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Master thesis | Original study

Does High Flow Nasal Cannula avoid intubation and improve the mortality of adult patients in acute respiratory failure in the intensive care setting, when compared to others methods as Conventional Oxygen Therapy or Non-Invasive Ventilation? A narrative review

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Abstract

High-flow oxygen therapy via nasal cannula (HFNC) has been used for many years to oxygenate patients in respiratory failure. However, scientific data in literature are divergent about its value to prevent invasive mechanical ventilation and mortality. The use of HFNC has increased following the COVID-19 pandemic. Our review considers the impact of HFNC on intubation rates and mortality compared with conventional oxygen therapy (COT) and noninvasive ventilation (NIV). HFNC would decrease the use of invasive mechanical ventilation compared to COT and would be equivalent to NIV. Combination of NIV and HFNC would have a benefit compared to NIV alone. Some etiologies of respiratory failure would benefit more from this technique as post-extubation critical ill patient or COVID-19 pneumonia. HFNC seems to reduce mortality in COVID-19 patients compared to NIV.
Several clinical studies are needed to refine the indications of this technique.

Keywords: **High flow nasal cannula, oxygen therapy, acute respiratory failure, non-invasive ventilation, intensive care unit.**

Introduction

Ventilatory support is the treatment of acute respiratory failure (ARF) to maintain suitable alveolar ventilation to provide oxygenation and carbon dioxide withdrawal (CO_2).

Different oxygenation procedures are available, among them Conventional Oxygen Therapy

(COT), High Flow oxygen therapy via Nasal Cannula (HFNC), Non-Invasive Ventilation (NIV), and invasive mechanical ventilation. HFNC appears to be a therapeutic substitute between invasive mechanical ventilation and COT. HFNC, which first appeared in the 2000's, has aroused a lot of interest in intensive care medicine. Indeed, HFNC is a less invasive therapy compared with mechanical ventilation[1].

In the current context of the SARS-CoV-2 pandemic, patients admissions for acute respiratory failure has significantly increased in intensive care units (ICU). Before the pandemic, many studies have been carried out on HFNC without allowing toreach consensus. Moreover, a 2016 review published in Acta Anaesthesiologica Belgica underlined the lack of evidence on safety and efficiency on some parts of the subject, especially on the subgroup that would benefit most from this technique[2].

As a consequence of that increased use of HFNC, the aim of this review is to determine whether the HFNC can avoid intubation and improve the mortality of adult patients in acute respiratory failure in the intensive care setting, when compared to others methods as COT or NIV.

This masterthesis was defended orally during the presentation of the master's work at the Catholic University of Louvain in Bruxelles.

Methods

Syntax

We performed a narrative review according to the Scale for the Assessment of Narrative Review Articles (SANRA)[3]. The research syntax was developed with the help of a methodologist and a librarian from the Université de Reims Champagne-Ardenne (URCA). Research was performed using the Medline database with the following syntax: (((((“high flow nasal”) OR (“nasal high flow”)) NOT (case reports[pt])) NOT (child*[Title])) NOT (pediatri*[Title])) NOT (neonat*[Title]).

Selection criteria

The research period spread across the last ten years, from 2012 to 2022. The language required was English or French.

We obtained 1878 results. Among them, 1800 articles were excluded. Reasons for exclusion are presented in the flowchart, fig. 1.

After analysis of the full manuscript of these articles, we have selected 78 articles to answer the Research question: 34 original studies and 44 systematic reviews.

Results

We selected a large sample of original studies and systematic reviews to answer our research question. Only the most relevant articles according to us are mentioned in this review.

However, the results of all included studies are summarized in the Table I.

