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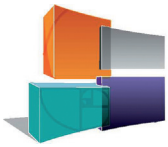

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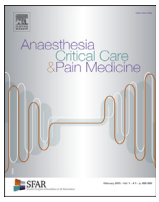

Editorial

Non-invasive ventilation and high-flow nasal oxygenation: Looking beyond extubation failure?

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Arnaud Thille, Jean-Pierre Frat and colleagues, one of the most active French groups in the field of non-invasive ventilation (NIV) and high-flow nasal oxygenation (HFNO), have recently published in the *Journal of the American Medical Association* the results of a new randomised controlled trial [1]. The trial focused on patients with high-risk post-extubation failure, defined as patients older than 65 years or those with underlying chronic cardiac or pulmonary diseases; a large and easy to identify population encountered in all intensive care units (ICU) world wide. Their Spanish counterparts, Gonzalo Hernández et al., have already shown that in this population, HFNO was non-inferior to NIV to reduce extubation failure [2]. The hypothesis was that NIV and HFNO might have an additive or synergistic effect; the same background they have used for the Florali trial [3]. After inclusion of 646 patients in 30 ICU in France, [4] the trial shown that NIV + HFNO was superior to HFNO alone to decrease the rate of reintubation at day 7, from 18.2% *vs.* 11.8%. The proportion of patients with post-extubation respiratory failure at day 7 (21% *vs.* 29%; $P = .01$) and reintubation rates up to ICU discharge (12% *vs.* 20% $P = 009$) were also decreased using NIV + HFNO.

The study is of undeniable interest for clinicians, especially owing to the level of evidence that determines the current recommendation to use NIV to prevent post-extubation respiratory failure in high-risk patients after extubation. Thus, despite being less convenient than using only HFNO for many ICU teams, it appears that the combination of NIV and HFNO provides the best support for patients at higher risk of reintubation. Physicians must be ready to treat high-risk patients with NIV and HFNO, and more particularly, probably among others, those with hypercapnia at the end of the spontaneous breathing trial (SBT). Despite a greater effect on hypercapnic patients, this trial, which is the largest ever published in this field, shows no difference in primary outcome between hypercapnic and non-hypercapnic patients on a multivariate analysis, meaning that unlike the results of other studies, these ones are not biased, or at least explained, by COPD patients [5].

NIV was used to prevent reintubation in high-risk patients, but also to treat acute respiratory failure when prevention had failed. Twenty-one per cent of randomised patients in the NIV + HFNO group presented acute respiratory failure and, surprisingly, half of them were not reintubated. Current guidelines, based on the results of randomised control trials, recommend not using NIV to treat respiratory failure post-extubation [6]. These guidelines also recommended not using NIV for non-hypercapnic respiratory failure excepted for surgical patients [7]. It is clear that the published data are not questionable, but there is a huge gap between data, the state of the art in general and physicians' beliefs. The 30% crossover in the HFNO group using NIV to cure acute respiratory failure is probably evidence of these beliefs, which are based on physiological background, while guidelines are supported by the paper of Esteban [8] on extubation failure and that of Jean-Pierre Frat for de novo acute respiratory failure [3]. However, in this trial, physicians were right; first, NIV + HFNO did not increased mortality, on the contrary, it decreased reintubation rate in patients with acute respiratory failure *versus* HFNO, which is the gold standard in this indication.

What has changed during the last 10-15 years, what are the lessons learned? Ending NIV, i.e. the decision of tracheal intubation followed by invasive ventilation, is much more difficult to take than NIV initiation. Objective criteria are needed for (re)intubation to avoid delayed intubation in clinical trials and at bedside for daily practice. In the trial by Esteban [8], comparing NIV and standard oxygen in patients with post-extubation respiratory failure, the mortality was 14% in the control group *versus* 25% for patients treated by NIV. The median time of reintubation was 2 hours in the control group *versus* 12 hours in the NIV group. The indication of reintubation was at physician discretion and just "recorded". Therefore, delaying tracheal intubation in patients with non-resolving respiratory failure increases patient mortality.

Ten years later, in the trial by the group of Thille, [3] comparing HFNO, oxygen and NIV + HFNO in de novo non-hypercapnic respiratory failure, the criteria for intubation were fixed a priori and physicians were "helped" with an algorithm deciding whether to intubate patients with non-resolving respiratory failure. Mortality was still higher in the NIV group even if time of

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intubation was nine hours in the three arms. Two reasons may be advocate. First, tidal volume was 9 ml/kg of predicted body weight, which is probably too high. Second, the upper limit of respiratory rate was 40 breaths by minute *versus* 35 in the present study. Despite a light difference, a surrogate of respiratory drive can be interpreted as the trigger of patient self-inflicted lung injury (P-SILI). During spontaneous breathing, airway pressure (plateau pressure) is lower than during controlled mechanical ventilation. If one focuses on transpulmonary pressure, the real pressure in the alveolus, computed as the difference between plateau pressure and pleural pressure, this assertion is no longer correct. In spontaneously breathing patients, the major determinant of pleural pressure is the inspiratory effort. As respiratory drive is increased during acute respiratory failure, transpulmonary pressure could be dramatically high, thus generating lung injury with a normal and apparently safe plateau pressure, P-SILI. In addition, the increase in transmural pulmonary vascular pressure swings caused by inspiratory effort may worsen vascular leakage. This new concept explains why, even with low pressure and without delaying intubation, hypoxemia or hypercarbia NIV may worsen patient outcomes. Recently, a comprehensive scale including heart rate, acidosis, consciousness, oxygenation and respiratory rate (the HACOR Scale) after one hour of treatment, has been shown to predict NIV failure in a prospective cohort of 450 patients with a specificity of 90% and sensitivity 72% [9]. In this cohort, early intubation improved hospital mortality among patients with a HACOR > 5. Is it the result of avoiding P-SILI? As this is a retrospective analysis, this question cannot be answered. Anyhow, this is one more argument to focus on the ending of NIV in patients with a non-resolutive respiratory failure. Should all patients with high respiratory drive be intubated? It is not sure, but in any case, the balance between the risk of P-SILI and the adverse events of invasive ventilation with sedative must be evaluated carefully at bedside for each patient. The same approach should be used with HFNO. The ROX index, defined as $Fi0_2/Sp0_2/RR$, has just been published and seems sensitive enough to detect, two hours after the initiation of HFNO, patients who will have a successful experience from the others [9]. In both cases, the control of respiratory rate is a major factor of success of non-invasive respiratory support, NIV and HFNO.

Then how should the results of this trial, and this discussion, be incorporated into clinical practice? This could be an opportunity to merge physician beliefs and scientific data. Yes, it does make sense to use positive pressure in post-extubation respiratory failure patients and moreover, it decreases reintubation rate. Notwithstanding, this must be carried out only under the conditions used in this trial, with patients comparable to those included in this trial. The major issue is that each ICU willing to use NIV in high-risk and post-extubation respiratory failure patients must have a written algorithm with the criteria of intubation, and physicians should follow them. Should NIV + HFNO be used for de novo respiratory failure? Obviously not, but the results of this trial represent one more step in the construction of the next trial. This trial will assess the role of NIV + HFNO in de novo respiratory failure, to validate if 20 years of research on NIV have been able to apply the concept in clinical practice. In the meantime, NIV should be used with caution. Non-invasive ventilation is not a "lite ventilation"; some patients may be saved by positive pressure, but others do not survive due to NIV misuse. In between are ICU physicians, who will continue or abort non-invasive ventilatory support.

Disclosure of interests

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The other authors declare that they have no competing interest.

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