

Sedation during non-invasive ventilation to treat acute respiratory failure

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Summary

Despite the increase popularity of noninvasive ventilation (NIV) to treat acute respiratory failure (ARF), up to a quarter of patients fails because of poor adherence or refusal to the ventilator treatment and therefore endotracheal intubation (ETI) with conventional mechanical ventilation (CMV) is required. The implementation of sedation-based strategy to rescue patients with poor co-operation and/or adaptation to NIV is appealing to enlarge its rate of success. Pilot studies suggest that continuous infusion of a single different sedative and analgesic agent titrated to obtain “conscious sedation” may decrease patient discomfort, with no significant effects on respiratory drive, respiratory pattern, or hemodynamic; in addition, gas exchange improve under NIV plus sedation. Despite these encouraging findings, the level of the evidence in favor of a large application of sedation during NIV is still limited and further larger and controlled trials are needed to clarify the indications of sedation during NIV and better select the patients who are mostly likely to benefit from this practice. Careful selection of candidates, setting of application, expertise of the team and capability of prompting intubating the patients are the key-ingredients necessary for attempting in safety this procedure which should be implemented within a strategy aimed at reducing the risk of NIV failure in poor tolerant subjects.

KEY WORDS: noninvasive ventilation; agitation; sedation; acute respiratory failure; COPD.

Background

The use of non invasive ventilation (NIV) to treat acute respiratory failure (ARF) has been tremendously ex-

panded in the last two decades, and therefore, NIV is now considered the ventilation modality of first choice for a large proportion of patients with ARF, such as exacerbation of chronic obstructive pulmonary disease (COPD), acute cardiogenic pulmonary edema (ACPE), pulmonary infiltrates in immunocompromised status, as

well as after endotracheal intubation (ETI) in the transition from invasive ventilation to spontaneous breathing in chronic hypercapnic respiratory failure (1). The main advantage of NIV is due to the chance of delivering an efficient ventilator support without the life-threatening complications correlated with conventional mechanical ventilation (CMV) delivered via endotracheal intubation (ETI) (2). Other benefits achievable with NIV as compared to CMV is the “wider window” in terms of both timing and settings of applications (i.e. NIV as prevention of CMV, NIV as facilitation of weaning from CMV, NIV in other than ICU environments), as well as “ceiling ventilator treatment” and as “pure palliative support” (1-4).

Conversely from CMV that requires a pharmacological sedative aid to allow the patient to keep the endo-tracheal tube in site, NIV requires a co-operation of the awake patient to keep the interface well fit outside the airways (i.e. masks, helmet, nasal pillows, mouth-piece). Consistently, the success of NIV is strongly dependent on how good is the degree of tolerance shown by the patient during ventilation. In fact, poor patient’s cooperation reduces the effectiveness of NIV to achieve the physiological goals of mechanical ventilation (MV) (unloading respiratory muscles, increasing alveolar ventilation, improving gas exchanges) mainly throughout claustrophobic refusal of the mask, excessive unintentional air leaks and patient-ventilation dys-synchronies (1,5,6). Neuro-psychological aspects correlated with both respiratory and metabolic alterations (i.e. hypercapnic encephalopathy, severe hypoxemia, extra-pulmonary organ dysfunctions) (7) and with hospitalization in ICU, especially for older patients suffering from comorbidities (8), may contribute to compromise the compliance to NIV. The level of acceptance of NIV is dependent on the curve of adaptation of the patient who has to learn how to breath in synchrony with ventilator-assisted acts which force the air to enter into the lungs by means of a positive driving pressure. Generally speaking, after an initial trial of a length of few hours, adherence to NIV tends to improve quickly depending on the expertise of the staff, the severity and the resolving timing of ARF. Therefore, as the duration of NIV augments, especially if delivered with high levels of pressures, the discomfort of the patient is likely to worsen mainly due to the complications correlated with the ventilator treatment

Consistently, the success of NIV is strongly dependent on how good is the degree of tolerance shown by the patient during ventilation.

(i.e. skin decubitus, gastro-abdominal distension, eye irritation, nose occlusion, dryness of upper airways, neuropsychological distress) (1,6). The attempts of nurses and therapists to reduce air leaks by tightening the security systems of the interfaces are likely to trigger a vicious circle throughout the occurrence of discomfort and decubitus lesions (9). Even though the rotation strategy of different interfaces is likely to reduce the risk of skin breakdown and to increase patient's tolerance (10), NIV delivered for several hours a day and for several days inevitably provoke devastating skin damage. As a matter of fact, pain and discomfort are the main determinant of mask intolerance that lead the patient to refuse ongoing NIV prompting its discontinuation and subsequent requirement of ETI or death (6). On the other hand, clinicians may experience a different scenario with a premature NIV failure occurring in patients who complaint marked claustrophobia that makes useless all attempts of wearing the interface (Figure 1).

