

Non-invasive ventilation in hypoxemic patients: does the interface make a difference?

Federico Longhini¹, Karim Abdalla², Paolo Navalesi^{1,3,4}

¹Anesthesia and Intensive Care, Sant'Andrea Hospital, ASL VC, Vercelli, Italy; ²Anesthesia and Intensive Care, A.O.U. Mater Domini, Catanzaro, Italy; ³Department of Translational Medicine, Eastern Piedmont University "A. Avogadro", Novara, Italy; ⁴CRRF Mons. L. Novarese, Moncrivello, VC, Italy

Correspondence to: Paolo Navalesi, MD. Department of Translational Medicine, Eastern Piedmont University "A. Avogadro", Via Solaroli 17, 28100, Novara, Italy. Email: paolo.navalesi@med.unipmn.it.

Submitted Aug 06, 2016. Accepted for publication Aug 12, 2016.

doi: 10.21037/atm.2016.09.20

View this article at: <http://dx.doi.org/10.21037/atm.2016.09.20>

Non-invasive ventilation (NIV) has been increasingly used in intensive care unit (ICU) for treatment of patients with acute respiratory failure (ARF) of varied etiologies. Randomized controlled trials (RCTs) have shown evidence in favour of NIV for patients with exacerbations of chronic obstructive pulmonary disease (COPD) (1) and cardiogenic pulmonary edema (2), while a clear indication for patients with hypoxemic ARF in general and the acute respiratory distress syndrome (ARDS) in particular (3).

According to the recent "Berlin" definition, ARDS is a form of hypoxemic ARF characterized by bilateral pulmonary infiltrates determining impairment of the ratio between arterial tension and inspiratory fraction of oxygen ($\text{PaO}_2/\text{FiO}_2$) while a minimum of 5 cm H_2O of positive end-expiratory pressure (PEEP) is applied, regardless of the ventilatory mode (4). The Berlin definition classifies ARDS as mild ($\text{PaO}_2/\text{FiO}_2$ between 201 and 300 mmHg), moderate ($\text{PaO}_2/\text{FiO}_2$ between 101 and 200 mmHg) and severe ($\text{PaO}_2/\text{FiO}_2$ below 100 mmHg) (4).

Thille *et al.* reported higher rates of NIV failure leading to intubation in ARDS (61%) than non-ARDS hypoxemic patients (35%) (5). In particular, patients with ARDS and $\text{PaO}_2/\text{FiO}_2 < 150$ mmHg were more likely to fail NIV (74%) than those with $\text{PaO}_2/\text{FiO}_2 \geq 150$ mmHg (45%), with a hazard ratio = 2.3 (95% CI, 1.04–5.06). Nonetheless, ICU mortality in moderate to severe ARDS was no different between patients intubated, either right away without prior NIV or after NIV failure (5). Carreaux *et al.* studied 62 ARDS patients of different severity undergoing mask NIV (6). The median expiratory tidal

volume was higher in patients failing NIV [10.6 (9.6–12.0) mL/kg of predicted body weight], as compared to those who succeeded NIV [8.5 (7.6–10.2) mL/kg]. This difference was mainly attributable to the patients with moderate to severe ARDS (6).

Some RCTs evaluated NIV as a first line ventilatory treatment for patients with hypoxemic ARF of varied aetiology, with controversial results (3). Very recently, Frat *et al.* raised a warning on the use of NIV in patients with *de novo* hypoxemic non-hypercapnic ARF, as defined by the presence of a respiratory rate ≥ 25 breaths/min and a $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg. Patients were randomized to receive either standard oxygen therapy (94 patients), or heated high-flow oxygen through a nasal cannula (HFNC) (106 patients), or NIV by facemask (110 patients) (7). They found NIV was no better than standard oxygen therapy and HFNC in reducing the rate of intubation (primary endpoint). However, 90-day mortality was significantly lower with HFNC, as opposed to both NIV and oxygen therapy. Of note, the patients randomized to HFNC reported better comfort and dyspnoea improvement than those receiving NIV or standard oxygen therapy. In addition, a *post hoc* analysis considering the subgroup of 238 patients with $\text{PaO}_2/\text{FiO}_2 \leq 200$ mmHg indicated a reduced risk for intubation with HFNC, as opposed to both NIV and standard oxygen therapy (7).

