighttime inspired O_2 fraction decreased with a modern noninvasive ventilation pattern, pressure target, and intentional leaks. This partial lack of O_2 therapy is likely to be harmful. It might explain the poor results in all but 2 randomized controlled trials on long-term noninvasive ventilation in COPD. (ClinicalTrials.gov registration NCT02599246.) *Key words: NIV; COPD; FiO2; oxygen therapy; leak; hypercapnic*. [Respir Care 2020;65(12):1897–1903. © 2020 Daedalus Enterprises]

Introduction

Long-term oxygen therapy improves survival in patients with hypoxemic COPD.[1,2] The minimum recommended duration of O_2 therapy is 15 h/d.[3] Noninvasive ventilation (NIV) is currently recommended for acute-on-chronic COPD respiratory distress, and chronic NIV use is recommended for hypercapnic COPD.[4] However, the recent Global Initiative for COPD proposed that NIV should be used in selected patients.[3] A number of clinical studies found that nocturnal NIV application improved the quality of life, blood gas values, and hospital admission rates.[5,6]

Drs Cardinale, Cungi, Esnault, Nguyen, Daranda, Bordes, Meaudre, and Goutorbe are affiliated with the Department of Anesthesiology and Intensive Care, Military Hospital, Hôpital d'Instruction des Armées Sainte-Anne, France. Dr Castagna is affiliated with the Underwater Operational Research Resident Team of the Biomedical Research Institute of the Armed Forces, Hôpital d'Instruction des Armées Sainte-Anne, France. Dr Arnal is affiliated with the Department of Intensive Care, Regional Hospital Sainte-Musse, France.

Dr Goutorbe discloses a relationship with Breas Medical, in addition, Dr Goutorbe has a patent systems and methods for automatically adjusting a determined supply of F_{IO_2} generated from a CPAP, NIV or other ventilator system issued. Dr Arnal discloses a relationship with Hamilton Medical. The remaining authors have no conflict of interest.

Supplementary material related to this paper is available at http://www.rcjournal.com.

The study was performed at Military Teaching Hospital Sainte Anne, Toulon, France.

Correspondence: Michael Cardinale MD, Fédération d'Anesthésie – Réanimation. Hôpital d'Instruction des Armées Sainte-Anne. Boulevard Sainte-Anne. BP 20545 - 83041 Toulon Cedex 9, France. E-mail: mickaelcardinale@hotmail.fr.

DOI: 10.4187/respcare.07570

Two studies recently demonstrated a reduction in mortality with chronic NIV use in subjects with COPD.[7,8] Most home ventilators deliver pressure support via a turbine and a constant O_2 supply.[9,10] In contrast, ICU ventilators have an integrated blender that delivers the appropriate O_2 levels for achieving the set F_{IO_2} during NIV. Because most home-care ventilators lack this delivery mode, we hypothesized that intentional and nonintentional leaks could influence the F_{IO_2} of the patient. Modern home ventilators compensate for leaks by delivering higher flows. However, the flow is increased with additional intake from room air (ie, $F_{IO_2} = 0.21$); thus, without changing the O_2 supply, the F_{IO_2} must decrease. To our knowledge, few clinical studies have assessed the F_{IO_2} delivered with a home-care ventilator.[11] In the present study, we aimed to compare the daytime F_{IO_2}, when O_2 was supplied with a nasal cannula, to the nighttime F_{IO_2}, when O_2 was supplied with NIV at the same O_2 flow, in patients with COPD, under real conditions, at the patient's home.

QUICK LOOK

Current knowledge

Physiologic effects of noninvasive ventilation (NIV) should counteract COPD ventilation disorders. Surprisingly, only 2 recent randomized study's showed mortality benefit to routine use of NIV in COPD. Only one study compared F_{IO_2} with normobaric oxygen with F_{IO_2} with NIV in COPD but during daytime in laboratory conditions.

What this paper contributes to our knowledge

In a physiologic observational study, we showed that the inspired fraction of oxygen is dramatically decreased by NIV. If we consider O_2 treatment as the number of F_{IO_2} points above 0.21, half of O_2 treatment was removed during NIV in our study. This partial withdrawing of an important treatment could explain the unexpected poor result of chronic NIV for COPD.