Acute Respiratory Failure

Clinical studies investigating the risk of intubation compared to conventional oxygenation and non-invasive ventilation have shown diverging results. In 2015, Frat et al conducted a multicenter randomized study of 310 patients with isolated hypoxemic acute respiratory failure comparing HFNC to NIV or COT. No significant difference in the risk of intubation in the overall population had been showed, but the study demonstrated a lack of power. However, 90-day mortality was lower in HFNC group compared to the two other groups.4 Subgroup analyses according to the PaO2/FiO_2 ratio <200 mmHg at inclusion showed a lower risk of intubation in the HFNC group compared to the two other groups[4].Recently, the lesser rate of intubation in case of severe respiratory failure (P/F<200 mmHg) with HFNC compared to COT (NNT=3) was also demonstrated by a Randomized Controlled Trial (RCT) (46 patients) without improvement of survival at Day-90[5]. By contrast, NIV via helmet seemed to be more effective than HFNC in preventing intubation of patients in ARF (P/F <200 mmHg, PaCO2 <45 mmHg) and decreased the duration of invasive ventilation. Tolerance of patients with this support was superior to face mask and this device allowed prolonged treatment with a high level of positive end-expiratory pressure.6 However, it did not show a significant difference in mortality[6]. Two retrospective studies looking into mortality of patients treated with HFNC or NIV had divergent results. The first study examined different etiologies of ARF in 578 patients. HFNC had a higher traitement failure for cardiogenic pulmonary edema with no difference in mortality. However, HFNC decreased 30-day mortality compared with NIV in cases of non-hypercapnic ARF or pneumonia[7]. Conversely, the second study, including more than 30.000 patients showed a mortality increase for intubated patients who received HFNC as a first line of treatment compared to those initially

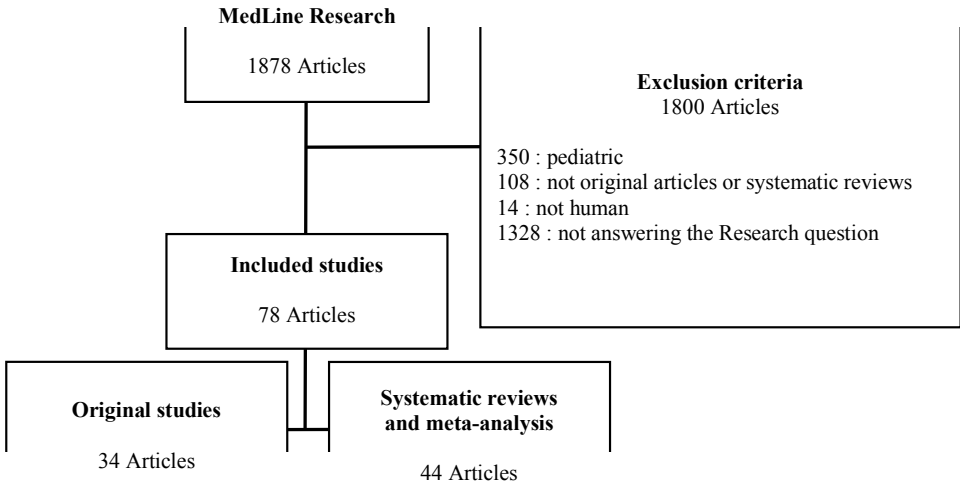

Fig. 1 — Flow chart.

Table I. — Results of the analyzed studies.

Authors year	Patients/ studies	Conclusion
Acute respiratory failure (except post-extubation/ immunocompromised/covid-19)		
Azevedo[58] 2015	30	RCT pilot study No significant difference in intubation rate HFNC vs NIV
Frat[4] 2015	310	RCT No significant difference in intubation rate but improved mortality for the HFNC group compared to the other two groups. Subgroup analysis showed a significantly lower intubation rate for the HFNC group compared to the other two groups in patients with P/F<200. After adjustment for pulmonary infiltrates, RR, pre-existing cardiac insufficiency, the risk of intubation is lower in HFNC group. Significant difference in mortality in favor of HFNC .
Kang[48] 2015	175	Retrospective observational study Intubation after or before 48 hours of HFNC Early intubation was better than late for ICU mortality.
Messika[59] 2015	607	Observational study No comparison with COT or NIV 40% Failure HFNC need intubation Additional organ dysfunction is associated with a higher HFNC failure rate.
Andino [5] 2020	46	RCT HFNC vs COT Significantly less intubation for HFNC No Significant difference in mortality.
Koga [7] 2020	578	Retrospective study HFNC vs NIV No significant difference in mortality at day 30 HFNC may decreased the mortality at day 30 in the case of pneumonia and nonhypercapnic respiratory failure.
Grieco [6] 2021	109	RCT Lower intubation rate for helmet NIV than HFNC. No significant difference in mortality
Miller [8] 2022	49853	Retrospective analysis In the case of subsequent intubation, mortality is higher in patients initially treated with HFNC than BiPAP.