Immunocompromised hypoxemic patients represent a category with a high potential for NIV benefit. Indeed, two RCTs compared NIV with standard oxygen therapy in

40 recipients of solid organ transplantation (8) and 52 patients with bilateral pulmonary infiltrates and immunosuppression by varied causes (9). NIV reduced the need for endotracheal intubation (8,9), septic complications (8,9), ICU (8,9) and hospital (9) mortality, and improved oxygenation (8,9), confirming the rationale for NIV in these patients. The results of these two relatively small single-center RCTs (8,9), however, have been challenged by a recent large RCT performed in 28 French ICUs (10). Lemiale *et al.* randomized 374 patients with hypoxemic ARF and immunodeficiency, as defined by the presence of solid tumor or hematological malignancy or long term steroid or immunosuppressive therapy, to receive either NIV by facemask or standard oxygen therapy (10). The found no difference in all cause 28-day mortality, need for invasive ventilation, rate of ICU-acquired infection rate, lengths of ICU and hospital stay (10).

Although in the less severe ARDS patients intubation after NIV failure does not seem to add harm (5) and the use of NIV in mild ARDS has been not contraindicated by the Berlin definition, the recent RCTs by Frat *et al.* (7) and Lemiale *et al.* (10), do not demonstrate any clinical improvement for the patients receiving NIV rather than standard oxygen therapy, and suggest a worsened outcome when compared to HFNC (7).

Very recent data by Patel *et al.*, however, open a new prospective on the use of NIV delivered through helmet in ARDS patients (11). The helmet is a transparent latex-free interface that, in its standard configuration, is secured to the patient by padded armpit braces (12). The study by Patel *et al.* enrolled 83 ARDS patients who had received NIV through a facemask for at least 8 hours. Patients were randomized either to continue NIV by facemask or switch to NIV by helmet. The median PaO₂/FiO₂ of the two cohorts were 144.0 (90.0–223.0) and 118.0 (93.0–170.0) mmHg for the mask and helmet group, respectively. The study was interrupted at the first interim analysis (i.e., one third of the planned enrolment) for efficacy, as the intubation rate was reduced from 61.5% with the mask to 18.2% with the helmet. The ventilator-free days were 12.5 (0.49–28.0) and 28.0 (13.7–28.0) with mask and helmet, respectively (P<0.001). The ICU length of stay was shorter [4.7 (2.5–8.7) vs. 7.8 (3.9–13.8) days] for the patients randomized in the helmet group, as opposed to the facemask group (P=0.04). Both hospital and 90-day mortality were also significantly lower in the helmet group (11). Noteworthy, in the study by Frat *et al.*, the subgroup of patients undergoing NIV with a PaO₂/FiO₂ ≤200 mmHg, resulting in a worse outcome

than those receiving HFNC and standard oxygen therapy, had an average PaO₂/FiO₂ of 126±36 mmHg and a rate of intubation of 58% (7), not dissimilar from those of the study by Patel *et al.* So, does the interface make such a big difference for NIV success in hypoxemic patients? And how can these differences be explained?

Indeed, the study by Patel *et al.* opens new perspectives for NIV in hypoxemic patients with ARDS, even considering its limitations that necessarily lead to a cautious interpretation of the results (11). In fact, first, the study is unblinded, second, it has been performed in a single center, making necessary further external validation, and third, it has been stopped after interim analysis, which may have exaggerated the magnitude of the effect size (11).

Following the seminal work by Antonelli *et al.* who showed lower rate of complications in hypoxemic patients undergoing NIV by helmet, as compared to a historical control group receiving NIV by facial mask (13), the helmet was repeatedly shown to be better tolerated over time, allowing longer continuous treatment periods with fewer interruptions (13,14). Compared with the facemask, the helmet offers several advantages: it is less sensitive to airleaks (15), it eliminates the risk of facial skin breakdown (13), and it can be applied to any patient regardless of the face contour (13). All these features may improve patient tolerance, which is a major determinant of NIV success. In a small single centre pilot RCT assessing NIV in the weaning of patients recovering from hypoxemic ARF, Vaschetto *et al.* allowed a rotational use of three interfaces to improve tolerance, the helmet being the first-choice interface (16). Interestingly, in 70% of patients the helmet was the only interface utilized, while in the remaining 30% all three interfaces were used (16).

Of note, in the RCT by Patel *et al.* (11) and in the previous studies (13–17), NIV was delivered through helmets originally designed for continuous positive airway pressure (CPAP). These helmets are more prone to intrinsic drawbacks, leading to poor patient-ventilator interaction and pressurization and triggering performance (17). Recently, a helmet of new generation has been developed and marketed in Europe and Asia, which has been shown to improve triggering and pressurization performance, either on bench (12), in healthy volunteers (18) and in ICU patients (19). These effects are likely achieved by reducing the upward displacement of the helmet during ventilator insufflation, while guaranteeing adequate comfort and eliminating the need for the armpit braces (12,19). While it is unclear whether these physiologic improvements translate

in better outcome improvement in hypoxemic ARF, a recent pilot RCT conducted in patients with COPD exacerbations, previously shown to be the worst population for helmet NIV (17), found this new device to be equally effective than the facial mask (20).