The rate of NIV failure due to patient's intolerance was reported to be variable between 9 and 22% (5,11-14). Team expertise, intensity of care (i.e. ratio nurse to patient), and type of setting may influence the compliance of patients to carry on with NIV. In our experience performed in 214 patients in a Respiratory Intensive Care Unit (RICU), poor adherence to ventilation, evaluated as a compliance lower than 50% of the total scheduled time, was registered in about one third of the cases and was significantly associated with premature discontinuation and failure of NIV (15). Furthermore, the cause of an insufficient adherence to NIV was due to interface's discomfort in 90% of cases (15). In a large multicenter ICU survey, Carlucci et al. (5) clearly demonstrated that both large amount of air leaks and poor patient's tolerance are both predictors of NIV failure. As unsuccessful NIV been shown to be an independent predictor of hospital mortality, it's

clear that refusal of NIV for discomfort becomes a strong negative prognostic index. This is particularly true in immuno-suppressed patients who are particularly vulnerable to septic complications of ETI-CMV (16). Consistently, in a series of immunosuppressed patients with ARF Rocco et al. reported a NIV failure rate related to interface intolerance of 13% associated with an 80% mortality rate (13).

Rationale and drawbacks of sedation during NIV

After considering other factors that may improve the adherence mask (i.e. changes of ventilator setting, rotation of interfaces, psychological support), sedation may be part of the strategy aimed at improving patient's tolerance in selected cases at a risk of ETI due to NIV failure. A short term administration of judicious sedation in carefully selected intolerant patients who otherwise should be intubated or left to die (i.e. DNI status) because of ensuing of discomfort, claustrophobia and agitation may allow clinicians to start or continue NIV and, therefore, increase the chance of success. This rationale for sedation during NIV may be evident both within the first hours of ventilation when the patient needs to be adapted to NIV and later when prolonged ventilation is required. A sedation-based strategy directed to rescue at least a proportion

A sedation-based strategy directed to rescue at least a proportion of patients who are failing NIV because of refusal for intolerance is likely to reduce hospital mortality by means of the prevention of CMV-related complications.

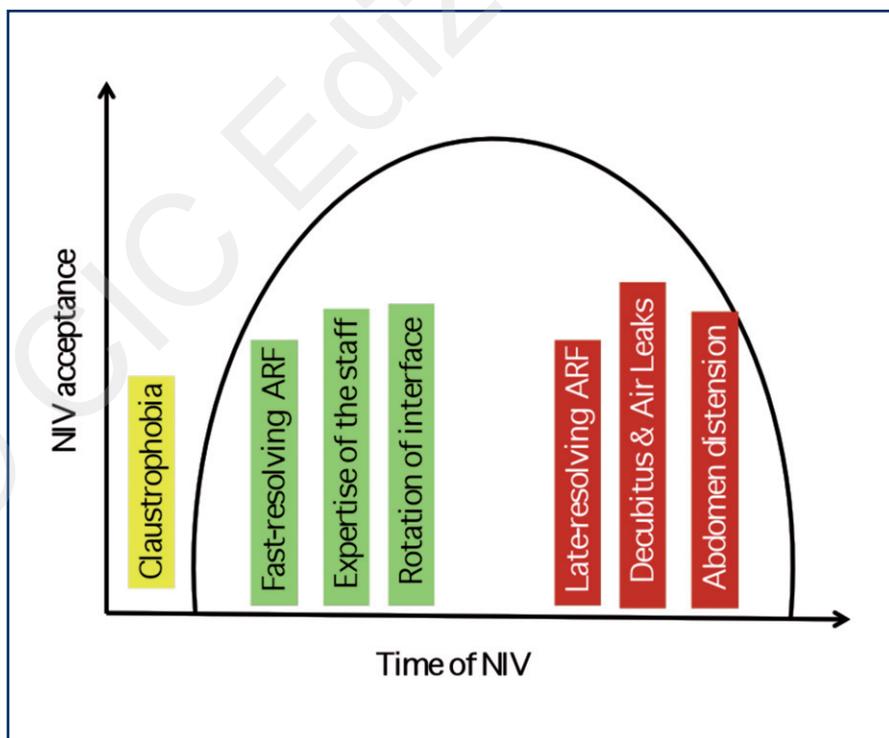


Figure 1 - Time-course and correlates of NIV acceptance.

of patients who are failing NIV because of refusal for intolerance is likely to reduce hospital mortality by means of the prevention of CMV-related complications (6,16). However, administering sedative in ARF patients without protection of airways is not free of several caveats: central respiratory drive depression, upper airway obstruction due to tongue replacement, reduced cough reflex and efficacy in removal secretions, vomiting and pulmonary aspiration, class-specific side effects (i.e. cardiovascular instability). The incidence and the severity of these sedative-related complications in patients admitted in ICU are variable depending on the dosage, type of drug, severity of ARF, expertise of the team. The large majority of the studies on sedation during MV deals with intubated patients supported with CMV so most of the aforementioned complications could be easily managed: tracheal suction, lack of leaks, protection of airways, hemodynamic monitoring.