Authors year	Patients/ studies	Conclusion
Acute respiratory failure (except post-extubation/ immunocompromised/covid-19)		
Xia[60] 2022	337	RCT HFNC vs COT Population COPD PaCO2> 45mmhg PH> 7,35. No significant difference in intubation rate. Only one patient death during hospitalization in the COT group. Mortality at day 90, no significant difference
Maitra [61] 2016	7	Systematic review and meta-analysis No information on intubation rate Only 2 RCT on mortality, no significant difference between HFNC vs COT and HFNC vs NIV.
Leeies [9] 2017	7	Systematic review and meta-analysis Intubation rate: COT+ NIVvs HFNC Mortality HFNC vs COT and HFNC vs NIV No significant difference for mortality or intubation rate. Subgroup analyze show a decrease in intubation rate for HFNC therapy > 24h vs COT.
Liesching [45] 2017	18	Systematic review and meta-analysis HFNC vs COT HFNC vs NIV No significant difference in intubation or reintubation rate compared to COT or NIV. Significant lower mortality HFNC vs NIV.
Lin[62] 2017	8	Systematic review and meta-analysis. Intubation HFNC vs COT or NIV Mortality HFNC vs NIV+ COT No significant difference in mortality in ICU and intubation rate.
Monro-Somerville [63] 2017	9	Systematic review and meta-analysis Compared to “usual care” (COT or NIV) No significant difference in mortality and intubation rate
Nedel [64] 2017	9	Systematic review and meta-analysis HFNC vs COT OR NIV No significant difference for mortality or intubation rate
Ni [25]	18	Systematic review and meta-analysis

Authors year	Patients/ studies	Conclusion
Acute respiratory failure (except post-extubation/ immunocompromised/covid-19)		
2017		HFNC vs COT or NIV HFNC reduce rate of intubation than COT No significant difference for the rate of intubation HFNC vs NIV. No significant difference in mortality HFNC vs COT or NIV.
Ou [10] 2017	6	Systematic review and meta-analysis HFNC vs COT or NIV HFNC decreased intubation rate vs COT No significant difference HFNC vs NIV for the intubation rate
Zhao[26] 2017	11	Systematic review and meta-analysis HFNC vs COT or NIV HFNC reduce the rate of intubation than COT especially use in post-extubation. No significant difference HFNC vs NIV for the intubation rate. No significant difference in mortality.
Zhu [11] 2017	4	Systematic review and meta-analysis HFNC vs COT HFNC > 24h may reduce intubation rate vs COT No significant difference for mortality
Bocchile [12] 2018	13	Systematic review and meta-analysis HFNC vs COT or NIV Reduction in intubation rate for HFNC vs COT. No significant result for mortality.
Leong [65]	5	Systematics review and meta-analysis NIV vs HFNC No significant difference for intubation rate. Conflicting mortality result due to very heterogeneous population.
Xu [27] 2018	18	Systematic review and meta-analysis HFNC vs COT or NIV Significant advantage for HFNC vs NIV to avoid intubation but not vs COT. No significant mortality difference.
Rochwerg [13] 2019	9	Systematic review and meta-analysis. HFNC vs COT HFNC decrease the need for tracheal intubation without impacting mortality

Authors year	Patients/ studies	Conclusion
Acute respiratory failure (except post-extubation/ immunocompromised/covid-19)		
Zayed [66] 2019	16	Systematic review and meta-analysis HFNC vs COT or NIV No significant difference between HFNC and COT or NIV for the tow outcomes. Excluded pulmonary oedema does not change result.
Ferreyro [67] 2020	25	Systematic review and network meta-analysis HFNC vs COT or Helmet NIV Lower mortality risk for helmet NIV vs HFNC. No significant difference for mortality between HFNC and face mask NIV or COT. Lower risk of intubation for HFNC vs COT but no significant difference between HFNC and facemask NIV.
Huang [68] 2020	8	Systematic review and meta-analysis HFNC vs NIV Hypercapnic population No significant difference in mortality and intubation rate No inferior for intubation rate. For improve mortality NIV seems more effective.
Baldomero [16] 2021	29	Meta-analysis for guideline American college of Physicians HFNC non difference in intubation or mortality vs COT (8 RCT) ; HFNC may reduce Intubation vs NIV (2 RCT), Reduction mortality HFNC vs NIV (1 RCT) Low certainty evidence
Liang [46] 2021	17	Systematic review and meta-analysis HFNC vs COT or NIV No significant difference for the reintubation rate, mortality 28days. Benefit of ICU survival compared to NIV but not compared COT.
Sakuraya [69] 2021	25	Systematic review and network meta-analysis ; HFNC vs COT No significant lower risk mortality or intubation rate for HFNC VS COT
Yasuda [15] 2021	27	Systematic review and network meta-analysis HFNC vs COT or NIV No significant difference for short-term mortality. Lower risk intubation for HFNC vs COT No difference between HFNC and NIV for intubation rate.
Xu [70] 2021	6	Meta-analysis and systematic review HFNC vs NIV

