Editorial

High flow on the rise—pediatric perspectives on the FLORALI trial

Christophe Milési[1], Julien Baleine[1], Julia le Bouhellec[1], Marti Pons-Odena[2], Gilles Cambonie[1]

[1]Pediatric Intensive Care Unit, Hôpital Arnaud de Villeneuve, CHU Montpellier, F-34000, France; [2]Unidad de Cuidados Intensivos Pediatricos, Hospital Universitario Sant Joan de Deu, Universitat de Barcelona, Esplugues de Llobregat, Barcelona, Spain

Correspondence to: Christophe Milési, MD. Unité de Réanimation Pédiatrique, Hôpital Arnaud de Villeneuve, CHU de Montpellier, 371 Avenue du Doyen G. Giraud, 34295 Montpellier Cedex 5, France. Email: c-milesi@chu-montpellier.fr.

Submitted Jul 24, 2015. Accepted for publication Jul 30, 2015.
doi: 10.3978/j.issn.2072-1439.2015.07.40
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.07.40

Over the last decade, noninvasive positive pressure ventilation (NIV) has been increasingly used in adult and pediatric medicine to reduce the lung injuries, pneumonia, and denutrition associated with mechanical ventilation, which is implicated in the high mortality observed in these patients (1). For adults with acute exacerbations of chronic obstructive pulmonary disease (2) or severe cardiogenic pulmonary edema (3), it is now an evidence-based practice. It may also be an effective strategy in the perioperative period, provided that patients are carefully selected (4). The benefits of NIV have nevertheless not been clearly established in clinical situations like status asthmaticus (5) or acute hypoxemic respiratory failure (AHRF) or as a means to facilitate earlier extubation (6). The conflicting results for ARHF may be due to its several etiologies, which has prompted new trials with less heterogeneous patient groups (7).

FLORALI was a multicenter open-label trial performed in 23 French and Belgian ICUs from the European network of research in artificial ventilation (8). This study examined whether high-flow oxygen therapy or NIV therapy would reduce the rate of endotracheal intubation and improve outcomes in patients with AHRF in comparison with standard oxygen alone. The study had many strengths: the very high number of ICUs and the carefully predefined criteria for inclusion and exclusion ensured the selection of a homogeneous group of 525 patients with PaO_2/FiO_2 <300 and no hypercapnia or chronic respiratory failure; a respectable 60% of the eligible patients were included and randomized into one of the three groups, suggesting that the results could be generalized to other ICUs; and the rigorously designed protocol and robust data analysis ensured very reliable clinical findings. The primary outcome of the study, intubation within 28 days of randomization, did not significantly differ between groups, although the range was from 28% with high-flow oxygen to 50% with NIV. However, post-hoc subgroup analysis of patients with the most severe hypoxemia, i.e., those with PaO_2/FiO_2 <200, revealed a lower intubation rate in the high-flow oxygen group than in the other two groups. A secondary outcome of particular importance, survival in the ICU and at 90 days, was improved with high-flow oxygen, with the hazards ratio for death at 90 days being 2.1 (range, 1.01-3.99) with standard oxygen and 2.5 (range, 1.31-4.98) with NIV versus high-flow oxygen. The number of ventilator-free days between day 1 and day 28 was higher in the high-flow oxygen group than in the other two, in the overall population and in the patients with the most severe AHRF.

A recent survey in North America and Europe estimated that AHRF prevalence in pediatric intensive care units (PICUs) is 10.8% (9). The use of NIV in children with AHRF has increased over the last decade, and this respiratory assistance is now considered as the first-line treatment in 15-20% of patients (10,11). Physiological studies have demonstrated that NIV is able to unload the respiratory muscles and improve alveolar ventilation and gas exchange in children with acute moderate hypercapnic respiratory insufficiency (12). However, data supporting the usefulness of NIV remain scarce. No trial involving the collaboration of a large number of centers, as for the FLORALI study, has been conducted in pediatrics to assess the clinical management of acute lung injury. Only one bicentric randomized controlled trial (RCT) compared NIV with bilevel positive airway pressure to standard treatment, i.e., mask oxygen, in 50 young infants admitted to a PICU for AHRF (13). As in FLORALI, pneumonia was the main condition precipitating respiratory failure, and most patients