Methods

Study Design

This single-center, prospective, observational study was conducted at the Military Teaching Hospital Sainte Anne, Toulon, France. The study protocol was reviewed and approved by the French ethical committee of the CPP Méditerranée I (2015-A01087-42), and it was registered at clinicaltrials.gov registration NCT02599246.

Study Participants

Eligible patients had COPD and received both normobaric long-term oxygen therapy and nighttime NIV at the same O_2 flow according to French common practice. Subjects were screened by the lung specialist at our hospital and 2 intensivists (PG, MC), who prescribed long-term oxygen therapy and NIV to patients with COPD. All the subjects provided signed informed consent. Exclusion criteria were the following: acute respiratory failure, history of cranial traumatism, history of epistaxis, local anesthetic intolerance, and high dependence on O_2 supply (O_2 flow of >3 L/min). We also excluded any patient who wanted to stop the study and withdrew consent.

Study End Points

The primary end point was the difference between the F_{IO_2} measured during NIV and the F_{IO_2} measured during daytime long-term oxygen therapy with a nasal cannula. The O_2 flow was similar in both treatments for each patient. The secondary end points were the following: the time spent below different reference O_2 levels during NIV (despite constant O_2 flow) and the level of O_2 adjustment needed to maintain a stable F_{IO_2} during NIV.

Data Collection and Measurements

We prospectively collected data on demographics, O_2 flow, the last arterial blood gas measurements, and spirometry for each subject. All subjects were studied in their home environment, and data collection started in the evening. The pharyngeal F_{IO_2} was measured during the day, whereas O_2 was delivered with a nasal cannula. Briefly, after local anesthesia, a nasopharyngeal cannula (Vygon SA, Paris, France) was introduced (an assembly diagram is provided, see the supplementary materials at http://www.rcjournal.com). Pharyngeal gases were analyzed with a side-stream gas analyzer (G5 gas module, Intellivue MP70 Philips, Philips Healthcare, Suresnes, France). The O_2 source was a 15-L hyperbaric bottle (Air Liquide SA, Paris, France). The O_2 flow was controlled with a precision flow meter (VT305 Gamida, Gamida SA, Paris, France). Several different O_2 flow were applied, and the corresponding F_{IO_2} was measured. The measurement of F_{IO_2} was done during closed mouth breathing. We started with the baseline flow (the subject's habitual O_2 flow) and then tested 150, 75, 50, and 25% of the baseline flow. For example, when the subject's baseline O_2 flow was 2 L/min, we measured pharyngeal F_{IO_2} at O_2 supply flows of 3, 2, 1, and 0.5 L/min. The F_{IO_2} was noted when stabilized for at least 8 cycles.

In a second phase, the subjects' prescribed NIV parameters were entered into the home ventilator controller (Vivo 50; Breas Medical AB, Mölnlycke, Sweden). The ventilator

was equipped with an F_{IO_2} sensor (E-17/J, Nuova, Ratzeburg, Germany) connected at the air outlet of the ventilator. The F_{IO_2} sensor was calibrated at the hospital site, immediately before going to the patient's home. The measurements were compared with the measurements obtained with an O_2 gas analyzer. Once the ventilator was in place, after removing the pharyngeal probe to avoid increasing leaks, we checked the accuracy of the ventilation parameters and the comfort of the mask (Comfort gel facial mask, Philips Respironics, Suresnes, France). All subjects used the same type of mask to standardize the intentional leak. To test the adequacy of the settings, we checked the F_{IO_2} delivered by the ventilator at the basal O_2 flow, then we titrated the O_2 flow to achieve the same F_{IO_2} as that measured during daytime oxygen therapy at the basal O_2 flow. Before we left the subject's home, we installed the ventilator in the subject's bedroom; the O_2 supply was set at the basal flow, controlled with the precision flow meter. We also measured the F_{IO_2} near the ventilator, but, on our home ventilators, O_2 was admitted at the rear of the ventilator, which probably provided a perfect mixing of gases through the turbine; therefore, the F_{IO_2} was unlikely to be overestimated. Also, the ventilator flow monitoring was exact because O_2 was admitted before the flow meter. Subjects received the prescribed NIV nighttime treatment. The next morning, the subject was visited again, and all materials were retrieved.