Authors year	Patients/ studies	Conclusion
Population COPD OR hypercapnic RF No significant difference in intubation rate and mortality (2/6 RCT on mortality)		
Oczkowski [17]	78	ERS guidelines HFNC vs COT: No significant difference mortality (short-term or 90 day) HFNC may reduce intubation. Moderate certainty HFNC vs NIV: HFNC may reduce mortality (very low certainty) and intubation (low certainty).
Okano [71] 2022	25	Systematic review and Network meta-analysis HFNC vs COT or NIV No significant difference in intubation rate and mortality.
Post-extubation		
Maggiore [53] 2014	105	RCT HFNC vs COT less reintubation at 48h post-extubation for the HFNC group
Stéphan [21] 2015	830	Randomized noninferiority trial HFNC vs NIV Population post-operative cardiothoracic surgery. No significant difference in intubation rate and ICU mortality
Hernandez [18] 2016	527	RCT multicenter HFNC vs COT Population at low risk for reintubation (authors definition) Significant reduction for the risk of 72h reintubation in HFNC group.
Hernandez [19] 2016	604	RCT multicenter HFNC vs NIV Population at high risk for reintubation (authors definition) HFNC noninferior to NIV for preventing reintubation.
YOO [72] 2016	73	Retrospective cohort analysis HFNC vs NIV No significant difference in reintubation rate and in ICU and hospital mortality.
Jing [73] 2019	42	RCT HFNC vs NIV Post-extubation COPD patients with hypercapnic respiratory failure No significant difference in 28-day mortality

Authors year	Patients/ studies	Conclusion
Post-extubation		
Thille [22] 2019	641	RCT Comparison HFNC vs HFNC + NIV Population high risk extubation failure Reduction reintubation risk HFNC + NIV compared HFNC alone No significant difference in ICU mortality No significant difference mortality in hospital, at day 28 and at day 90.
Cho [73] 2020	60	RCT HFNC vs COT High risk for reintubation population No significant difference for intubation rate and mortality.
Ko [75] 2020	327	Retrospective propensity score-matched cohort study. HFNC vs COT Population elderly (median 73years) high risk of reintubation No significant different in retubation rate No significant different in mortality
Tan[76] 2020	96	RCT Multicenter HFNC vs NIV Population: post-extubation COPD patients with hypercapnic respiratory failure No significant difference in reintubation rate and 28-day mortality.
CI [20] 2021	214	RCT HFNC vs NIV Significant benefice for HFNC vs NIV on intubation rate and mortality
Liu [77] 2021	801	Retrospective study HFNC vs NIV No significant difference in the 28-day reintubation or 28-day mortality 48hours reintubation rate lower HFNC.
Thille [23] 2021	150	Post hoc analysis of RCT HFNC + NIV vs HFNC COPD population Reintubation rate significant lower with NIV + HFNC than HFNC alone but no significant difference in mortality.