Assessment of sedation in critical patients

It's important that at least one clinical tool is used to assess the neurological status of patients under NIV with the aim of obtaining the desired neurological sedative effect for the delivered dose of the chosen drug.

A crucial point in the management of critically ill patients submitted to invasive and non-invasive MV is the evaluation of the effectiveness of the dose and type of drug delivered in terms of control of discomfort, pain and distress correlated with MV. Assessing and describing the level of sedation in critically ill patient can be difficult. Different clinical tools have been used to quantify

the depth of sedation (Figure 2): Ramsay Sedation Score (RSS) (17), Observer's assessment of alertness and sedation (OAA/S) scale (18), Riker Sedation-Agitation Scale (RSAS) (19), Richmond Agitation-Sedation Scale (RASS) (20), Bispectral Index (BIS) (21) (Figure 2). Thank to its easy application, RSS is the most widely used observational assessment tool for evaluating sedation. Even if no one of the reported scales has been shown to be more reliable as compared to the others to monitor the effects of sedative drugs, it's important that at least one clinical tool is used to assess the neurological status of patients under NIV with the aim of obtaining the desired neurological sedative effect for the delivered dose of the chosen drug.

Pharmacologic profile of sedative and analgesic drugs

The ideal sedation should guarantee a good control of anxiety, agitation and discomfort induced by NIV with less significant respiratory drive depression and easier arousal. This would help patients to discharge their secretions and avoid aspiration, ultimately leading to an increase in the rate of adherence to NIV and, hopefully, the chance of success in avoiding ETI and CMV. Whatever the drug used, the goal is to achieve the "conscious sedation" while the patients are awake or easily arousable with a sufficient mitigation of NIV-induced discomfort (6).

The introduction into clinical use of new synthetic opioids with limited adverse effects, particularly on the respiratory system, has offered an option for the analgo-sedation of critically ill patients.

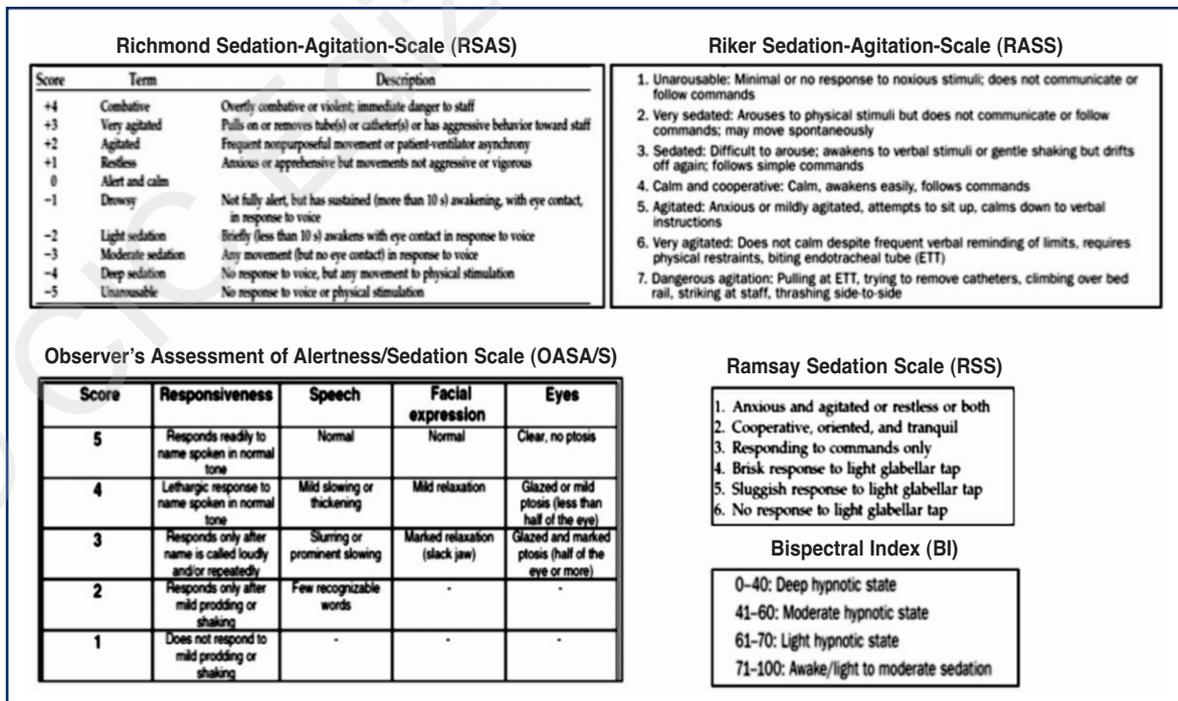


Figure 2 - Neurological scales used to assess the sedative drug effects during noninvasive ventilation (NIV).