The recorded ventilator parameters from the night recordings were analyzed with Breas software (software that allows recovery of the recorded ventilator parameters and that extracts them in the form of an Excel table, Microsoft Ireland Operations, Dublin, Ireland). For each breath, the following parameters were available: F_{IO_2}, tidal volume, total flow (from the ventilator), minute volume (of the patient), and breathing frequency. With the ventilator (Vivo 50, Breas) intentional leaks (from the mask) and nonintentional leaks are not distinguished. Therefore, we calculated the mean airway pressure for each subject to estimate the intentional leaks (due to the mask).

Statistical Analysis

For this observational study with consecutive sampling, we performed a statistical power analysis with $\alpha = 0.05$, $\beta = 0.2$, and an estimated 6.375% drop in F_{IO_2} overnight compared with the daytime F_{IO_2}. The analysis indicated that at least 10 subjects should be included. This analysis was based on a 9-subjects sample in which the same measurement was done in a short NIV trial in an ICU. (see the supplementary materials at http://www.rcjournal.com.)

All statistical analyses were performed with Graph Pad Prism version 6.5 (GraphPad software, San Diego). Continuous data are reported as the mean ± SD. The Shapiro-Wilk test was applied to test the normal distribution of data. When data were not normally distributed, we reported the median and interquartile range [25th–75th percentile]. Nominal variables are reported as the number and proportion (%). A univariate analysis was conducted with the chi-square test to compare categorical variables. The Wilcoxon signed-rank test and Student *t* test were used to compare continuous variables (medians and means, respectively) between groups. For all tests, $P < .05$ was considered statistically significant.

Results

Between December 2015 and March 2016, we enrolled 14 subjects in the study, 11 men and 3 women, with a mean ± SD age of 71 ± 1.65 y. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of air-flow limitation,[3] we classified 6 subjects as GOLD stage 4, 5 subjects as GOLD stage 3, and 3 subjects as GOLD stage 2. All the subjects were previously prescribed a treatment with nighttime pressure-support ventilation; the O_2 flow and ventilator settings are summarized in Table 1.

Day Time Pharyngeal F_{IO_2}

The mean ± SD pharyngeal F_{IO_2} with a normobaric baseline O_2 flow was 0.308 ± 0.026. The mean ± SD F_{IO_2} gain was 2.6 ± 0.7 points above 0.21 for each 0.5 L/min increase in O_2 supply.

Daytime NIV Short Adaptation Trial

The mean F_{IO_2} measured during a daytime NIV trial was 0.244. The mean ± SD NIV O_2 flow that was required to reach an F_{IO_2} equal to the previous pharyngeal F_{IO_2} was 4.7 ± 1.4 L/min, equivalent to a mean ± SD increase in the baseline flow by 2.5 ± 0.7–fold.

Nighttime NIV

We recorded 104 h 22 min of nocturnal NIV in 14 subjects. The mean ± SD individual NIV use was 7 h 27 min ± 1 h 3 min. The mean flow from nonintentional leaks was 4 L/min.

F_{IO_2} during Nighttime NIV

The F_{IO_2} values (recorded breath by breath) during nocturnal NIV were compared with the subjects' own daytime pharyngeal F_{IO_2} level at the same O_2 flow. The results of all 14 subjects showed that the mean ± SD nighttime F_{IO_2} measurement (0.251 ± 0.01) was much lower than the mean ± SD daytime measurement (0.308 ± 0.026; $P <$

Table 1. Subject Characteristics and Ventilators Setting

Age, y	BMI, kg/m^2	GOLD Classification Stages	Ventilator Mode	IPAP, cm H_2O	EPAP, cm H_2O	Backup Rate	O_2 Flow, L/min
63	25	4	PSV	22	6	16	2
72	31	3	PSV	18	6	8	2
65	22	3	PSV	18	6	8	2
71	33	4	PSV	20	8	10	2
63	41	2	PSV	14	6	8	2
77	23	4	PSV	24	8	18	1.5
72	18	4	PSV	18	8	10	2
68	36	2	PSV	16	10	10	1.5
76	26	4	PSV	16	6	8	2
70	37	2	PSV	20	12	10	2
85	23	3	PSV	18	6	10	2
76	21	4	PSV	24	6	10	2
68	23	3	PSV	20	6	8	2
78	25	3	PSV	16	10	10	2

BMI = body mass index; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IPAP = inspiratory positive airway pressure; EPAP = expiratory positive airway pressure; PSV = pressure-support ventilation.