Authors year	Patients/ studies	Conclusion
Post-extubation		
Thille [24] 2021	146	Post hoc analysis of RCT NIV + HFNC vs HFNC Post-extubation failure population >1h to <7days after extubation. No significant difference in reintubation rate but less reintubation in the hypercapnic group vs no hypercapnic. No significant difference in mortality except for the subgroup hypercapnic who NIV + HFNC group had lower mortality rate.
Ni 78 2017	8	Systematic review and meta-analysis HFNC vs COT or NIV Significant difference For HFNC VS COT in the intubation rate but not in ICU mortality No significant difference between HFNC and NIV.
Zhao 79 2017	11	Systematic review and meta-analysis Sous group analysis HFNC vs COT HFNC reduce the rate of intubation than COT if it's use in post-extubation.
Huang [31] 2018	7	Systematic review and meta-analysis HFNC vs COT or NIV No significant difference in reintubation rate overall. Significantly decreased reintubation rate in critical ill patient in favor HFNC. No significant difference in post-operative.
Xu [80] 2018	18	Systematic review and meta-analysis HFNC vs COT or NIV HFNC significantly decrease intubation rate vs COT but not vs NIV (Only 2 trials/18 HFNC vs NIV)
Zhu [81] 2019	10	Systematic review and meta-analysis HFNC vs COT or NIV No significant difference for intubation rate and mortality.
Granton[28] 2020	8	Systematic review and meta-analysis HFNC vs COT or NIV HFNC decreased reintubation rate vs COT but no effect on mortality No effect on reintubation or mortality vs NIV
Sang [82] 2020	22	Systematic review and meta-analysis HFNC vs COT or NIV No significant difference in intubation rate and mortality

Authors year	Patients/ studies	Conclusion
Post-extubation		
Baldomero[16] 2021	3	Systematic review and meta-analysis for guideline from American college of physician. No significant difference in intubation rate and mortality HFNC vs NIV or COT low certainty evidence
Xiang [32] 2021	6	Systematic review and meta-analysis HFNC vs COT Post-operative patient at high-risk pulmonary complication. Intubation or NIV were analyzed with non-significant difference HFNC vs COT. Only one study evaluate mortality with no significant result.
Yasuda [29] 2021	15	Systematic review and network meta-analysis HFNC vs COT or NIV Lower reintubation risk in the HFNC group than COT group but not than NIV group. No reduction in short term mortality.
Fernando [30] 2022	36	Systematic and network meta-analysis HFNC vs COT or NIV Reduction intubation rate for HFNC compared to COT but not compared to NIV. No reduction in short-term mortality HFNC vs COT.
Oczkowski [17] 2022	78	ERS guidelines; Post-operative HFNC vs COT: No reduction mortality (moderate certainty), small reduction intubation (low certainty) HFNC vs NIV: increase mortality (low certainty), no difference reintubation (moderate certainty) Non-surgical patients HFNC vs COT: reduction intubation rate (moderate certainty), no effect on mortality (moderate certainty) HFNC vs NIV: increase rate of intubation (high certainty), increase mortality (moderate certainty)
Immuno-compromised		
Lemiale [83] 2015	100	RCT HFNC vs COT for 2 hours.

No significant difference between HFNC and COT for mechanical ventilation (NIV and IMV)		
Coudroy [47] 2016	115	Observational cohort study HFNC vs NIV Mortality at day 28 and intubation rate were lower in HFNC group Mortality patient who needed intubation is lower in the HFNC group than NIV.