suffered from severely impaired oxygenation with baseline mean PaO_2/FiO_2 <200 in both groups. NIV improved oxygenation, reduced respiratory effort and diminished the need for intubation by 47%. Another more recent RCT showed that bilevel NIV improved clinical scores and physiological measurements, but this study involved only children with status asthmaticus (14). In the context of moderately severe acute viral bronchiolitis, two randomized trials found short-term improvements in respiratory distress signs, blood gases and respiratory muscle load in infants receiving continuous positive airway pressure (CPAP) versus conventional oxygen therapy (15,16). Conversely, numerous retrospective or prospective pediatric observational studies have repeatedly reported the association between AHRF and NIV failure, with intubation rates of 50-80% (11,17-19) in acute respiratory distress syndrome (ARDS). Several early predictors of subsequent intubation have been identified, particularly SpO_2/FiO_2 (19), FiO_2 (20), pH (21), and respiratory or heart rate (17,22) evolution in the 1-6 hours following NIV initiation. A recent Pediatric Acute Lung Injury Conference Consensus stated that NIV should not be indicated in severe pediatric ARDS (23). If initiated, a close monitoring is essential to recognize the early signs of failure which indicate prompt recourse to invasive ventilation (19).

The particularly disappointing performance of NIV in the FLORALI study—a failure rate of nearly 60% in the most severe subgroup—will certainly not prompt a change in this recommendation. Two remarks can nevertheless be made about NIV management. First, in the FLORALI study NIV was used for approximately 8 hours on the first 2 days, whereas it is currently used 24 hours per day in children with moderate-severe hypoxemic failure. It can be argued that derecruitment due to intermittent NIV could be deleterious and may increase the work of breathing of the NIV group, ultimately worsening the outcome. Second, the patients experienced no improvement in respiratory comfort following NIV initiation. Discomfort is also commonly observed in the practice of NIV in children. Agitation may occur, particularly during the initial placement of the mask, but this poor tolerance rarely forces to discontinuation (24). A few studies have demonstrated the role of discomfort in NIV failure and assessed the optimal pharmacological support to provide in this context. A recent prospective, observational, multicenter study that included 390 episodes of NIV found that sedatives were used in 49.2% of cases (19). Discomfort may have multiple origins, including gastric distension, skin breakdown caused by the mask, and conjunctivitis due to air leaks (23). Another very common source of patient's discomfort is patient-ventilator asynchrony, particularly frequent in infants and in children during NIV with pressure support (25). Three recent studies indicated that neurally adjusted ventilatory assist (NAVA) mode during NIV improved the patient-ventilator interaction (25-27). Further trials are required to assess whether NIV specific ventilators with automatic triggers and/or neural trigger of NIV NAVA are more comfortable and efficient than NIV done with conventional ventilators in pediatric AHRF.

The most striking finding from FLORALI was the consistent results in favor of oxygen delivery through high-flow nasal cannula (HFNC). This finding was particularly surprising because HFNC did not seem to provide greater respiratory support compared with NIV (28). In pediatrics, as well, there is currently strong agreement that HFNC has not been shown to be as effective as NIV (23). In addition, the pathophysiological mechanisms involved in alleviating respiratory distress have not been fully demonstrated with this device. Yet despite these considerations, HFNC use is rising in popularity because the system is easily set up and is well tolerated by patients. The heated and humidified mixture of air and oxygen is administered at a flow generally close to 2 L/kg/min in infants and 1 L/kg/min in children (29). As suggested by the self-report dyspnea and comfort scales in FLORALI, the gas mixture conditioning may rapidly improve inspiratory flow and reduce the sensation of respiratory distress. In a physiological study, we demonstrated that a nasal cannula with a flow rate equal to or above 2 L/kg/min was able to generate a CPAP $\geq$4 cmH_2O in infants with acute viral bronchiolitis (30). Although modest, this increase was clinically relevant, with an approximately 50% reduction in respiratory effort and rapid improvement in breathing pattern and respiratory distress signs. Measurements of diaphragmatic electrical activity and esophageal pressure swings confirmed the effectiveness of this device to reduce the work of breathing (31). In this disease, it is likely that HFNC mainly offsets the patient's inspiratory effort to overcome intrinsic end-expiratory pressure, thereby decreasing the dynamic collapse of the very compliant airways at this young age. The favorable effect of this technique on the ventilation/perfusion ratio, however, has not been clearly established. A theoretical explanation is that washout of nasopharyngeal dead space increases the rate of minute ventilation that participates in gas exchange (28). On a practical level, the FLORALI results suggest that HFNC is superior to the other strategies in cases of AHRF because it is able