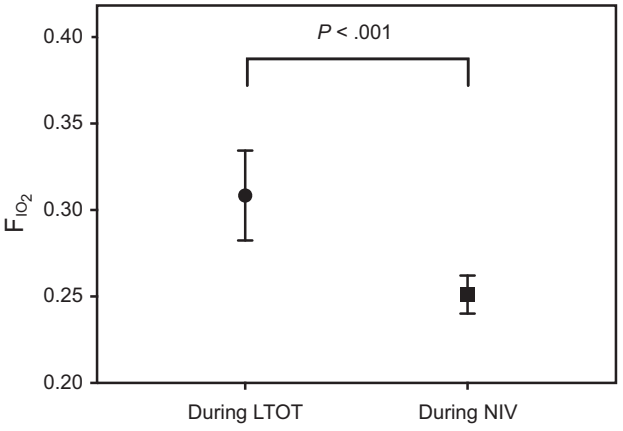

Fig. 1. Nighttime F_{IO_2} during noninvasive ventilation (NIV) and daytime pharyngeal F_{IO_2} during oxygen therapy, measured at the same O_2 flow. Values show the mean ± SD. LTOT = long-term oxygen therapy.

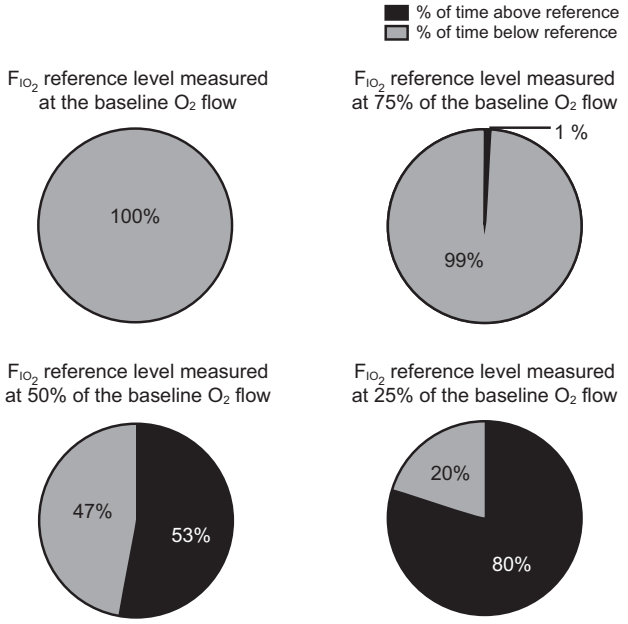

Fig. 2. The percentage of the time that the noninvasive ventilation supported F_{IO_2} levels were above or below the daytime F_{IO_2} reference levels, measured at different O_2 flows.

.001) (Fig. 1). For each subject, we stratified the nighttime F_{IO_2} according to the daytime measured at the baseline O_2 flow and at 75, 50, and 25% of the baseline O_2 flow. During nocturnal NIV, none of the subjects achieved a F_{IO_2} that corresponded to the F_{IO_2} recorded during the day with baseline O_2 flow.

Twelve subjects spent the entire night with an F_{IO_2} level below the F_{IO_2} level that corresponded to 75% of baseline flow (ie, 1.5 L/min for a subject with 2 L/min baseline flow). Three subjects spent the entire night with an F_{IO_2} level below the F_{IO_2} level that corresponded to 50% of baseline flow. When considering the entire patient population ($N = 14$), the F_{IO_2} measured during NIV was below the baseline F_{IO_2} flow level for 100% of the time; below the 75%-flow F_{IO_2} level for 99% of the time; below the 50%-flow F_{IO_2} level for 47% of time; and below the 25%-flow F_{IO_2} level for 20% of the time (Fig. 2). The mean nonintentional leakage was low in our study: 4 L/min.