The large majority of the published data concerning the use of sedative drugs in critically ill patients deal with ETI-CMV. Sedation is required during CMV to allow the tolerance of endotracheal tube, facilitate patient-ventilator interaction, allays anxiety, encourage sleep, and modulate physiologic responses to stress such as tachycardia and hypertension. Similar goals should be achieved for intolerant patients undergoing NIV except for the interface. For decades, γ -aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines such as midazolam) have been the most commonly administered sedative drugs for ICU patients worldwide (22, 23) as they are able to provide long-term sedation in mechanically ventilated patients if administered in continuous infusion owing to its short half-life. However, well known hazards are associated with prolonged use of midazolam. Accumulation and prolonged sedative effects have been reported in critically ill patients who are obese, have low albumin levels or renal failure (24, 25). Paradoxical agitation has been observed in about 1% of patients during light sedation and may be the result of drug-induced amnesia and disorientation (23).

More recently, as alternative or in addition to sedatives, opioids, especially morphine and fentanyl, are widely used in the critically ill patient because of their efficacy in pain control and mitigation of psychological discomfort. This is consistent with the modern concept that patients admitted in ICU requiring MV should be offered not only a pharmacologically help to reduce the consciousness level in order to tolerate the endotracheal tube and other invasive devices (i.e. "pure sedation") but also a support to achieve an adequate control of psychological and physical components of the pain ("analgesia" plus "sedation"= "analogo-sedation strategy") (26). This may be particularly true for patients undergoing NIV who have to cope with the distress induced by breathing under positive pressure delivered with a noninvasive interface.

The introduction into clinical use of new synthetic opioids with limited adverse effects, particularly on the respiratory system, has offered an option for the analogo-sedation of critically ill patients. Conti et al. (27) showed that the continuous infusion of sufentanil may be used as a single sedative agent in patients receiving CMV, allowing mitigation of discomfort and obtaining the desired level of awake sedation, with no significant effects on respiratory drive, minute volume, respiratory frequency, respiratory pattern, blood gases, or hemodynamics. However, sufentanil is not a short-acting opioid with a liver metabolism so its long-term infusion may cause drug accumulation with which may delay patient recovery with augmented risk of respiratory depression (28). Furthermore, Cavaliere et al. (29) have demonstrated similar results with a low-dose continuous infusion of remifentanil.

Remifentanil is a newly developed anilidopiperidine opioid with pharmacodynamic properties similar to those of other opioids but with a peculiar pharmacokinetic profile. Remifentanil is a potent, short-acting opioid with a μ -selectivity. Its metabolism is not influenced by hepatic or renal dysfunction, being metabolized by nonspecific blood and tissue esterases into a pharmacology-inactive metabolite. The elimination half-life of remifentanil is less than 10 min, which is independent of infusion duration (31). Remifentanil is indicated for the induction and maintenance of general anesthesia and for the administration of analgesia in mechanically ventilated patients for up to

3 days (31). Remifentanil has an onset of action of about 1 min and quickly achieves a steady state. These characteristics make remifentanil very easy to titrate to effect and allow administration of opiates without concerns about accumulation and unpredictable and/or delayed recovery.

Dexmedetomidine is an α -2 adrenoreceptor agonist with a unique mechanism of action, providing sedation and anxiolysis via receptors within the locus ceruleus, analgesia via receptors in the spinal cord, and attenuation of the stress response with no significant respiratory depression (32). Due to its pharmacologic profile, it has been used as useful sedative in ICU patients: sedation is obtained when patients are undisturbed, but they can be easily aroused with minimal stimulation, allowing for the performance of neurological examination (33). Moreover, dexmedetomidine has been successfully used to facilitate weaning from CMV in patients with COPD and asthma (34). As regards safety profile, a caution should be taken after the initial loading dose as it may cause cardiovascular adverse drug reactions, such as hypertension, hypotension, or bradycardia (35).

