F_{IO_2}, P_{aO_2}, or Else – What Matters in Noninvasive Ventilation in Stable COPD?

To the Editor:

We read with great interest the article by Cardinale et al[1] on F_{IO_2} delivered by noninvasive ventilation (NIV) compared with long-term oxygen therapy (LTOT) at the same flow. We would like to add some comments regarding this study.

The article offers evidence that in NIV with home-care ventilators, the addition of oxygen does not deliver the same F_{IO_2} as the same flow of oxygen applied via nasal cannula (0.25 vs 0.30). This is not surprising, given the oxygen dilution in higher NIV flows. However, F_{IO_2} does not directly translate into P_{aO_2} when different modalities of oxygen delivery are used. Therefore, the comparison of nasal cannula and NIV is inappropriate, and some key points have to be addressed.

First, the authors have not provided data on P_{aO_2} achieved under different oxygen delivery modalities. Oxygenation data would provide crucial information on the clinical relevance of the difference in F_{IO_2} observed in the study. It has been established that NIV alone influences gas exchange. Ambrosino et al[2] compared spontaneous breathing with pressure-support ventilation without oxygen supplementation and reported a significant improvement in pH, P_{aCO_2}, and P_{aO_2} under NIV. Therefore, the combined effect of NIV and oxygen likely compensates for lower F_{IO_2} delivery by NIV. The effect on arterial gases cannot be assumed from F_{IO_2} but should be determined directly through arterial gas measurement. In our clinical practice, oxygen supplementation is titrated during NIV to reach target oxygen saturation and P_{aO_2} regardless of F_{IO_2} and is not simply translated from LTOT flows. In Table 1 we provide data on 3 patients with COPD on NIV at follow-up in recent months to show the comparison of blood gases on spontaneous and pressure-support ventilation, measured within hours. All 3 subjects signed an informed consent, the study was approved by the ethics council. The analysis demonstrates higher P_{aO_2} on NIV compared to LTOT on the same or lower oxygen flow. Cardinale et al[1] reported that a 2.5-fold increase of LTOT oxygen flow was required during NIV to achieve the same F_{IO_2}. This is inconsistent with our clinical experience with NIV oxygen flows (Table 1) and is a further sign that F_{IO_2} during NIV is not the sole determinant of P_{aO_2}. Additionally, published data,[3] our clinical experience (Table 1), and the present study itself show that patients with COPD require relatively low flows of oxygen during NIV. Therefore we believe the real clinical target in oxygenation is P_{aO_2} and not F_{IO_2}.

Table 1. Comparison of P_{O_2} Between Pressure-Support Ventilation and LTOT Spontaneous Breathing in Patients With COPD

Age, y	Body Mass Index, kg/m^2	COPD Stage	NIV Mode	IPAP, cm H_2O	EPAP, cm H_2O	Backup Rate, breaths/min	NIV O_2 Flow, L/min	LTOT Flow, L/min	P_{O_2}, NIV, mm Hg	P_{O_2}, LTOT, mm Hg
47	16	D	PSV	18	5	16	0.5	1	65	61
77	26	D	PSV	24	9	18	1	1	81	74
78	19	D	PSV	20	6	16	1	1	88	61

LTOT = long-term oxygen therapy
NIV = noninvasive ventilation
PSV = pressure support ventilation
IPAP = inspiratory positive airway pressure
EPAP = expiratory positive airway pressure

Second, it is encouraging that the study demonstrated on average similar F_{IO_2} during the daytime and during the nighttime NIV trials (0.24 vs 0.25), although the same mask type was utilized for all subjects. Potential poor fit of the mask could cause higher unintentional leakage (and further F_{IO_2} decrease) overnight, but the study found low levels of leakage. Nevertheless, results reported by Storre et al[4] indicate that major leaks influence both F_{IO_2} and P_{aO_2}, but, more importantly, F_{IO_2} and P_{aO_2} were measured and compared within different NIV circuit setups. In our opinion, the issue of leaks influencing F_{IO_2} should be addressed with optimal mask selection and with oxygen titration for the specific NIV circuit setup used for a patient.

Finally, the authors speculate that lower F_{IO_2} during NIV might explain the lack of benefits of NIV across some earlier studies performed in patients with COPD. Even if we assume that significant arterial hypoxemia does occur during NIV (which the present study did not demonstrate), we believe that the lack of benefit in these studies is better explained by lower inspiratory pressures used in earlier studies and failure to significantly influence the level of P_{CO_2}.[5] Furthermore, nocturnal oxygen desaturation itself is frequent in patients with COPD (ie, present in up to 48%).[6] Several studies have reported that the addition of nocturnal oxygen and correction of nocturnal oxygen desaturation do not influence the survival of subjects with COPD with nocturnal oxygen desaturation per se.[6] However, the 2 studies of NIV in COPD demonstrating the survival benefit of NIV used higher inspiratory pressures and achieved a significant reduction of P_{CO_2}.[7] Higher inspiratory pressures lead to higher leaks, which in turn will decrease F_{IO_2}. Considering all these facts, it is more likely that the survival benefit of NIV in COPD is linked to increased alveolar ventilation when higher pressures are used, and that the potential of lower F_{IO_2} does not seem to be crucial.