Authors year	Patients/ studies	Conclusion
Post-extubation		
Frat [84] 2016	82	Post-hoc subgroup analysis from RCT HFNC vs COT and HFNC vs NIV Higher risk of intubation for NIV No significant difference HFNC vs COT Mortality for NIV group is higher than HFNC. No significant difference between HFNC and COT.
Azoulay[33] 2018	776	RCT HFNC vs COT Mortality at 28 days not significant different Intubation rate not significant different
Coudroy [56] 2022	299	RCT HFNC vs NIV + HFNC No significant difference in mortality
Sklar [38] 2018	13	Systematic review and meta-analysis HFNC vs COT or NIV Decreased mortality in HFNC group vs NIV. No significant difference in intubation rate.
Cheng [34] 2019	8	Systematic review and meta-analysis HFNC vs COT or NIV Lower intubation rate for HFNC vs COT or NIV No significant difference
Cortegiani[85] 2019	4	Systematic review and meta-analysis HFNC vs COT Reduction in intubation rate No significant difference for mortality
Kang [86] 2020	8	Systematic review and meta-analysis HFNC reduce intubation rate vs COT but not vs NIV. No significant difference in mortality
Zayed [37] 2020	9	Network meta-analysis HFNC vs COT or NIV No significant reduction of intubation rate No significant difference in mortality
Covid-19		
Bonnet [87] 2021	138	Retrospective study HFNC vs COT Lower rate of intubation for HFNC, propensity score does not change the results. No significant difference in mortality after propensity score.
Covid-ICU group[39] 2021	4754	Prospective cohort study No difference between HFNC/ NIV/ COT on intubation rate. HFNC has no significant effect on mortality (OR 0,90 95% CI 0,61-1,33) but NIV would increase mortality (OR 2,75 95% CI 1,79-4,21 P<0,001)
Crimi [88] 2021	364	RCT HFNC vs COT No significant difference in mortality No significant reduction in escalation of respiratory support.
Duan [89] 2021	46	Retrospective observational study HFNC vs NIV No difference in intubation rate and mortality
Nair [90] 2021	109	RCT HFNC vs NIV Significant reduction intubation rate at 7day but not 48 hours. No significant reduction hospital mortality
Perkins [41] 2022	1273	RCT Primary outcome: intubation or mortality at 30day. No difference HFNC vs COT
Beran [91] 2022	19	Systematic review and meta-analysis HFNC vs NIV No significant difference of intubation rate Mortality was lower in NIV group
Glenardi [40] 2022	10	Systematic review and meta-analysis HFNC vs NIV (only 1RCT on 10 study analyzed) HFNC lower mortality than NIV HFNC non inferior to NIV to reduce intubation rate.
He [92] 2022	9	Systematic review and meta-analysis HFNC vs NIV No significant difference intubation rate Significant reduction of 28days mortality

treated with Bilevel Positive Airway Pressure (BIPAP)[8]. Numerous metaanalysis have looked into the intubation rate and mortality of HFNC therapy compared to NIV or COT. Seven showed less intubation rates with HFNC compared with COT on the intubation rate with no improvement in survival[9-15]. In order to develop guidelines, 29 RCTs were analyzed for the American College of Physicians. Compared to COT, no difference in intubation or mortality has been demonstrated. Compared to NIV HFNC would decrease the intubation rate and improve survival. These results on mortality have to be confirmed as only one RCT compared HFNC to NIV for mortality and two for intubation[16]. Recent 2022 European Respiratory Society guidelines recommend the use of HFNC for patients in respiratory failure rather than COT. In addition, the cost of HFNC is higher than COT but lower than invasive mechanical ventilation. Compared to NIV, HFNC seems equivalent. Guidelines recommend to adapt depending on each situation. On the one hand, HFNC would be preferred in case of contraindication to NIV and on the other hand, NIV would be more adequate in case of respiratory muscle fatigue, increase of respiratory work or cardiac failure[17].

Post-extubation period

Studies have investigated the use of HFNC in the post-extubation period, in medical or surgical critically ill patients. One spanish study compared HFNC with COT, initiated preventively, in 527 patients with a low risk of reintubation, defined as age <65 years, APACHE score <12 on the extubation day, BMI <30, effective cough, simple ventilatory weaning, 0 to 1 comorbidity, absence of heart failure, moderate to severe chronic obstructive pulmonary disease (COPD), airway obstruction or absence of mechanical ventilation for more than 7 days. Reintubation rate at 72 hours was lower in the HFNC group (4,9% vs 12,2%, pvalue = 0,004)[18]. On the other hand, the high-risk population (n=604 patients) of extubation failure had been studied, defined as having at least one of the following criteria: age > 65 years, APACHE score > 12 on day of extubation, BMI > 30, ineffective cough, prolonged or difficult ventilatory weaning, > 1 comorbidity, mechanical ventilation for cardiac failure, moderate or severe COPD, airway obstruction, mechanical ventilation >7 days. HFNC was not inferior to NIV to prevent reintubation or post-extubation respiratory failure in the postextubation period in high-risk patients[19]. For patient acute respiratory failure in the postoperative setting, significant benefit (p-value<0.05) of HFNC vs NIV was demonstrated by a RCT (n=214) on intubation rate and mortality in post-operative trauma-related patients[20]. A larger randomized study in respiratory failure in postoperative cardiothoracic surgery patients showed that HFNC was not inferior to BiPAP[21]. Thille et al compared intermittent NIV associated with HFNC versus HFNC alone in a population with a high risk of extubation failure. The authors demonstrated a risk reduction of reintubation when combining the two techniques compared to HFNC alone when used immediately after extubation. However, they did not show a significant difference in mortality. A subgroup analysis showed an advantage of this combination (HFNC+NIV) in hypercapnic patients for both outcomes[22-24]. Most of the meta-analysis showed a decrease in the rate of reintubation in favor of HFNC compared to COT without demonstrating a benefit in terms of mortality[25-30].