Clinical studies of sedation during NIV to treat ARF (Tables 1, 2)

The first report of the use of sedation during NIV is found in a trial performed in patients with ALI/ARDS, when morphine was used with success in 9 of 12 patients, alone or in combination with midazolam in six patients, to allow them to tolerate face mask (36).

In a preliminary study (37) performed in a small series of 13 patients (10 with hypoxemic and 3 with hypercapnic

ARF), Constantin et al. assessed the feasibility and the safety of remifentanil in the management of NIV failure due to discomfort and/or refusal to continue ventilation. Continuous remifentanil perfusion during NIV titrated to obtain a conscious sedation (RSS between 2 and 3), with the need of propofol in 3 cases, improved respiratory rate and blood gases after 1 hour and avoided ETI in 9 out of 13 patients. All four patients were intubated after the first session of NIV. Twelve of the 13 patients left the ICU. No aspiration pneumonia were reported using the blue methylene-based bronchoscopic evaluation.

In a larger following observational uncontrolled study, Rocco et al. (38) assessed the effectiveness and safety of remifentanil-based analog-sedation in 36 patients with hypoxemic ARF who complained of discomfort and intolerance to two different interfaces (helmet and total face mask) and asked for interruption of NIV. The rate of the infusion of the drug was titrated to achieve a target sedation (RSS between 2 and 3) as well as patient's comfort. Sixty one percent of the patients continued NIV after remifentanil infusion. None patient had respiratory drive or hemodynamic alterations during the study period. In addition, arterial blood gases and respiratory rate improved after 1 hour of NIV with remifentanil-analogseda-

Dexmedetomidine initiated at a low initial loading dose followed by continuous infusion can provide adequate and safe sedation for milder degree of agitation with poor acceptance of NIV.

Table 1 - Main findings of the published studies on the use of sedation during noninvasive ventilation (NIV).

Author, study (reference)	Patients (type of disease)	Interface	Baseline physiologic data	Type of sedative drug	Timing of sedation	Length of sedation	Side-effects of sedation	Main outcome results
Rocker, NCT (36)	10 (12 ARF)	FFM	P/F 102; APACHE II 16 M (6)	Mo (9),	At NIV starting	64.5 hrs	None	Improved P/F in 9/12; ETI 20%; Mortality 30%
Constantin, NCT (37)	13 (10 ARF; 3 AHRF) SAPS II 32	FFM	pH 7.38; P/F 134; RR 32; acceptance	RM (3 Pr)	Poor NIV	90 hrs	None	Improved ABG/RR; ETI 31%; Mortality 7.7%
Rocco, NCT (38)	36 (ARF)	FFM, Helmet	P/F 157; RR 34; SAPS II 36	RM; acceptance	Poor NIV	2.5 hrs (F), 52 hrs (S)	None	Improved ABG/RR; ETI 39%; Mortality 28%
Akada, NCT (39)	10 (ARF)	FFM	pH 7.38; P/F 219; PaCO ₂ 45.8; RR 29	D plus Mo (1) and Pr (1)	Poor NIV acceptance	16.5 hrs	None	Improved ABG/RR; None intubated or died
Takasaki, NCT (40)	2 (SAA)	TFM	pH 7.38; PaO ₂ 56; PaCO ₂ 45 (O ₂ 7 lpm) pH 7.25; PaO ₂ 66, PaCO ₂ 48 (O ₂ 5 lpm)	D	Poor NIV acceptance	8 hrs (case 1) ND (case 2)	None	Improved ABG/RR; None intubated and died
Senoglu, RCT (41)	40 (COPD)	FFM	RR 25 (D) 25 (M); pH 7.29 (D) 7.30 (M); PaO ₂ 59 (D) 59 (M); PaCO ₂ 70 (D), 70 (M) APACHE II 21.5 (D), 21.4 (M)	D (20) vs M (20)	At NIV starting	24 hrs	None	Improved ABG/RR in both groups; lower HR and BP in D; fewer adjustment of doses in D; None intubated or died
Huang, RCT (42)	62 (ACPE)	TFM, Helmet	RR 36 (M), 35 (D); pH 7.22 (M), 7.23 (D); P/F 183.3(M), 176.6 (D); APACHE II 21.4 (M), 22.6 (D)	D (=33) vs M (29)	Poor NIV acceptance Respiratory	57.5 (D) vs 93.4 hrs (M) infections/vomiting (M)	Bradycardia (D);	Improved ABG/RR in both groups; Lower ETI, LOS and Mortality in D vs M
Clouzeau, NCT (43)	10 (7 ARF, 3 AHRF)	FFM	pH 7.32; P/F 144; PaCO ₂ 57.8; SAPS II 37	Pr	Poor NIV acceptance		2 hrs	transient low SpO ₂ (n=1) Improved ABG; ETI 30%; Mortality 20%

