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Invasive mechanical ventilation is the cornerstone therapy for the acute respiratory distress syndrome (ARDS). However, because invasive mechanical ventilation is also associated with side effects and complications leading to substantial morbidity or even mortality, physicians have developed strategies to prevent endotracheal intubation. One of these strategies is non-invasive ventilation (NIV), which is the application of positive airway pressure via an external (noninvasive) interface.

Recently, a newer noninvasive device has seen increasing use that allows delivery of heated and humidified high-flow gas at body temperature and saturation and flows up to 60 l/min with FIO2 adjustable up to 100 % through a soft wide-bore nasal cannula (HFNC).

Physiologic rationale for NIV and HFNC in ARDS

From a theoretical and physiological point of view, NIV and HFNC may both be beneficial in patients with mild ARDS. Fine-tuning of the fraction of inspired oxygen (FIO_2) apart, these two techniques work via different mechanisms. On one hand, NIV applies end-expiratory positive airway pressure and pressure support, the former increasing functional residual capacity and opening collapsed alveoli, thereby improving ventilation-perfusion matching and reducing intrapulmonary shunt as well as improving lung compliance, thus reducing respiratory load. The latter assists respiratory muscles during inspiration, reducing work of breathing and dyspnea.

On the other hand, HFNC generates a small positive pressure spike at end-expiration that depends on the nasal air flow and on the extent of mouth opening and appears to work mainly by flushing the nasal airspaces, reducing anatomical dead space [1]. In addition, by delivering warm and well-humidified gas through the nostrils and by avoiding the discomfort generated by the pressure that NIV masks exert on the face skin, HFNC is extremely well tolerated, much better than NIV, and can be applied continuously for long periods of time.

It is important to keep in mind that the major goal of NIV and HFNC in treating ARDS is to achieve a sufficient level of oxygenation. In this regard, NIV and HFNC may be viewed as "bandaid" therapies – if they aren't addressing the underlying pathology sufficiently (eg septic shock or multiorgan system failure), alternative therapy such as endotracheal intubation with invasive mechanical ventilation should be initiated without delay.

Results of clinical trials and meta-analyses

Relatively few studies have focused on the role of NIV in avoiding intubation in ARDS *per se.* In a prospective cohort study, Antonelli et al applied NIV to 147 ARDS patients admitted to the ICU not yet intubated [2]. Fifty-four per cent of these patients avoided intubation and had fewer ventilator associated pneumonias (2% vs. 20%; P <0.001), and a lower ICU mortality (6% vs. 53%; P<0.001).

To date, only ten randomized controlled studies have been conducted on use of NIV in patients with *de novo* hypoxemic acute respiratory failure [3-10] (Table 1), most at centres that are expert at delivery of NIV. Among these studies, three were performed on immunocompromised patients [5, 8, 9] and two in patients who had recently undergone surgery [11, 12]. Only two randomized controlled studies have thus far evaluated NIV in non-hypercapnic and immunocompetent patients with *de novo* hypoxemic acute respiratory failure. One suggested that NIV may reduce intubation rate and even mortality in a very selected population of patients [7] and the other reported no beneficial effects and a higher number of adverse events in patients receiving NIV consisting of continuous positive-end expiratory pressure (CPAP) [6]. A meta-analysis focusing on these two randomised controlled studies and another conducted in recipients of solid organ transplant [5-7] concluded that the addition of NIV to standard care in patients with ARDS did not reduce the intubation rate or ICU mortality [13].

Regarding HFNC, the only large randomized controlled trial in adults admitted to the ICU with acute hypoxemic respiratory failure (PaO_2/FiO_2 <300 mmHg) has shown that HFNC did not reduce the overall intubation rate compared to standard oxygen or NIV (38, 47 and 50%, respectively, p =0.18) although intubation rate was significantly less with HFNC in the subgroup of patients with a PaO_2/FiO_2 <200 mmHg (35, 53 and 58%, respectively, p=0.009, post hoc analysis) [14]. In addition, HFNC reduced ICU and 90 day mortality as compared to standard oxygen and NIV. The authors speculated that the greater mortality with NIV might have been related to the use of tidal volumes of > 9 ml/kg, predisposing to ventilator induced lung injury. However, it is worth noting that refractory shock was encountered more frequently in the NIV group, possibly suggesting a sicker cohort.

Potential risks of NIV and HFNC in ARDS patients

In ARDS patients, the reported rate of NIV failure averages 52% (from 14% to 70%) [15]. However, this failure rate is much lower in mild ARDS (34%) than in moderate or severe ARDS (68%) [16]. Moreover, crucial predisposing factors for NIV failure include altered level of consciousness and shock [16].