The benefit seems to be greater in medical critical ill patients than in postoperative patients. Huang et al showed a significant reduction in reintubation in the medical critical ill patient subgroup. However, only two RCT were included[31]. Another meta-analysis concerning only postoperative patients did not show a significant difference[32]. On the other hand, the

American College of Physicians' evidence report showed in the post-extubation setting that HFNC would increase reintubation and mortality compared to NIV. Again, few RCTs were found on the subject[16]. In the same way, the ERS guidelines conclude that HFNC increased reintubations and mortality compared to NIV in patients at high risk of extubation failure. However, the data available for this group was based on five RCT, including 2 COPD selected population and one comparing HFNC combined with NIV to HFNC alone[17].

Immunocompromised patients

A large RCT (776 patients) did not show any difference in intubation rates and mortality for HFNC compared to COT. The wide variety of etiologies of immunosuppressive states included in this study may have influenced the results[33]. However, a decrease in the rate of intubation by HFNC compared to COT had been demonstrated by several meta-analysis without any survival improvement[34-37], except for the meta-analysis of Sklar et al in 2018, which highlighted a decrease in mortality in the HFNC group compared to NIV without significant difference on the intubation rate. However, this meta-analysis must be interpreted with caution because it only included 4 RCTs (including 2 post-hoc analyses) out of 13 included studies[38]. HFNC would be an alternative to NIV in this population given the lack of significant difference in intubation and mortality[36]. ERS guidelines do not make any recommendation for the

immunocompromised population due to a lack of data to draw conclusions[17].

COVID-19 pandemic

During the pandemic, the use of HFNC largely increased. A multicenter prospective cohort study on 4.754 COVID-19 patients was conducted. This study showed a reduction of the use of invasive mechanical ventilation with HFNC but not with NIV. Mortality at 90 days increased with the use of NIV[39]. A recent meta-analysis confirmed these results. On nine observational studies and one RCT studied, the mortality decreased with HFNC compared to NIV but without reducing the intubation rate[40]. A large RCT, the RECOVERY—RS trial compared HFNC to continuous positive airway pressure (CPAP) and COT. The primary composite outcome was intubation or 30-day mortality. It did not show a significant difference between COT and HFNC. This study did not achieve the required power due to a decline in pandemic. Another limitation was a lack of standardization of intubation criteria.

Also, this study was biased by crossovers between the different techniques assessed[41].

Discussion

The advantage of HFNC can be explained by its physiological effects. HFNC allows non-invasive oxygenation at a high flow rate and a high oxygen fraction. Besides, this technique is associated with a decrease in upper airway dryness compared to conventional procedures, the latter with lower flow rates (up to 15 L/min) which are generally not or less humidified. 42 But a lower tolerance to the high oxygen flow may be described. 43 Furthermore, the inspiratory flow rate of patients in acute respiratory failure generally ranges between 30 and 100 liters/min. Therefore, the lower conventional flow rate is less[42].

Measurements of esophageal pressure changes, reflecting intrathoracic pressure variations, during HFNC and COT showed lesser changes for the HFNC group. The authors concluded that HFNC would reduce respiratory effort. Minute ventilation appeared to be lower with no change in $PaCO_2$ and arterial pH[44]. Pulmonary compliance was also improved in the HFNC group. That conclusion was led by estimating compliance via a ratio between tidal volume (measured by electrical impedance tomography) and variation in esophageal pressure. The overall pulmonary volume was increased for an unchanged tidal volume, suggesting the generation of a positive end-of-expiration pressure by HFNC.44 Washing-out of the upper airways associated with higher gas flow in HFNC group and reduction in CO_2 production due to reduction in respiratory effort could explain the $PaCO_2$ decrease[44]. Lower mortality with HFNC compared to NIV could be explained by the higher incidence of ventilator-induced lung injury (VILI) during the NIV when tidal volumes were significantly higher. VILI appeared when the volume delivered by the respirator exceeded 9 mL/kg of predicted weight[4].