to match patient inspiratory demands. Several RCTs with HFNC are currently underway in neonates, children and adults to examine these important issues. We coordinated a multicenter, randomized, noninferiority trial during the 2014-2015 respiratory syncytial virus (RSV) epidemic season (TRAMONTANE study, NCT02457013). One hundred and forty-two infants were assigned to treatment with either HFNC (2 L/kg/min) or nasal CPAP (7 cm of water). The primary outcome was treatment failure within 24 hours. Two other RCTs, conducted in the British Columbia Children's Hospital (Hi-Flo study, NCT01498094) and the Children's Hospitals and Clinics of Minnesota (HHFNC study, NCT01662544), compared length of hospital stay and respiratory distress score with HFNC as opposed to standard therapy for RSV bronchiolitis. These trials are now completed and should provide clinicians with evidence on HFNC efficacy for treating this leading cause of AHRF in pediatrics. Meanwhile specific research is conducted in pediatrics for severe hypoxemic patients, a cautious use of both HFNC and NIV should be recommended.

Acknowledgements

We thank the nursing staff of the pediatric intensive care unit of Arnaud de Villeneuve University Hospital for their patience and cooperation. We thank C. Stott-Carmeni for translating the manuscript and for editorial assistance.

Footnote

Provenance: This is a Guest Editorial commissioned by the Section Editor Wan-Jie Gu (Department of Anesthesiology, Affiliated Drum Tower Hospital, Medical College of Nanjing University, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Esteban A, Frutos-Vivar F, Muriel A, et al. Evolution of mortality over time in patients receiving mechanical ventilation. Am J Respir Crit Care Med 2013;188:220-30.
2. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. Chest 2008;133:756-66.
3. 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.
4. Pelosi P, Jaber S. Noninvasive respiratory support in the perioperative period. Curr Opin Anaesthesiol 2010;23:233-8.
5. Lim WJ, Mohammed Akram R, Carson KV, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. Cochrane Database Syst Rev 2012;12:CD004360.
6. Cabrini L, Landoni G, Oriani A, et al. Noninvasive ventilation and survival in acute care settings: a comprehensive systematic review and metaanalysis of randomized controlled trials. Crit Care Med 2015;43:880-8.
7. AlYami MA, AlAhmari MD, Alotaibi H, et al. Evaluation of efficacy of non-invasive ventilation in Non-COPD and non-trauma patients with acute hypoxemic respiratory failure: A systematic review and meta-analysis. Ann Thorac Med 2015;10:16-24.
8. 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.
9. Santschi M, Jouvet P, Leclerc F, et al. Acute lung injury in children: therapeutic practice and feasibility of international clinical trials. Pediatr Crit Care Med 2010;11:681-9.
10. Farias JA, Fernández A, Monteverde E, et al. Mechanical ventilation in pediatric intensive care units during the season for acute lower respiratory infection: a multicenter study. Pediatr Crit Care Med 2012;13:158-64.
11. Wolfler A, Calderini E, Iannella E, et al. Evolution of Noninvasive Mechanical Ventilation Use: A Cohort Study Among Italian PICUs. Pediatr Crit Care Med 2015;16:418-27.
12. Essouri S, Durand P, Chevret L, et al. Physiological effects of noninvasive positive ventilation during acute moderate hypercapnic respiratory insufficiency in children. Intensive Care Med 2008;34:2248-55.
13. Yañez LJ, Yunge M, Emilfork M, et al. A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med 2008;9:484-9.
14. Basnet S, Mander G, Andoh J, et al. Safety, efficacy, and tolerability of early initiation of noninvasive positive pressure ventilation in pediatric patients admitted with status asthmaticus: a pilot study. Pediatr Crit Care Med 2012;13:393-8.
15. Thia LP, McKenzie SA, Blyth TP, et al. Randomised controlled trial of nasal continuous positive airways pressure (CPAP) in bronchiolitis. Arch Dis Child

