

## **A randomized trial study: HFO with NIMV compared with HFO alone in adult patients affected by acute hypoxemic respiratory failure due to pneumonia.**

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### **Introduction**

This work is an open-label randomized controlled trial; our purpose is to investigate the efficacy of alternating Non Invasive Mechanical Ventilation (NIMV) and High Flow Oxygen (HFO) compared to HFO alone on gas exchange and prognosis in pneumonia-associated acute hypoxemic respiratory failure. Both NIMV and HFO through nasal cannula are widely used in the setting of acute hypoxemic respiratory failure of heterogeneous etiology. HFO is a broadly approved method for treatment hypoxia in paediatrics and neonatal Intensive Care Unit since a lot of years, because of its high comfort and feasibility; recent literature had produced a lot of works about that technique even in adult care; one of the first and more important work was FLORALI study by Frat et al., [1] that compared HFO with NIMV and conventional oxygen treatment (COT) in adult patients affected by acute hypoxemic respiratory failure due to pneumonia (CAP and HAP) and demonstrated, in a post-hoc analysis, a less orotracheal intubation rate in HFO group in severe ARF patients ( $\text{PaO}_2/\text{FiO}_2 < 200$ ). Starting from this study, there are a lot of reviews and works about comparison of these methods, but with no definitive evidence for the superiority of one technique on the other; in particular, a lot of studies include patients affected by hypoxemic acute respiratory failure from heterogeneous etiologies, i.e. acute pulmonary oedema, ARDS, post-surgery etc [2-4].

The aim of our trial is to determine whether alternating NIV and HFO brings any advantage on gas exchanges and prognosis compared to the use of HFO alone in the homogeneous setting of pneumonia-associated acute hypoxemic respiratory failure. We enrolled adult patients affected by community-acquired pneumonia (CAP) or health-care acquired pneumonia (HAP) with moderate to severe acute hypoxemic respiratory failure ( $\text{PaO}_2/\text{FiO}_2 \leq 300$ ) after at least 15 minutes conventional oxygen therapy with a  $\text{FiO}_2 \geq 50\%$ , clinical signs of respiratory distress (respiratory rate  $\geq 25$ , use of accessory muscles) and informed consent to study participation. We excluded paediatric patients, acute hypercapnic respiratory failure ( $\text{PaCO}_2 \geq 60$  mmHg) patients or those with other causes of hypoxia (i.e. pulmonary

embolism, acute pulmonary oedema), patients with orotracheal tube indication (i.e. GCS  $< 8$ , respiratory arrest, agitation) or tracheostomy tube owners, hemodynamic instability with necessity for use of inotropes and/or vasopressors, patients with a DNR (do not resuscitation) or DNI (do not intubate) indication, acquired immunodeficiency and patients using domestic CPAP. Patients admitted to the study were randomized in two different groups; the first one was treated with HFO continuously, the second one alternated HFO with NIMV with 3 hours each. Both of groups continued therapy for 48 hours. We programmed mandatory controls of gas exchange, vital signs and laboratory tests at beginning, 1 hour, 21 hours and 45 hours, and optional measures can be taken at 3 and 9 hours. Our primary outcome is efficacy of alternating NIV and HFO compared to HFO alone in the determination of an improvement of  $\text{PaO}_2/\text{FiO}_2$  at 21 hours compared to baseline  $\text{PaO}_2/\text{FiO}_2$ . Secondary outcomes are: rate of admission to Intensive Care Unit in the two arms during the study and at 30 days from beginning, subjective sensation of device comfort and dyspnoea during treatment, time to downgrade to conventional oxygen therapy (calculated in total hours of using a device), in-hospital mortality and mortality at 30 days, new hospital admission within 30 days.

We planned 2 years of investigation, starting in November 2017 till November 2019. The principal investigator is Emergency Department of Niguarda Hospital (Milan, Italy) with a collaboration of Emergency Department of San Carlo Borromeo Hospital (Milan) from February 2019. We performed also an intermediate analysis in June 2018. We collected a CRF for each patient and summarized data in an Excel database; analysis was performed following an intention to treat principle, describing data using mean value, median, standard deviation, and quartile. We performed also Wilcoxon non-parametric test and Fisher test. This preliminary analysis includes 28 patients; one was excluded after informed consent because of using nocturnal domiciliary CPAP. Among the remaining 27 patients, 13 were enrolled in HFO arm and 14 in NIMV/HFO. In the HFO group, 9 patients completed the study with this method, 1 patient underwent mechanical ventilation and survived at 30 days, 3 patients failed and shift in NIMV arm, one of which died in hospital. In NIMV arm, 3 patients