Variability of Nighttime F_{IO_2}

Because of the latency of the chemical O_2 probe, we could not directly correlate F_{IO_2} and turbine flow. We found a good correlation between the SD of the turbine flow and SD of F_{IO_2}: R^2 0.48 (Fig. 3).

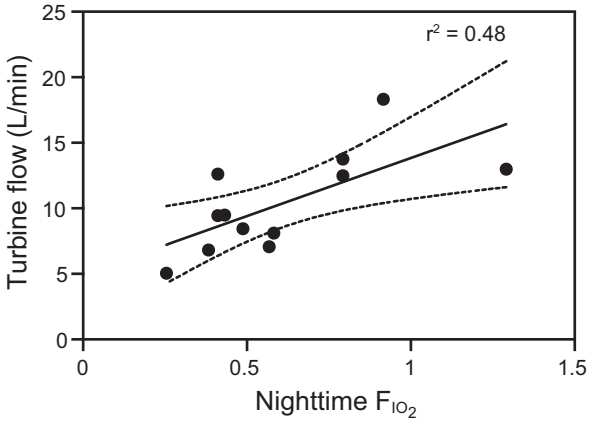

Fig. 3. Linear regression between F_{IO_2} SD and total-flow SD.

Discussion

To our knowledge, this study was the first to compare daytime pharyngeal F_{IO_2}, measured during normobaric O_2 flow, with nighttime F_{IO_2}, measured during NIV with the same O_2 flow, in subjects with COPD. Moreover, measurements were performed at home in the real condition of NIV use with the mode, ventilator settings, and circuit used on a daily basis by the subjects. Our main finding was that, with NIV, the nighttime F_{IO_2} (mean ± SD 0.251 ± 0.011) was much lower than that achieved during daytime O_2 therapy (mean ± SD 0.308 ± 0.026; $P < .001$).

Few previous studies measured pharyngeal F_{IO_2} during low O_2 flow. The most relevant was performed by Wettstein et al.[12] They reported a pharyngeal F_{IO_2} of 0.30 when O_2 was delivered at 2 L/min through a nasal cannula in 20 subjects. However, that study was conducted under physiologic conditions in healthy volunteers. Bazuaye et al[13] studied F_{IO_2} in subjects with COPD who received O_2 at 2 L/min through a nasal cannula. The mean ± SD F_{IO_2} at 2 L/min was 0.293 ± 0.137 (indirect measurement). In our study, the mean ± SD daytime F_{IO_2} of 0.304 ± 0.62 was consistent with previous findings, but we measured F_{IO_2} directly in the subjects with COPD. With an average F_{IO_2} gain of 0.0245 above 0.21 for each 0.5 L/min increase in O_2 supply, our findings are a little above the common 0.02 F_{IO_2} gain for each 0.5 L/min of O_2 supply.

It is well established that NIV has numerous positive physiologic effects in COPD. In one study, NIV reduced the effort in breathing and increased endurance muscle strength, counteracted intrinsic PEEP, and improved gas exchange.[14] Therefore, it is surprising that so few studies demonstrate an impact of NIV on mortality. This lack of benefit might be explained by our finding that the F_{IO_2} decreased during nighttime NIV. Moreover, we believe that leakages were the key cause of the drop in F_{IO_2}.In fact, previous studies showed that F_{IO_2} could decrease with O_2 leaks during NIV.[11] Samolski et al[15] studied 10 healthy volunteers to evaluate determinants in F_{IO_2} with intermittent positive pressure. They found that continuous airway pressure provided greater F_{IO_2} than bi-level positive airway pressure.[15] The investigators explained this result by showing that important leaks were present with bi-level positive airway pressure.[15]

