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Remifentanil-based sedation to treat noninvasive ventilation failure: a preliminary study

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Abstract *Objective:* To assess the feasibility and safety of remifentanil-based sedation during noninvasive ventilation (NIV) in patients with NIV failure. *Design and setting:* Prospective clinical investigation in a 16-bed intensive care unit of a university hospital in France. *Patients:* Thirteen patients in NIV failure due to discomfort and/or refusal to continue this ventilatory support: 10 with acute respiratory failure and 3 with acute hypercapnic respiratory failure. *Intervention:* Patients were administered methylene blue and were sedated (Ramsay scale 2–3) by a continuous perfusion of remifentanil during NIV. Cardiorespiratory and ventilatory parameters, blood gas analysis, and adverse events were prospectively recorded. *Measurements and results:* The 13 patients received a total of 125 NIV sessions, totaling 1200 h, of NIV under remifentanil-based sedation (mean remifentanil dose 0.1 ± 0.03 μg/kg per minute). Three patients also required propofol. PaO_2/FIO_2 ratio increased from 134 ± 69 to 187 ± 43 mmHg after 1 h. In patients with acute respiratory failure respiratory rate decreased from 34 ± 12 per minute before remifentanil to 25 ± 4 per minute after 1 h. In the three patients with acute hypercapnic respiratory failure $PaCO_2$ decreased from 69 ± 7 to 42 ± 5 mmHg. Four patients required endotracheal intubation without aspiration pneumonia. Twelve of the 13 patients left the ICU. *Conclusion:* This pilot study shows that remifentanil-based sedation is safe and effective in the treatment of NIV failure due to low tolerance.

Keywords Noninvasive ventilation · Acute respiratory failure · Mechanical ventilation · Remifentanil · Critical care · Sedation

Introduction

Recent studies have shown that noninvasive ventilation (NIV) reduces the risk of pneumonia [1], barotraumas [2] and even mortality in patients with acute respiratory failure [3, 4], particularly in immunosuppressed patients [5]. Girou et al. [6] recently demonstrated that implementing routine use of NIV in critically ill patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) or severe cardiopulmonary edema is associated with improved survival and reduction in nosocomial infections. Despite the advantages of NIV in critically ill patients this procedure is associated with a large number of failures, including patient refusal to continue the often uncomfortable sessions [7]. Analgesia-based sedation is provided for invasive ventilation, to increase tolerance of the interface and respirator. In a recent study Conti et al. [8] have shown that the continuous infusion of sufentanil may be used as a single sedative agent, allowing mitigation of patient discomfort and the obtaining of the desired level of awake sedation, with no significant effects on respiratory drive, minute volume, respiratory frequency, respiratory pattern, blood gases, or hemodynamics [8]. However, sufentanil is not a short-acting

opioid [9], and it is metabolized by the liver. Its long-term infusion may cause accumulation phenomena, which may delay patient recovery and augment the risk of respiratory depression [10]. Due to the lack of protection of the respiratory tract and unpredictable and/or delayed recovery in patients under discontinuous ventilation, sufentanil-based sedation is both difficult and dangerous for NIV [9, 11].

Remifentanil is a newly developed anilidopiperidine opioid with pharmacodynamic properties similar to those of other opioids but a unique 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 [9, 12]. Remifentanil is indicated for use during the induction and maintenance of general anesthesia and for the administration of analgesia in critically ill, mechanically ventilated patients for up to 3 days [13]. 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, possibly even in NIV [14].

The purpose of this study was to assess, for the first time, feasibility, and safety of remifentanil-based sedation during NIV in patients with NIV failure.