The decrease in the rate of intubation could be interesting in patient if correlated with an improvement in survival. However, few studies have shown an advantage of HFNC over COT and/or NIV on mortality[4,7,24,38,45-47].One of the hypotheses is that HFNC delays intubation and therefore, may increase mortality for some patients. Studies on early intubation (less than 48 hours after the initiation of HFNC) in critically ill patients with acute respiratory failure showed a decrease mortality[48,49]. Intra-hospital mortality was higher when intubation occurred more than 12 hours after the initiation of HFNC[50]. In addition, early intubation would result in faster ventilatory weaning, more successful extubation and fewer ventilation days[48,50]. As a result, the identification of risk factors of HFNC failure seems to be essential.

In 2019, the ROX index was described to predict the outcome of patients treated with HFNC in the context of pneumonia-associated hypoxemic respiratory failure. ROX is the ratio between the oxygen saturation measured by a pulse oximeter and the fraction of inspired oxygen divided by the respiratory rate ((SpO_2/FiO_2)/RR). It was validated through a 2-year prospective study in 5 centers in France and Spain on 191 patients[50]. A ROX index greater than or equal to 4.88 measured at 2, 6 or 12 hours after initiation of HFNC is associated with a lower risk of intubation. A ROX index less than 2.85 after 2 hours of HFNC or 3.47 after 6 hours or 3.87 after 12 hours is associated with a greater risk of HFNC failure[50]. The ROX index has also been studied in the context of the COVID-19 pandemic. A meta-analysis showed that ROX is a good predictor of HFNC failure when used for COVID-19 patients treatment with a cut-off of 5 (within the 24h of admission) (Sensitivity 0.7 95% CI (0.59-0.8), specificity 0.79 (95% (0.67-0.88)). However, this analysis included prospective and retrospective cohort studies and no RCT, with high heterogeneity[51]. A modified ROX index where SpO_2 was replaced by PaO2 was evaluated in a retrospective cohort study for all-cause acute hypoxemia respiratory failure. 52 The advantage of PaO_2 is a better reflection of the patient' oxygenation (the relationship between PaO_2 and SpO_2 is not linear). Nevertheless, advantage of SpO_2 is the non-invasive aspect of the measurement. The modified ROX index would be better to predict

outcomes two hours following HFNC therapy. A mROX index > 4,3 after two hours therapy was associated with a success of the technique defined by respiratory improvement without the need for intubation (Sp 71%, Se 96%)[52]. Future prospective studies are needed to confirm previous data.

Many meta-analysis did not show significant results on mortality and intubation rate, which could be explained by various designs, few RCT and case-mix heterogeneity . In addition, criteria to initiate intubation was not always well defined and sometimes left to the discretion of the clinician as well as the criteria to adapt FiO_2, HFNC flows or NIV parameters. One of the recurrent weaknesses of these studies was the absence of blinding for obvious reasons.

Even if the effect on survival improvement was not proved, HFNC seemed to be better tolerated than COT and NIV[53-55]. HFNC, through its humidifier, results in less dryness in the airways and also improves mucociliary function and sputum[54]. Compared to face mask NIV, nasal cannulas are more comfortable[53,56]. They are less likely to cause skin soresthan NIV[21,16]. Furthermore, nasal cannulas allows speaking, drinking, oral feeding. However, the high oxygen flow may also cause reflux and may increase the risk of aspiration[57].

Conclusion

The use of HFNC has received a lot of attention from ICU physicians during those last years without any real benefit on mortality being conclusively proven. HFNC is probably superior to COT in the post-extubation setting, to prevent from re-intubation. During the postextubation period, the combination of NIV + HFNC seems to have an interest. Conversely, HFNC (without NIV) may increase the risk of intubation and mortality compared to NIV post-extubation. HFNC also seems to be an alternative to NIV in immunocompromised patients and reduce mortality in COVID-19 patients compared to NIV. Further randomized clinical trials seem necessary to clarify. Numerous meta-analysis describe a lack of quality in RCTs to obtain definitive conclusions. Further clinical studies are still necessary to refine the indications of this technique.

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