ABG= Arterial Blood Gases; ACPE= Acute Cardiogenic Pulmonary Edema; APACHE= Acute Physiology And Chronic Health Evaluation; ARF= Acute hypoxemic Respiratory Failure; AHRF= Acute Hypercapnic Respiratory Failure; BP= Blood Pressure; D= Dexmedetomidine; ETI= Endotracheal intubation; FFM= Full-face mask; HR= Heart rate; LOS= Length of stay in hospital; M= Midazolam; Mo= Morphine; ND= Non defined; NCT= Non-controlled trial; P/F= PaO₂ to FiO₂ ratio; Pr= Propofol; R= Remifentanyl; RCT= Randomized Controlled Trial; RR= Respiratory Rate; SAA= Severe Asthmatic Attack; SAPS= Simplified Acute Physiology Score; TFM= Total-Face Mask.

All numeric values are reported as mean or median unless otherwise stated; PaO₂ and PaCO₂ are expressed in mmHg

Table 2 - Doses of the sedative drugs used during noninvasive ventilation (NIV).

Drug	Bolus dose	Maintenance infusion dose	Sedative target ranges
Dexmedetomidine (41)	1 µg/kg	0.2-0.7 µg/kg/hr (step up/down dose: 0.1 µg/kg/hr)	RSS= 2-3, RSAS=3-4, BISlevel >85
Midazolam (41)	0.05 mg/kg	0.05-0.1 mg/kg/hr (step up/down dose: 0.05 µg/kg/hr)	RSS= 2-3, RSAS=3-4, BISlevel >85
Remifentanyl (38)	————	0.025 µg/kg/min (step up/down dose: 0.01 µg/kg/hr)	RSS=2-3
Propofol TCI (43)	————	0.4 µg/ml* (step up/down: 0.2 µg/ml)*	OAA/S= 3-4

BI= Bispectral Index; OAA/S= Observer's Assessment of Alertness/sedation Scale; RSS= Ramsay Sedation Scale; RSAS= Richmond Agitation-Sedation Scale; TCI= Target Controlled Infusion.

* Serum concentration of the drug

tion either with helmet or total face mask. Fourteen patients failed to continue NIV and were intubated after a mean of 2.5 hours because of persistent discomfort (n=12), probably worsened by the concomitant persistence of dyspnea and hypoxemia, and of hemodynamic in-

tolerance due to septic shock (n=2). Importantly, ICU mortality rate in the failure group was 50% versus 14% in the success group (p<0.05). In conclusion, the results of these two preliminary studies suggest that remifentanyl-based analogo-sedation in patients who could not toler-

ate NIV and, therefore, should be switched to CMV is feasible and safe.

In a pilot Japanese study of feasibility and safety, Akada et al. (39) investigated the effects of continuous perfusion of dexmedetomidine after a low loading dose in 10 patients receiving NIV who became subsequently uncooperative, rated as RSS=1 and RASS \geq 1. After 1 hour of infusion the authors registered a significant improvement of both neurologic scores which were kept within the desired target levels (RSS between 2 and 3; RASS between 0 and -2) for all the duration of NIV. Blood gases and respiratory rate improved over time. All patients were successfully weaned from NIV, with none intubated, and all were discharged alive from ICU. Other two of sedative and analgesics were used (morphine and propofol) in two patients. No substantial hemodynamic changes were reported. Subsequently, Takasaki et al. (40) reported 2 cases in which dexmedetomidine facilitated the adaptation to NIV for the treatment of ARF caused by severe asthma without inducing respiratory depression. The results of these preliminary studies suggest that for milder degree of agitation with poor acceptance of NIV, dexmedetomidine initiated at a low initial loading dose followed by continuous infusion can provide adequate and safe sedation.

Two recent RCTs compared the effectiveness and safety of sedation with dexmedetomidine vs midazolam in patients at risk of NIV failure due to refusal of treatment for discomfort and agitation. However, these two small studies differ from the underlying disease (COPD vs ACPE), timing of sedation (at the beginning vs during treatment) design (different primary end-points).