underwent mechanical ventilation, and one of which died in hospital, 3 dropped out to HFO; 9 patients completed 48 hours treatment with NIMV, 3 of which died (2 patients in hospital and 1 at 30 days). We analysed differences in the two group in  $\text{PaO}_2$  and  $\text{PaO}_2/\text{FiO}_2$  (Figures 1 and 2); at 1 hour ( $T_1$ ) both variables were significantly better in NIMV group to the other (median  $\text{PaO}_2$  77.8 and median P/F 210), whereas at 21 hours ( $T_{21}$ ) those values were almost the same. We also performed a comparison between absolute (A) and relative (R) differences of those two values ( $\Delta\text{PaO}_2$  and  $\Delta\text{P/F}$ ) in the two intervals ( $T_0$ - $T_1$  and  $T_0$ - $T_{21}$ ), using Wilcoxon test. We observed a significant difference in  $T_0$ - $T_1$  interval (both  $\Delta\text{APaO}_2$  and  $\Delta\text{RPaO}_2$ ) in NIMV group on the other. We interpreted these results as better performance of NIMV in the acute phase, because of higher positive airway pressure, whereas better outcome of HFO in long term because of its high comfortability with less interruption of therapy. Numbers of fails and drop-out were the same; the firsts happened because of respiratory distress and need of high pressure support, the second because of intolerance (masks, claustrophobia, facial lesions). No differences were observed in weaning time in the two groups. Even for mortality (7.69% in HFO vs 28.6% in NIMV) we didn't conclude for significant differences, because of paucity of the sample. Oro-tracheal intubation was globally 14.8% at mean time 8h from hospitalisation.

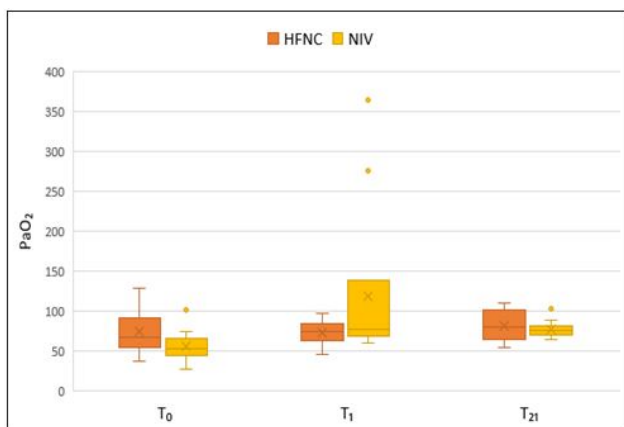


Figure 1.  $\text{PaO}_2$  in the two arms.

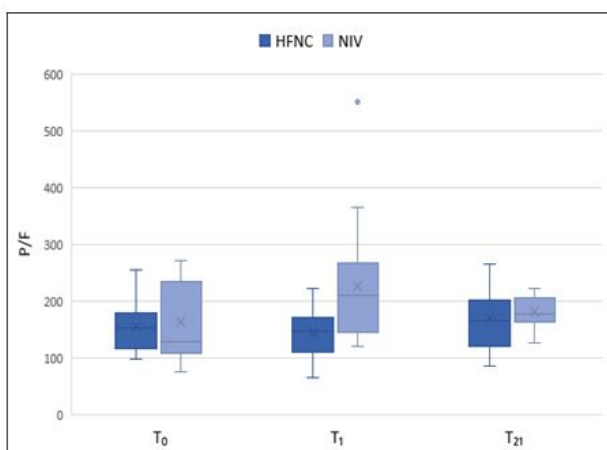


Figure 2.  $\text{PaO}_2/\text{FiO}_2$  in the two arms.

## Conclusion

Intermediate data analysis demonstrate a substantially superiority of NIMV to HFO at 1 hour from hospitalisation in term of oxygenation; whereas better tolerance of HFO to NIMV, which can lead to a more constant treatment, can explain better results in long term and comparable gas exchange at 21 hours. HFO is an applicable device in patients with pneumonia, although need of a high clinical monitoring for non-responsive patients who could beneficiate from mechanical ventilation in the firsts hours. We didn't find any difference in term of mortality and oro-tracheal intubation. Our results, even if preliminary, seem comparable to literature. Our principal limit is paucity of sample; we hope for a stronger conclusion at the end of the study.

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