To conclude, the results of the study by Cardinale et al[1] demonstrate lower F_{IO_2} at the same oxygen flows in NIV compared to spontaneous breathing, but further studies are needed to determine the impact of this finding on oxygenation or relevant clinical outcomes.

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DOI: 10.4187/respcare.08560

REFERENCES

1. Cardinale M, Cungi PJ, Esnault P, Castagna O, Nguyen C, Daranda E, et al. In COPD, nocturnal noninvasive ventilation reduces the FIO2 delivered compared with long-term oxygen therapy at the same flow. Respir Care 2020;65(12):1897-1903.
2. Ambrosino N, Nava S, Bertone P, Fracchia C, Rampulla C. Physiologic evaluation of pressure support ventilation by nasal mask in patients with stable COPD. Chest 1992;101(2):385-391.
3. Windisch W, Haenel M, Storre JH, Dreher M. High-intensity non-invasive positive pressure ventilation for stable hypercapnic COPD. Int J Med Sci 2009;6(2):72-76.
4. 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.
5. Windisch W, Storre JH, Köhnlein T. Nocturnal non-invasive positive pressure ventilation for COPD. Expert Rev Respir Med 2015;9(3):295-308.
6. Hatipoğlu U, Stoller JK. Supplemental oxygen in patients with stable chronic obstructive pulmonary disease: evidence from Nocturnal Oxygen Treatment Trial to Long-term Oxygen Treatment Trial. Curr Opin Pulm Med 2018;24(2):179-186.
7. Storre JH, Callegari J, Magnet FS, Schwarz SB, Duiverman ML, Wijkstra PJ, Windisch W. Home noninvasive ventilatory support for patients with chronic obstructive pulmonary disease: patient selection and perspectives. Int J Chron Obstruct Pulmon Dis 2018;13:753-760.

Reply to: F_{IO_2}, P_{aO_2}, or Else – What Matters in Noninvasive Ventilation in Stable COPD?

To the Editor:

We read with interest the comments from Sarc et al[1] about our previous study on F_{IO_2} delivered by noninvasive ventilation (NIV) compared with long-term oxygen therapy at the same flow.[2] We want to give some precision in response to their comments. Sarc et al[1] state that our result of a decrease in F_{IO_2} delivered by NIV at the same oxygen flow delivered by nasal cannula is not surprising. Indeed, it is an expected result related to the dilution of oxygen by the NIV flow. To our knowledge, this had not yet been clearly demonstrated in real-life home conditions.

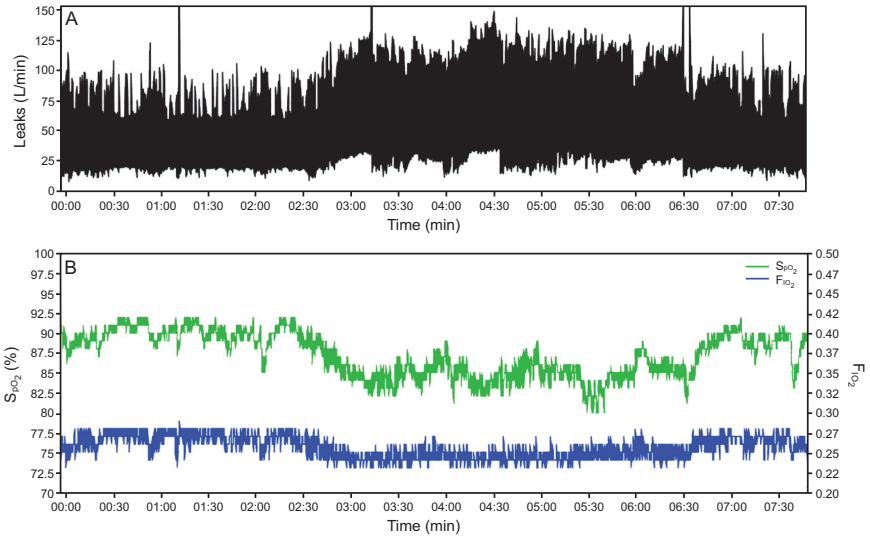

Fig. 1. Leaks, S_{pO_2} and F_{IO_2} variations during nocturnal noninvasive ventilation.