In the first RCT performed in Turkey ICU (41), the Authors assessed 40 COPD patients undergoing NIV via face mask to treat an acute exacerbation but considered uncooperative while in spontaneous breathing as defined by RSS=1 and RASS \geq 1. Patients were randomized to receive sedation during NIV by means of a continuous infusion of either dexmedetomidine (n=20) or midazolam (n=20) after an initial loading dose with the adjustment of the infusion rate according to desired sedation levels (RSS between 2 and 3, RSAS between 3 and 4, BISlevel $>$ 85). Concerning the primary end-point (i.e. effects on neurological scores over 24 hours) in both groups, RSS significantly increased and RSAS levels and BIS values significantly decreased after the loading dose as compared to baseline. However, dexmedetomidine group showed RSS levels significantly lower beginning from the 4th hour, RSAS levels significantly higher beginning from the 8th hour and BIS values significantly higher throughout the study period vs midazolam group. Moreover, the number of times a change in the infusion rate was needed was significantly lower in dexmedetomidine vs midazolam group. Gas exchange and respiratory rate improved in both group similarly as compared to baseline. As regards hemodynamic profile, dexmedetomidine group had significantly lower heart rate levels throughout the study and systolic and diastolic pressure during the first two hours as compared midazolam group. However, no patient experienced adverse cardiovascular effects related to the loading dose or maintenance infusion of the sedatives requiring interruption or treatment. Oversedation (RSS $>$ 4 or RSAS $<$ 2) occurred in one patient after 8 hours of midazolam infusion and required cessation of the infusion. Moreover, two patients

of midazolam group were still agitated after 2 increases in the infusion rate and were withdrawn from the study. It has to be underlined that no patient experienced NIV failure during the study period. In conclusion the authors asserted that both midazolam and dexmedetomidine were found to be effective for sedation in noninvasively ventilated COPD patients during the 24 hour study time and no significant difference in beneficial effects on respiratory physiology were observed. Patients treated with dexmedetomidine needed significantly fewer adjustment to maintain adequate sedation and cooperation with NIV.

Some caveats of this study should be remarked: 1) evaluation in patient with initial altered levels of agitation/sedation scores before experiencing NIV (maybe, not necessary sedation in all cases?); 2) no cases of NIV failure (not too sick patients, who could have gone well without sedation?); 3) short-term analysis (what would happen for the scheduled time of NIV in COPD exacerbations, usually 5-7 days?).

In another Chinese RCT Huang et al. (42) compared the efficacy and safety of sedation with dexmedetomidine vs midazolam in a population of 62 patients with ACPE and hypoxemia in NIV failure due to refusal to continue ventilation because of discomfort, claustrophobia or marked agitation. The patients were sedated (RS= 2-3) by a continuous perfusion of midazolam (29 cases) or dexmedetomidine (33 cases) during the NIV session delivered by either total-face mask or helmet. In both groups, the expected sedative scores were obtained but patients who received dexmedetomidine were more easily aroused with adequate sedation. Oxygenation index, pH value, and respiratory rate were significantly improved in both groups. In the dexmedetomidine-treated group, the patients had a further decreased percentage of NIV failure requiring ETI (21.2 vs 44.8%; p=0.043) and a more prolonged mean time to ETI (27.6 vs 17.8 hours; p=0.024). There were no significant differences in the cause of ETI between the groups even though there was a trends towards a rate of failure due to copious tracheal secretions with midazolam and for severe hemodynamic instability with dexmedetomidine. Furthermore, when compared with the midazolam group, the overall duration of MV in successfully treated patients and the duration of ICU hospitalization in the dexmedetomidine group were markedly decreased and weaning from NIV was easier. Despite the fact that more dexmedetomidine-treated patients developed bradycardia (18.2% vs. 0, p=0.016), no patients required an intervention or interruption of study drug infusion. Conversely, the incidence of respiratory infections and vomiting was lower in the dexmedetomidine-treated patients probably due to the less interference with cough efficacy reflex as compared as with midazolam group. However, there were no recorded serious adverse events, and none of the patients stopped study drug infusions because of adverse events. The authors concluded that despite the similarity in the sedation levels induced by the two drugs, dexmedetomidine appears to provide several advantages and safe control for NIV sedation in ACPE patients, due to a more desired level of awake sedation, a shortened time to removal from MV, and a reduced length of ICU stay, as well as a decreased prevalence of nosocomial infections.

However, this study presents important limitations: 1) statistical bias due to the lack of evaluation of the sample

size for the primary end-point (ETI rate); 2) typology of the chosen population, ie. ACPE, who is fast-responding to NIV.