Although NIV failure in patients with *de novo* acute respiratory failure has been associated with a high mortality regardless of the severity of acute respiratory failure [17], a more recent study from francophone ICUs suggests that not only does the use of NIV in *de novo* acute respiratory failure seem to be decreasing, but also NIV failure is no longer associated with higher mortality. These recent data suggest improved patient selection and NIV application [18].

Reasons why NIV failure raises the risk of death in *de novo* hypoxemic acute respiratory failure include delay of needed intubation as the underlying condition progresses until the situation becomes catastrophic [6] and a high level of pressure support in

combination with deep inspiratory efforts that could generate high tidal volumes and excessive transpulmonary pressures, increasing lung stress and contributing to ventilator induced lung injury (VILI) [14]. Emerging studies suggest that HFNC has fewer adverse effects than NIV and may be less apt to contribute to VILI, perhaps because lung stretch is less [13]. On the other hand, a recent retrospective study [16] suggests that, just as with NIV, delayed intubation should be avoided with HFNC.

So can we avoid intubation in ARDS using noninvasive approaches?

For reasons stated above, NIV has been plagued by poor tolerance and high failure rates when used to treat ARDS. Although studies like that by Antonelli et al [2] demonstrate that NIV success in ARDS is associated with many fewer complications and a higher survival rate than NIV failure, randomized controlled trials have been unable to demonstrate convincingly that NIV improves outcomes, even intubation rate, in comparison to standard oxygen and intubation if necessary. HFNC might offer a suitable alternative to NIV, especially in patients with moderate or severe ARDS (PaO2/FIO2 < 200), amongst whom intubation rate was lower than in standard oxygen and NIV groups in the Frat study [14]. It is important to emphasize, however, that this was a post-hoc analysis and needs to be confirmed in future studies. In the meantime, what do we do? When ARDS patients become difficult to oxygenate using standard oxygen approaches, HFNC, by virtue of its better tolerance and ability to reduce room air entrainment and wash out dead space, is a logical next choice (Figure 1). Whether some patients failing HFNC could be salvaged by escalating to NIV is currently unclear. In either case, patients must be monitored very closely in an ICU with particular attention paid to the course during the first hour or two. Patients manifesting further deterioration or even failure to improve should be intubated without undue delay.

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Figure Legend

Figure 1. Algorithm for a practical use of high flow nasal canulae (HFNC) and non-invasive mechanical ventilation (NIV) in acute respiratory distress syndrome (ARDS)

Table 1. Summary of the main studies on non-invasive ventilation in de novo hypoxemic respiratory failure

Study	Patients	PaO_2/FiO_2, *mmHg*	Patients included (n)		Intubation rate (%)		ICU Mortality rate (%)	
			NIV	CTL	NIV	CTL	NIV	CTL
Antonelli et al. 1998 [10]	Pneumonia, trauma, postoperative, ACPE	NIV 116±24 CTL 124±25	32	32	31	100	31	50
Confalonieri et al. 1999 [3]*	Pneumonia, COPD	NIV 165±30 CTL 164±52	16	17	6	8	38[a]	24[a]
Delclaux et al. 2000 [6]	Pneumonia, aspiration, near drowning, ACPE	CPAP 140 (59–288) CTL 148 (68–283)	56	60	38	40	21	25
Antonelli et al. 2000 [5]	Solid organ transplant recipiants	NIV 129±30 CTL 129±30	20	20	20	70	20	50
Martin et al. 2000 [4]*	Hypoxemic and hypercapnic respiratory failure	NIV 103±35 CTL 110±43	14	18	36	67	29	56
Auriant et al. 2001 [11]	Postoperative, lung resection	NIV 127±42 CTL 127±43	24	24	21	50	13[a]	38[a]
Hilbert et al. 2001 [8]	Immunocompromized patients	NIV 141±24 CTL 136±23	26	26	46	77	38	69
Ferrer et al. 2003 [7]	Pneumonia, trauma, ACPE, ARDS	NIV 102±21 CTL 103±23	51	54	25	52	18	39
Lemiale et a. 2015 [9]	Immunocompromized patients	NIV 156 (95–248) CTL 130 (86–205)	191	183	38	45	24[b]	27[b]
Jaber et al. 2016 [12]	Postoperative, abdominal surgery	NIV 201±69 CTL 188±71	148	145	33	46	15[c]	22[c]

NIV, non-invasive ventilation; CTL, control; ACPE, acute cardiogenic pulmonary edema, COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure.
Continuous variable are expressed as mean ± or median (interquartile range) and categorical variable as number (%).
*Data restricted to the "hypoxemic" acute respiratory failure group.
[a] hospital mortality; [b] all cause 28-days mortality; [c] all cause 90-days mortality.