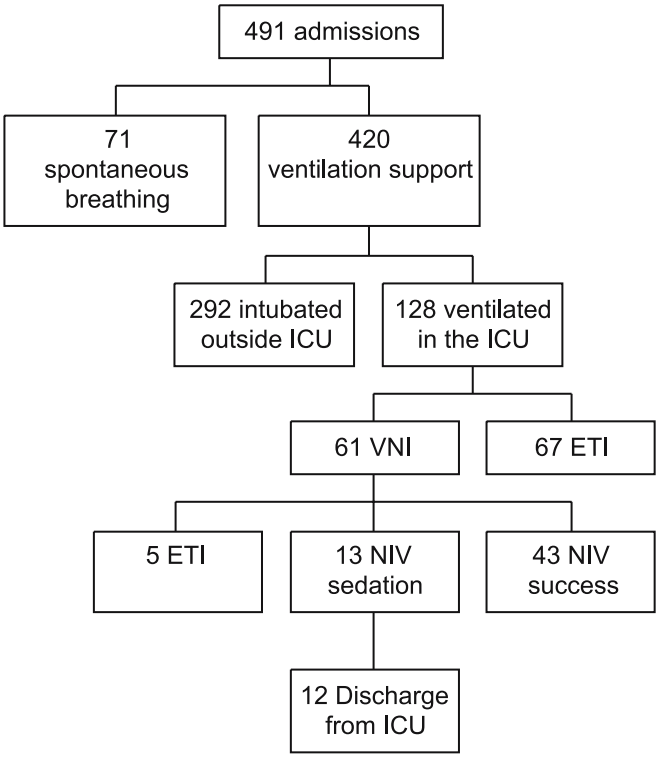

Fig. 1 Flow chart of admissions in the ICU during the study period according to mechanical ventilation. *NIV* Noninvasive ventilation; *ETI* endotracheal intubation

Patients and methods

Patient selection

The study cohort consisted of 13 patients with acute respiratory failure (without congestive heart failure) under NIV for an 8-month period (mean age 51 ± 22 years; 4 women, 9 men; mean Simplified Acute Physiology Score II 32 ± 10; Fig. 1). Inclusion criteria were NIV failure due to patient refusal to continue the NIV sessions (due to discomfort), relapsing hypoxemia upon interruption of the NIV, and marked agitation. Exclusion criteria were NIV failure due to impossibility of managing copious secretions, severely decreased consciousness (Glasgow Coma Scale score less than 9) not caused by hypercapnia, absence of improved gas exchange after 30 min of NIV, severe hemodynamic instability despite fluid challenge and use of vasoactive agents (systolic arterial blood pressure less than 70 mmHg), respiratory arrest, high digestive tract hemorrhage, glucose 6 phosphate dehydrogenase deficiency (contraindication to methylene blue), known allergy to remifentanil or propofol, incomprehension of the study or refusal to participate, or inclusion in another research protocol. Five patients presented with acute kidney failure, including one on continuous venovenous hemodiafiltration, and six were immunocompromised. Their reasons for admission to the intensive care unit, and the causes of respiratory distress and NIV failure are listed in Table 1. Each of patients had a score on the Glasgow Coma Scale higher than 11 at study inclusion. Ten patients presented with acute hypoxemic respiratory failure, defined as a PaO_2/FIO_2 ratio less than 300 mmHg without left cardiac decompensation. Three presented with acute hypercapnic respiratory failure (AHRF) with pH below 7.3 and $PaCO_2$ above 50 mmHg. One patient (no. 4) died (after the end of the study) due to care limitation after another stroke. The experimental protocol was approved by our institutional review board for human subjects. Written informed consent was obtained from each study patient or next of kin.

Study design

Patients were administered a methylene blue capsule, as a marker of regurgitation, either by mouth or through a gastric tube; if necessary, the gastric tube was blocked throughout the NIV session. Remifentanil ($0.025\ \mu g\ kg^{-1}\ min^{-1}$) was infused through a dedicated line of the central catheter. The goal was to achieve sedation between 2 and 3 on the Ramsay scale [15]

Table 1 Patients' clinical characteristics (SAPS Simplified Acute Physiology Score, *ARF* acute renal failure, *AHRF* acute hypercapnic respiratory failure)

Patient no.	Age (years)	Sex	Cause of ICU admission	SAPS	NIV indication	ARF	Intubation	ICU length of stay (days)	Outcome
1	20	F	Pneumonia	18	Hypoxemia	No	Yes	23	Alive
2	80	F	Pulmonary fibrosis	51	Hypoxemia	No	No	12	Alive
3	20	M	Pneumonia	15	Hypoxemia	No	No	6	Alive
4	65	M	Stroke	32	AHRF	No	Yes	29	Dead
5	43	M	Hepatic encephalopathy	41	Hypoxemia	No	No	19	Alive
6	61	M	Sepsis	41	Hypoxemia	Yes	No	11	Alive
7	67	M	Esophagus surgery	25	Hypoxemia	No	No	34	Alive
8	56	M	Aspiration pneumonia	24	Hypoxemia	Yes	Yes	13	Alive
9	21	F	Cystic fibrosis	32	AHRF	Yes	No	9	Alive
10	51	M	Acute pancreatitis	43	Hypoxemia	No	No	27	Alive
11	85	F	Pneumonia	42	Hypoxemia	Yes	Yes	23	Alive
12	39	M	Aspiration pneumonia	27	Hypoxemia	No	No	10	Alive
13	65	M	Hepatectomy	29	AHRF	No	No	31	Alive
Mean ± SD	51 ± 22	–	–	32 ± 10	–	–	–	19 ± 9	–