Their main remark concerns the lack of data on P_{aO_2}, stating that F_{IO_2} cannot be directly translated into P_{aO_2} and suggests that the decrease in F_{IO_2} would be compensated by the increase in alveolar ventilation; in other words, the decrease in P_{aCO_2}. We are not totally agreed with this point. F_{IO_2} is the main determinant of alveolar oxygen pressure (P_{AO_2}): $P_{AO_2} = P_{iO_2} - P_{aCO_2} / R = (PB - PH_2O) F_{IO_2} - (P_{aCO_2} / R)$. In the the studies by Murphy et al[3] and Köhnlein et al,[4] the change in P_{aCO_2} associated with NIV use was 5 mm Hg and 6.75 mm Hg, respectively. With a commonly accepted respiratory coefficient of 0.82, P_{AO_2} variation would be from 6.1 to 8.2 points. In our study, the P_{AO_2} change related to the decrease in F_{IO_2} (from ~31% with daytime oxygen therapy to 25% on average with NIV) would be ~42.8 points. Therefore, the drop in P_{aCO_2} cannot compensate for the drop in P_{iO_2} (linked to the drop in F_{IO_2} related to compensation for leaks). This results in a drop in P_{AO_2} and, therefore, in P_{aO_2}. In addition, a study by Storre et al[5] demonstrated that significant leaks influence both F_{IO_2} and P_{aO_2}. In our study[2], monitoring S_{pO_2} was usable in 5 subjects; in all the subjects, we noticed a drop in S_{pO_2} when the leaks increased and the F_{IO_2} decreased (Fig. 1).

The consequences of nocturnal hypoxemia are multiple, and nocturnal oxygen supplementation can improve arrhythmias and reduce blood pressure surges.[6,7] The benefits for sleep quality are not well established.[8,9] The association between nocturnal oxygen desaturation and the development of chronic pulmonary hypertension remains unclear. Data on mortality and its association with nocturnal oxygen desaturation in COPD are scarce and have not demonstrated a survival benefit when corrected by oxygen supplementation. However, the 2 studies that looked at this topic were carried out on small cohorts and concerned subjects with low hypoxemia (mean P_{aO_2} of 76 mm Hg and 62.7 mm Hg).[10,11]

Finally, Sarc et al[1] state that oxygen flow should be titrated to P_{aO_2}. However, this is difficult to achieve in the daily practice at the patient's home. We believe that it is simpler in daily practice to determine the oxygen flow according to the F_{IO_2} delivered. Like the servo flow regulator that titrates oxygen flow based on pulse oximetry feedback,[12] technologic innovation would be the introduction of an oxygen flow regulator based on the flow of the home ventilator turbine and, therefore, of the leaks, so that the increase in the oxygen flow would limit the drop in F_{IO_2} linked to leaks.

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Dr Goutorbe discloses a relationship with Breas Medical, in addition, Dr Goutorbe has patent systems and methods for automatically adjusting a determined supply of FIO2 generated from a CPAP, noninvasive ventilation, or other ventilator systems issued. Drs Cardinale, Esnault, Cungi, and Meaudre declare no conflict of interest.

DOI: 10.4187/respcare.09172

REFERENCES

1. Sarc I, Ziherl K, Esquinas A. F_{IO2}, P_{aO2} or else - what matters in noninvasive ventilation in stable COPD? Respir Care 2021;66 (8):1368-1369.
2. Cardinale M, Cungi P-J, Esnault P, Castagna O, Nguyen C, Daranda E, et al. In COPD, nocturnal noninvasive ventilation reduces the F_{IO2} delivered compared with long-term oxygen therapy at the same flow. Respir Care 2020;65(12):1897-1903.
3. 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.
4. 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.
5. 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 CO_2 exhalation systems and leakages. Respir Care 2014;59(1):113-120.
6. Flick MR, Block AJ. Nocturnal vs diurnal cardiac arrhythmias in patients with chronic obstructive pulmonary disease. Chest 1979;75 (1):8-11.
7. Fletcher EC, Levin DC. Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease. The effect of short- and long-term oxygen. Chest 1984;85(1):6-14.
8. Calverley PM, Brezinova V, Douglas NJ, Catterall JR, Flenley DC. The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. Am Rev Respir Dis 1982;126(2):206-210.
9. Fleetham J, West P, Mezon B, Conway W, Roth T, Kryger M. Sleep, arousals, and oxygen desaturation in chronic obstructive pulmonary disease. The effect of oxygen therapy. Am Rev Respir Dis 1982;126(3):429-433.
10. Fletcher EC, Luckett RA, Goodnight-White S, Miller CC, Qian W, Costarangos-Galarza C. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime P_{aO2} above 60 mm Hg. Am Rev Respir Dis 1992;145(5):1070-1076.
11. Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Ehrhart M, Schott R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J 1999;14(5):1002-1008.
12. Cirio S, Nava S. Pilot study of a new device to titrate oxygen flow in hypoxic patients on long-term oxygen therapy. Respir Care 2011;56(4):429-434.