2008;93:45-7.
16. Milési C, Matecki S, Jaber S, et al. 6 cmH2O continuous positive airway pressure versus conventional oxygen therapy in severe viral bronchiolitis: a randomized trial. Pediatr Pulmonol 2013;48:45-51.
17. Essouri S, Chevret L, Durand P, et al. Noninvasive positive pressure ventilation: five years of experience in a pediatric intensive care unit. Pediatr Crit Care Med 2006;7:329-34.
18. Muñoz-Bonet JI, Flor-Macián EM, Brines J, et al. Predictive factors for the outcome of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med 2010;11:675-80.
19. Mayordomo-Colunga J, Pons M, López Y, et al. Predicting non-invasive ventilation failure in children from the SpO_2/FiO_2 (SF) ratio. Intensive Care Med 2013;39:1095-103.
20. Bernet V, Hug MI, Frey B. Predictive factors for the success of noninvasive mask ventilation in infants and children with acute respiratory failure. Pediatr Crit Care Med 2005;6:660-4.
21. Dohna-Schwake C, Stehling F, Tschiedel E, et al. Non-invasive ventilation on a pediatric intensive care unit: feasibility, efficacy, and predictors of success. Pediatr Pulmonol 2011;46:1114-20.
22. Mayordomo-Colunga J, Medina A, Rey C, et al. Predictive factors of non invasive ventilation failure in critically ill children: a prospective epidemiological study. Intensive Care Med 2009;35:527-36.
23. Essouri S, Carroll C, Pediatric Acute Lung Injury Consensus Conference Group. Noninvasive Support and Ventilation for Pediatric Acute Respiratory Distress Syndrome: Proceedings From the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16:S102-S110.
24. Abadesso C, Nunes P, Silvestre C, et al. Non-invasive ventilation in acute respiratory failure in children. Pediatr Rep 2012;4:e16.
25. Vignaux L, Grazioli S, Piquilloud L, et al. Patient-ventilator asynchrony during noninvasive pressure support ventilation and neurally adjusted ventilatory assist in infants and children. Pediatr Crit Care Med 2013;14:e357-64.
26. Baudin F, Pouyau R, Cour-Andlauer F, et al. Neurally adjusted ventilator assist (NAVA) reduces asynchrony during non-invasive ventilation for severe bronchiolitis. Pediatr Pulmonol 2014. [Epub ahead of print].
27. Ducharme-Crevier L, Beck J, Essouri S, et al. Neurally adjusted ventilatory assist (NAVA) allows patient-ventilator synchrony during pediatric noninvasive ventilation: a crossover physiological study. Crit Care 2015;19:44.
28. Lee JH, Rehder KJ, Williford L, et al. Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. Intensive Care Med 2013;39:247-57.
29. Milési C, Boubal M, Jacquot A, et al. High-flow nasal cannula: recommendations for daily practice in pediatrics. Ann Intensive Care 2014;4:29.
30. Milési C, Baleine J, Matecki S, et al. Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study. Intensive Care Med 2013;39:1088-94.
31. Pham TM, O'Malley L, Mayfield S, et al. The effect of high flow nasal cannula therapy on the work of breathing in infants with bronchiolitis. Pediatr Pulmonol 2015;50:713-20.

Cite this article as: Milési C, Baleine J, le Bouhellec J, Pons-Odena M, Cambonie G. High flow on the rise—pediatric perspectives on the FLORALI trial. J Thorac Dis 2015;7(8):E230-E233. doi: 10.3978/j.issn.2072-1439.2015.07.40