by increasing the infusion rate by 0.025 μg kg^{-1} min^{-1} every minute to a maximum of 0.15 μg kg^{-1} min^{-1}. If the required level of sedation was not obtained, propofol was administered at a dose of 10 mg/h, increasing 10 mg/h every minute to a maximum of 50 mg/h. Once the correct sedation level was achieved, the NIV session was initiated in pressure-support ventilation (without mandatory cycles) on an Evita 2 Dura ventilator (Dräger, Lübeck, Germany) with heated humidifiers [16, 17] (Fisher & Paykel, MR 730, Panmure, New Zealand). When a nasogastric tube was used for patient care, it was placed on a specific device (Mertro seal, Rusch, Germany) to limit air lick during NIV. The 13 patients received a total of 125 NIV sessions lasting an average of 9 ± 2 h (range 3–20) for a total of 1200 h (Fig. 2), without clinical gastric dilation, vomiting, or facial skin lesions. The mean number of sessions per patient was 10 ± 8 (range 1–26).

The ventilator was set according to the following protocol [5]. After the mask (Vmask 7600, Rusch, Germany) was secured, the level of pressure support was progressively increased and adjusted for each patient to obtain an expired tidal volume (Vt) of 7–10 ml/kg body weight and a respiratory rate of fewer than 35 breaths per minute. Positive end-expiratory pressure (PEEP) was repeatedly increased by 2 cmH_2O to a maximum of 10 cmH_2O until the FIO_2 requirement was 65% or less. For AHRF in patients with COPD, PEEP was set to ovoid intrinsic PEEP. The diagnosis of COPD was based on clinical history, physical examination, and prior pulmonary function tests.

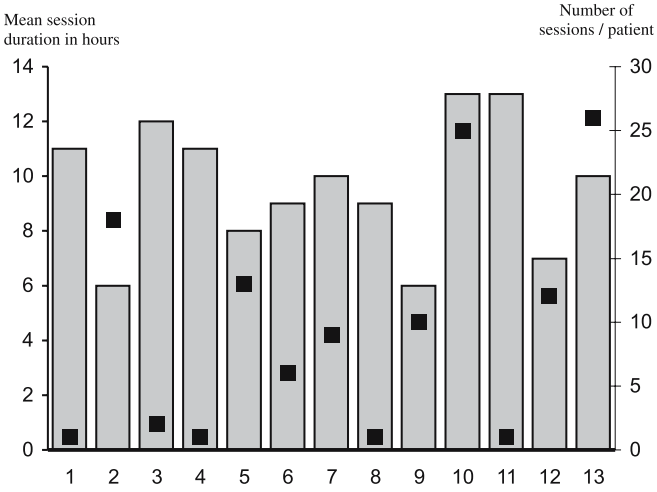

Fig. 2 NIV sessions for all patients. Mean duration (*bars*) and number (*closed squares*) of NIV sessions for each patient. Patient nos. 1, 4, 8, and 11 required ETI at the end of the first session

Adverse events, including gastric dilation, vomiting, and facial skin and eye lesions, were recorded every hour. Five minutes before the end of the first NIV session, after FIO_2 was increased to 100%, a nasotracheal fibroscopy was performed to search for traces of methylene blue in the upper respiratory tract and trachea (BF-TE2, Olympus, Tokyo, Japan). This fibroscopy was performed at the end of the first session, after increase FIO_2 at 100%. During other sessions fibroscopy was performed only if inhalation was suspected or after endotracheal intubation (ETI).

Sedation was interrupted, and at recovery (eyes opening and shaking hand to verbal command) patients were separated from the ventilator. Blood gas analysis was performed before the beginning, 1 h after beginning, and at the end of each NIV session. Respiratory parameters, including respiratory rate (RR), expiratory Vt, inspiratory Vt, minute ventilation, PEEP and SpO_2, and hemodynamic parameters, including heart rate, systolic blood pressure, and diastolic blood pressure, were measured continuously. All patients had an arterial catheter for clinical management. Remifentanil and propofol doses were recorded every 15 min and at every change in administration rate.