In spite of these considerations, a widespread use of NIV in hypoxemic patients in general, and of those with ARDS in particular, is presently not recommended (3). A practical algorithm has been proposed that designs a role for NIV in patients with PaO₂/FiO₂ between 150 and 300 mmHg while spontaneously breathing, no indication for immediate intubation, and no response to HFNC (3). Worth remarking, these patients must always be treated in ICU, assessing the response to NIV within 1 hour. Should we change this approach following the results of the RCT by Patel *et al.*? We do not think so. Taking into account its limitations, we are persuaded this trial is mainly a pilot study propedeutic for stringently designing future multicentre RCTs. Should we consider the helmet for delivering NIV in hypoxemic patients? When considering the results of this RCT and those of previous non-randomized studies, we are led to believe there is a role for this interface in the management of NIV in hypoxemic patients.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned by Section Editor Jianrong Zhang, MD (Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, Guangzhou, China).

Conflicts of Interest: Dr. Navalesi's research laboratory has received equipment and grants from Intersurgical S.p.A. Dr. Navalesi contributed to the development of the helmet Next, whose licence for patent belongs to Intersurgical S.P.A., and receives royalties for that invention. And other authors have no conflicts of interest to declare.

Comment on: Patel BK, Wolfe KS, Pohlman AS, *et al.* Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA 2016;315:2435-41.

References

1. Lightowler JV, Wedzicha JA, Elliott MW, et al. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ* 2003;326:185.
2. Vital FM, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2013;(5):CD005351.
3. Demoule A, Hill N, Navalesi P. Can we prevent intubation in patients with ARDS? *Intensive Care Med* 2016;42:768-71.
4. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526-33.
5. Thille AW, Contou D, Fragnoli C, et al. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. *Crit Care* 2013;17:R269.
6. Carreaux G, Millán-Guilarte T, De Prost N, et al. Failure of Noninvasive Ventilation for De Novo Acute Hypoxemic Respiratory Failure: Role of Tidal Volume. *Crit Care Med* 2016;44:282-90.
7. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185-96.
8. Antonelli M, Conti G, Bufi M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA* 2000;283:235-41.
9. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001;344:481-7.
10. Lemiale V, Mokart D, Resche-Rigon M, et al. Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA* 2015;314:1711-9.
11. Patel BK, Wolfe KS, Pohlman AS, et al. Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA* 2016;315:2435-41.
12. Olivieri C, Costa R, Spinazzola G, et al. Bench comparative evaluation of a new generation and standard helmet for delivering non-invasive ventilation. *Intensive*

- Care Med 2013;39:734-8.
13. Antonelli M, Conti G, Pelosi P, et al. New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet--a pilot controlled trial. *Crit Care Med* 2002;30:602-8.
 14. Rocco M, Conti G, Alessandri E, et al. Rescue treatment for noninvasive ventilation failure due to interface intolerance with remifentanyl analgesedation: a pilot study. *Intensive Care Med* 2010;36:2060-5.
 15. Cammarota G, Olivieri C, Costa R, et al. Noninvasive ventilation through a helmet in postextubation hypoxemic patients: physiologic comparison between neurally adjusted ventilatory assist and pressure support ventilation. *Intensive Care Med* 2011;37:1943-50.
 16. Vaschetto R, Turucz E, Dellapiazza F, et al. Noninvasive ventilation after early extubation in patients recovering from hypoxemic acute respiratory failure: a single-centre feasibility study. *Intensive Care Med* 2012;38:1599-606.
 17. Navalesi P, Costa R, Ceriana P, et al. Non-invasive ventilation in chronic obstructive pulmonary disease patients: helmet versus facial mask. *Intensive Care Med* 2007;33:74-81.
 18. Vaschetto R, De Jong A, Conseil M, et al. Comparative evaluation of three interfaces for non-invasive ventilation: a randomized cross-over design physiologic study on healthy volunteers. *Crit Care* 2014;18:R2.
 19. Olivieri C, Longhini F, Cena T, et al. New versus Conventional Helmet for Delivering Noninvasive Ventilation: A Physiologic, Crossover Randomized Study in Critically Ill Patients. *Anesthesiology* 2016;124:101-8.
 20. Pisani L, Mega C, Vaschetto R, et al. Oronasal mask versus helmet in acute hypercapnic respiratory failure. *Eur Respir J* 2015;45:691-9.

Cite this article as: Longhini F, Abdalla K, Navalesi P. Non-invasive ventilation in hypoxemic patients: does the interface make a difference? *Ann Transl Med* 2016;4(18):359. doi: 10.21037/atm.2016.09.20