A new technology, the target-controlled infusion (TCI), was implemented in a recent study with the aim of better optimize the loading dose and the maintenance infusion rate of a drug in according to the level of sedative effect desired. In a pilot study, Clouzeau et al. (43) assessed the feasibility and safety of TCI of propofol for conscious sedation during NIV in 10 ARF patients (7 hypoxemic and 3 hypercapnic) with NIV failure due to discomfort, claustrophobia, severe agitation and/or refusal. TCI is a modern way of administering anesthetics based on a pharmacokinetic protocol assisted by a computerized mathematical calculation predicting the blood drug concentration associate with delivery of a given amount of the drug (44). TCI allows rapid and precise adjustment of the propofol concentration according to the clinical response of the patients. For the first NIV session, the target effect-site concentration of propofol was initially set at 0.4 mcgr/ml; subsequently, it was increased of steps of 0.2 mcgr/ml until the sedation goal was achieved (OAA/S level between 3 and 4; i.e. "response to verbal stimulation"). The patients received a total of 85 NIV sessions with a mean duration of 2 hours for a total of 180 hrs. Comfort was evaluated as "good" or "excellent" by all of the patients. Some patients presented episodes of over-sedation, but 98.9% of the total infusion time was passed at the desired level of sedation. Recovery was prompt in all patients. NIV under TCI with propofol significantly improved blood gases as compared to baseline. No significant hemodynamic changes and apnea or significant desaturation were registered during NIV. No modifications of ventilator setting were required for clinical reason (i.e. airway obstruction) and no increase of air leaks was recorded. Three patients required ETI, two due to the evolution of the underlying disease and one because of seizure disorder. Eight patients were discharged from ICU and two died. The medical consumption time was only 3.9% of the ventilator time, mainly during the first NIV session. According to this preliminary study, TCI-based propofol administration was judged to be safe and effective for the treatment of NIV failure due to low tolerance. A part from the small sample of the study, one limitation is the type of the selection of the patients in whom NIV has failed due to difficulties in application and not due to the severity of ARF.

The "Real life" scenario

The number of nurses influenced the decision to use sedative during NIV.

A cross-sectional Web-based survey (45) carried out on almost 3,000 American and European physicians concluded that most physicians infrequently use sedation and analgesic therapy for ARF patients receiving NIV, but practices differ widely

within and among specialties and geographic regions. Sedation was administered more often by intermittent intravenous bolus (78%) rather than continuous infusion (30%) or by mouth (11%). Despite the fact that the majority (51%) of the surveyed physicians agreed that protocols

are useful to optimize sedation during NIV only few centers (14%) used protocol designed ad hoc for NIV. In the "real life" the effects of sedation was assessed by nurses using clinical end-points (63%) rather than by sedation scales (32%). A benzodiazepine alone was the most preferred (33%), followed by an opioid alone (29%). Lorazepam (18%) was next in frequency use, followed by midazolam (15%), morphine (12%), and fentanyl (8%). Propofol-containing regimens (7%) and dexmedetomidine-containing regimens (5%) were rarely chosen as first-line sedative strategy. Europeans were less likely to use a benzodiazepine alone (25 vs. 39%, $p<0.001$) but more likely to use an opioid alone (37 vs. 26%, $p<0.009$). North Americans more commonly used sedation, analgesia, and hand restraints than Europeans. The survey highlighted that few data exist regarding current sedation practices during NIV and practices vary widely and between specialties.

It's important to highlight that all the reported studies were performed in high-intensity settings, such as ICU or RICU, with a long experience in NIV therapy and in handling sedative drugs and where the patient is closely monitored and adequately cared and last but not least ETI is promptly available if NIV fails. Close monitoring is mandatory and must include continuous assessment of cardio-respiratory and ventilator parameters, blood gas analysis, at least one sedation scale, and adverse events (6). According to the recent survey (45), not unexpectedly, nurses (67%) and, less often, physicians (28%) were the healthcare professionals most responsible for monitoring sedation. The number of nurses influenced the decision to use sedative during NIV; specifically, the ideal nurse-to patient ratio for monitoring NIV-treated patients receiving sedation was most often believed to be 1:2 (65%), followed by 1:3 (26%) and 1:1 (9%). Consistently, even if the use of NIV for the treatment of ARF is increasing outside ICU in low-intensity of care setting (46), it's highly recommended that sedation during NIV should be restricted to ICU or expert RICUs (47).

Conclusions

Despite the increase popularity of NIV to manage ARF, up to a quarter of patients fails because of poor adherence or refusal to the ventilator treatment and therefore ETI-CMV is required. The implementation of sedation-based strategy to rescue patients with poor co-operation and/or adaptation to NIV is appealing to enlarge its rate of success. Pilot studies suggest that continuous infusion of a single different sedative and analgesic agent titrated to obtain a "conscious sedation" may decrease patient discomfort, with no significant effects on respiratory drive, respiratory pattern, or hemodynamic; in addition gas exchange improved under NIV plus sedation. However, the level of the evidence in favor of a large application of sedation during NIV is still limited and further larger and controlled trials are needed to clarify the indications of sedation during NIV. Careful selection of candidates, setting of application, expertise of the team and capability of prompting intubating the patients are the key-ingredients necessary for attempting in safety this procedure which should be implemented within a strategy aimed at reducing the risk of NIV failure in poor tolerant subjects.

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