Storre et al[16] investigated the effects of leaks. First, they showed that leakage might be better compensated with ventilators that were pressure limited rather than volume limited.[16] Recently, they studied oxygen supplementation in noninvasive home mechanical ventilation.[17] They compared F_{IO_2} in subjects who received daytime ventilation with 4 different kinds of ventilatory circuits; leakages led to worse F_{IO_2} levels.[17] The highest F_{IO_2} level was achieved with an active valve circuit with no artificial leak; and the lowest F_{IO_2} level was achieved with intentional and artificial leaks.[17] In the latter configuration, they found mean F_{IO_2} levels of 0.249 near the mask and 0.33 near the ventilator.[17] With the "no leak" circuit, the mean F_{IO_2} levels were 0.362 and 0.33, respectively.[17] The difference represented a 16.7 mm Hg P_{aO_2} drop between the "no leak" and "maximal leak" circuits. These investigators found a higher F_{IO_2} than that found in our study with NIV. This difference could be explained by the higher O_2 flow used in their study (2.7 L/min vs 1.9 L/min[17]) and probably by the greater leaks that occurred during nighttime NIV, particularly with the mask we used. Indeed, our mask had intentional leaks of 18.9, 27.4, and 39.4 L/min at pressures of 5, 10, and 20 cm H_2O, respectively.[18]

What is the clinical impact of these results? Long-term oxygen therapy is currently recommended in severe COPD for at least 15 h/d.[5] We found that, during nocturnal NIV (average time, 7 h 20 min), 50% of the time, the F_{IO_2} was below the F_{IO_2} measured at half the flow needed for adequate oxygen therapy. Alveolar hypoxia is known to induce pulmonary vasoconstriction, and long-term oxygen therapy was shown to lower or to stabilize pulmonary hypertension.[19,20] Therefore, we should be concerned about delivering constant O_2 treatment.[21]

Although high-intensity NIV might seem to be more effective,[8] in fact, the F_{IO_2} decreased further during high-pressure ventilation.[22] Several studies demonstrated that applying the highest pressure led to the greatest leaks,[22-24] which, in turn, led to lower F_{IO_2} levels. We believed that withdrawing half of the O_2 treatment during the night would worsen pulmonary hypertension evolution.

According to the GOLD recommendation,[3] the aim of chronic NIV use is to clear the CO_2. Mask exhalation ports reduce CO_2 rebreathing.[3,25,26] Therefore we must not avoid an intentional leak.

Should we maintain F_{IO_2} throughout the night? During the short evening NIV trial that we performed to allow the subjects to adapt to the mask and ventilator settings, we

titrated the O_2 flow to achieve the previous pharyngeal F_{IO_2} level obtained at the baseline O_2 flow (nasal cannula). The daytime F_{IO_2} was achieved with NIV by increasing the baseline O_2 flow by an average of 2.46-fold (minimum, 1.5-fold; maximum, 4.25-fold). Modern O_2 concentrators are able to achieve those O_2 flows. Thus, the increase in the O_2 flow could correct the decrease in F_{IO_2} linked to leaks. However, an increase in the patient's inspiratory effort will also result in an increase in the turbine flow and, therefore, in a decrease in F_{IO_2} despite the increase in the O_2 flow.

Limitations

This study had the limitations inherent in an observational physiologic study. The F_{IO_2} measurement during nasal cannula O_2 delivery was done only once, with the patient's mouth closed. But this one-time measurement may not reflect the O_2 delivery consistency over the entire daytime and especially during the increase of the subject's inspiratory efforts. We did not perform a second-night measurement, in which we increased the O_2 flow; therefore, we could only hypothesize that increasing the flow might correct the F_{IO_2}. Further prospective studies that evaluate long-term NIV in subjects with COPD should pay attention to nighttime F_{IO_2} levels.

Conclusions

We demonstrated that, with a modern NIV pattern of application, a pressure target, and intentional leaks, the nighttime F_{IO_2} decreased during NIV in subjects with COPD. We speculated that this partial reduction in O_2 therapy might be harmful. Moreover, it might explain the poor results reported previously, in all but 2 randomized controlled trials on long-term NIV in COPD.[9,24]