The predetermined criteria for ETI were as follows: failure to maintain a PaO_2/FIO_2 ratio greater than 85, development of conditions requiring ETI to protect the airways (e.g., seizure disorder or vomiting); development of copious tracheal secretions; increase in the partial pressure of arterial carbon dioxide accompanied by a pH of 7.30 or less; severe hemodynamic instability, defined as a systolic blood pressure of less than 70 mmHg; or evidence on electrocardiography of ischemia or clinically significant ventricular arrhythmias. In the case of ETI a tracheal fibroscopy was performed (from the trachea to the right and left mean bronchi and through the endotracheal tube), after the hemodynamic and ventilatory stabilization period, to search for methylene blue.

Statistical analysis

All data are expressed as mean ± standard deviation. The hemodynamic and ventilatory variations at the various time points were subjected to analysis of variance with repeat measurements and a post-hoc test. A p value less 0.05 was taken to indicate statistical significance.

Results

Patients' anthropometric and respiratory characteristics during the first NIV session are summarized in Table 2. During all the sessions, we observed no decrease in blood pressure or heart rate greater than 20% from baseline. Respiratory rate decreased from 34 ± 12/min before remifentanil infusion to 25 ± 4/min ($p < 0.01$) after 1 h of NIV but never dropped below 20/min. The mean PaO_2/FIO_2 ratio increased from baseline 134 ± 69 to 187 ± 43 mmHg after 1 h of NIV ($p < 0.05$) and to 196 ± 52 mmHg at the end of the sessions (NS). In hypoxemic patients $PaCO_2$ increased from 33 ± 22 to 36 ± 21 mmHg after 1 h to 39 ± 8 mmHg at the end of the session (NS), and pH decreased from 7.49 ± 0.07 to 7.43 ± 0.07 at 1 h to 7.40 ± 0.03 at the end. In the three patients with AHRF $PaCO_2$ decreased from 69 ± 7 to 42 ± 5 mmHg after 1 h ($p < 0.001$), and pH increased from 7.21 + 0.02 to 7.33 ± 0.01 ($p < 0.001$).

The mean remifentanil dose was 0.1 ± 0.03 μg/kg per minute. Three patients (nos. 1, 3, and 9) also required 0.9 ± 0.3 mg/kg per hour propofol. Four patients required ETI during the study (median 11 h), all during the first NIV session and all due to an inability to maintain a PaO_2/FIO_2 ratio above 85 mmHg; bronchial fibroscopy through an endotracheal tube detected no methylene blue. No methylene blue was detected by fibroscopy in the nine other patients at the end of the first NIV session, and no inhalation was suspected. We also did not observe signif-

Table 2 Patients' anthropometric and respiratory characteristics [*BMI* body mass index, *RR pre-NIV* respiratory rate, *RR peri-NIV* respiratory rate during the first session of NIV, *Vt* tidal volume during the first session of NIV (mean five cycles)]

Patient no.	Weight (kg)	Height (cm)	BMI	Nasogastric tube	RR pre-NIV (min^{-1})	PaO_2 (mmHg)[a]	$PaCO_2$ (mmHg)[a]	pH[a]	Mean Vt (ml)	RR peri-NIV (min^{-1})
1	52	169	18	No	45	54	25	7.53	410	17
2	48	157	19	Yes	39	41	34	7.4	390	28
3	81	188	23	No	40	48	22	7.58	630	14
4	87	168	31	Yes	22	61	78	7.27	570	19
5	61	177	19	Yes	28	64	31	7.38	520	18
6	75	170	26	No	34	62	27	7.42	710	26
7	92	179	29	Yes	29	46	39	7.36	640	14
8	83	174	27	No	24	72	35	7.34	780	22
9	42	161	16	No	38	53	82	7.21	410	14
10	97	175	32	Yes	34	59	32	7.44	620	16
11	44	156	18	No	22	44	40	7.34	330	18
12	84	194	22	No	26	55	30	7.49	810	20
13	85	180	26	Yes	42	48	64	7.19	640	30
Mean ± SD	71 ± 19	172 ± 11	23 ± 5		32 ± 7	54 ± 9	41 ± 20	7.38 ± 0.11	573 ± 153	19 ± 5

[a] Before the first session of NIV

icant desaturation ($SpO_2 < 95\%$) during fibroscopy. No patient presented with confirmed or suspected aspiration pneumonia during follow-up in the hospital.