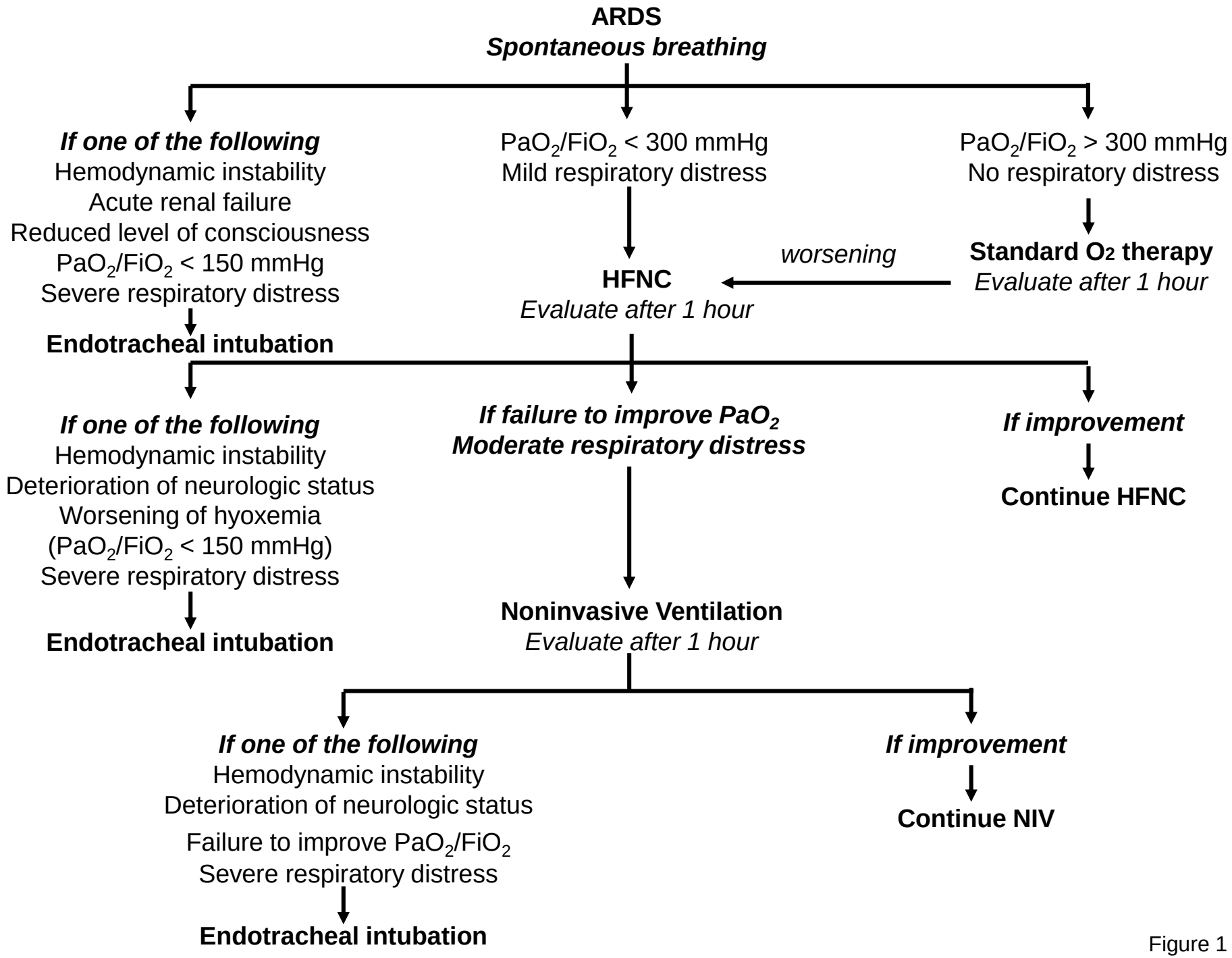
ARDS
Spontaneous breathing
If one of the following
Hemodynamic instability
Acute renal failure
Reduced level of consciousness
PaO2/FiO2 < 150 mmHg
Severe respiratory distress
Endotracheal intubation
PaO2/FiO2 < 300 mmHg
Mild respiratory distress
HFNC
Evaluate after 1 hour
worsening
PaO2/FiO2 > 300 mmHg
No respiratory distress
Standard O2 therapy
Evaluate after 1 hour
If one of the following
Hemodynamic instability
Deterioration of neurologic status
Worsening of hyoxemia
(PaO2/FiO2 < 150 mmHg)
Severe respiratory distress
Endotracheal intubation
If failure to improve PaO2
Moderate respiratory distress
Noninvasive Ventilation
Evaluate after 1 hour
If improvement
Continue HFNC
If one of the following
Hemodynamic instability
Deterioration of neurologic status
Failure to improve PaO2/FiO2
Severe respiratory distress
Endotracheal intubation
If improvement
Continue NIV

Figure 1