REFERENCES

1. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Annals of Internal Medicine. Available at: http://www.annals.org/content/93/3/391.abstract?sid=79927bd3-e7f2-4273-baab-19b98e3d4991, *Accessed September 1, 1980*.
2. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema: report of the Medical Research Council Working Party. Lancet 1981;I(8222):681-686.
3. Patel Avani R, Patel Amar R, Singh Shivank, Singh Shantanu, Khawaja I. Global Initiative for Chronic Obstructive Lung Disease. Cureus 2019;11(6):e4985.
4. Ergan B, Oczkowski S, Rochwerg B, Carlucci A, Chatwin M, Clini E, et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. Eur Respir J 2019;54(3):1901003.
5. Casanova C, Celli BR, Tost L, Soriano E, Abreu J, Velasco V, Santolaria F. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest 2000;118(6):1582-1590.
6. Clini E, Sturani C, Rossi A, Viaggi S, Corrado A, Donner CF, Ambrosino N; Rehabilitation and Chronic Care Study Group, Italian Association of Hospital Pulmonologists (AIPO). Chronic Care Study Group IAOHPA. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J 2002;20(3):529-538.
7. Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med 2014;2(9):698-705.
8. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. JAMA 2017;317(21):2177-2186.
9. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabill J, Farre R, Fauroux B, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J 2005;25(6):1025-1031.
10. Crimi C, Noto A, Princi P, Cuvelier A, Masa JF, Simonds A, et al. Domiciliary non-invasive ventilation in COPD: an international survey of indications and practices. COPD 2016;13(4):483-490.
11. Goutorbe P, Daranda E, Asencio Y, Esnault P, Prunet B, Bordes J, et al. Leaks can dramatically decrease FiO2 on home ventilators: a bench study. BMC Res Notes 2013;6:282.
12. Wettstein RB, Shelledy DC, Peters JI. Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. Respir Care 2005;50(5):604-609.
13. Bazuaye EA, Stone TN, Corris PA, Gibson GJ. Variability of inspired oxygen concentration with nasal cannulas. Thorax 1992;47(8):609-611.
14. Kallet RH, Diaz JV. The physiologic effects of noninvasive ventilation. Respir Care 2009;54(1):102-115.
15. Samolski D, Antón A, Güell R, Sanz F, Giner J, Casan P. Inspired oxygen fraction achieved with a portable ventilator: determinant factors. Respir Med 2006;100(9):1608-1613.
16. Storre JH, Bohm P, Dreher M, Windisch W. Clinical impact of leak compensation during non-invasive ventilation. Respir Med 2009;103(10):1477-1483.
17. Storre JH, Huttmann SE, Ekkernkamp E, Walterspacher S, Schmoor C, Dreher M, Windisch W. Oxygen supplementation in noninvasive home mechanical ventilation: the crucial roles of CO2 exhalation systems and leakages. Respir Care 2014;59(1):113-120.
18. Borel JC, Sabil A, Janssens JP, Couteau M, Boulon L, Lévy P, Pépin JL. Intentional leaks in industrial masks have a significant impact on efficacy of bilevel noninvasive ventilation: a bench test study. Chest 2009;135(3):669-677.
19. Chaouat A, Bugnet A-S, Kadaoui N, Schott R, Enache I, Ducoloné A, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172(2):189-194.
20. Weitzenblum E, Chaouat A, Kessler R. Pulmonary hypertension in chronic obstructive pulmonary disease. Pneumonol Alergol Pol 2013;81(4):390-398.
21. Xiong W, Zhao Y, Gong S, Zhao Q, Liu J. Prophylactic function of excellent compliance with LTOT in the development of pulmonary hypertension due to COPD with hypoxemia. Pulm Circ 2018;8(2):2045894018765835.
22. Schwartz AR, Kacmarek RM, Hess DR. Factors affecting oxygen delivery with bi-level positive airway pressure. Respir Care 2004;49(3):270-275.

23. Thys F, Liistro G, Dozin O, Marion E, Rodenstein DO. Determinants of Fi,O2 with oxygen supplementation during noninvasive two-level positive pressure ventilation. Eur Respir J 2002;19(4):653-657.
24. Chen H, Liang B-M, Xu Z-B, Tang YJ, Wang K, Xiao J, et al. Long-term non-invasive positive pressure ventilation in severe stable chronic obstructive pulmonary disease: a meta-analysis. Chin Med J (Engl) 2011;124(23):4063-4070.
25. Schettino GPP, Chatmongkolchart S, Hess DR, Kacmarek RM. Position of exhalation port and mask design affect CO2 rebreathing during noninvasive positive pressure ventilation. Crit Care Med 2003;31:2178-2182.
26. Saatci E, Miller DM, Stell IM, Lee KC, Moxham J. Dynamic dead space in face masks used with noninvasive ventilators: a lung model study. Eur Respir J 2004;23(1):129-135.