Discussion

Since the pilot study by Rocker et al. [18] NIV has been considered as an alternative in the management of acute lung injury. Ten years ago they reported the use of sedation to allow NIV in hypoxemic patients. Physiological studies on the effects of analgesia-based sedation on respiratory mechanics [8, 19, 20] and new opioids with adapted pharmacokinetics can now allow NIV while patients are under sedation.

We show here that remifentanil-based sedation during NIV is effective and safe in selected patients with NIV failure. In contrast to previous reports, in which 50% of patients had COPD and 14% had hypoxemic respiratory failure [1], the patients included in our study suffered essentially from acute hypoxic respiratory failure (77%) or from AHRF with COPD (23%). Patients with cardiogenic pulmonary edema were excluded from this study. The proportion of hypoxemic patients who experience NIV failure is generally higher than among patients with AHRF. The severity scores and patient age in this study were comparable to those previously reported [1]. Although 77% of patients in that study required ETI [1], only 30% of our patients required this procedure.

The use of opioids as single sedatives has been restricted, especially in patients receiving partial ventilatory support [21] due to their effects on respiratory drive, which sometimes occurs even at low doses. Morphine and fentanyl act on all opioid receptor subtypes, providing effective analgesia at the price of a marked reduction in respiratory drive. Sufentanil and remifentanil, two recently developed synthetic opioids, possess attractive properties for continuous infusion in ICU patients, since they interact almost exclusively with μ_1-receptors. Sufentanil-based sedation has been used in patients under pressure support ventilation, since they increase comfort without decreasing respiratory drive [8]. Since sufentanil is not a short acting opioid, however, its long-term infusion may cause accumulation phenomena that may delay patient recovery [10]. We therefore preferred remifentanil-based sedation for patients in NIV. Moreover, we needed to obtain a good level of sedation quickly, and the pKa of remifentanil (i.e., pH at which the opioid is 50% ionized) is lower than physiological pH, allowing this drug to penetrate the blood-brain barrier and leading to rapid equilibration of its concentration.

Our findings are consistent with earlier results showing that low doses of remifentanil ($0.05\ \mu g\ kg^{-1}\ min^{-1}$ provide analgesia and sedation in critically ill patients without decreasing respiratory drive [19]. The doses that we used were slightly higher than those used elsewhere, but they induced a similar level of sedation [20, 22]. We found that $PaCO_2$ increased 9% after 1 h, but this increase was not statistically significant. Our data do not support or refute the hypothesis that remifentanil decreases respiratory drive. Before NIV the ten patients in acute renal failure presented with respiratory alkalosis due to hypoxemia. An increase in PaO_2 could reduce hyperventilation. In the other hand, $PaCO_2$ decreased 64% after 1 h of NIV under sedation in patients with AHRF whereas respiratory rate decreased 36% but never dropped below 20/min. Continuous transcutaneous monitoring of PCO_2 [23, 24] may clarify this and may be helpful in clinical practice.

Although continuous intravenous weight-adjusted infusion of remifentanil is the routine practice in our ICU, it is probably not the best way to administer this drug. Target-controlled infusion of remifentanil is routinely used for perioperative analgesia because less drug is required and because of its smooth mode of administration [25]. These results suggest that target-controlled infusion of remifentanil is a more efficient route of administration in spontaneously breathing patients.

As previously reported [19], the required level of sedation in three patients was not achieved with the maximum allowed dose of remifentanil. To avoid high doses of opioids, which decrease respiratory drive [19, 20], we used a combination of propofol and remifentanil, resulting in a reduction in the dose requirement for both agents [26], especially of propofol [27]. However, when the association remifentanil and propofol is infused for a prolonged period, there is possible risks of propofol accumulation.

An important limitation of our study was the relatively small number of patients, which may not have allowed us to detect all possible complications. Moreover, these results were obtained in an intensive care unit of a department of anesthesiology which is experienced in routine NIV therapy and in the use of remifentanil for ventilated patients. Analgesia-based sedation can mask the side effects of NIV, such as gastric dilation and facial skin lesions. Using a precise, written nursing protocol, however, we did not observe any adverse events over 1200 h of NIV.

Conclusion

This small pilot study reports the feasibility and safety of remifentanil-based sedation during NIV in patients with NIV failure. If a reduction in the rate of ETI is confirmed in controlled, randomized trials, the use of analgesia-based sedation to treat NIV failure would be an interesting alternative.

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