Noninvasive Ventilation. The Essentials
Under the Auspices of the International Association of Non-invasive Mechanical Ventilation
Series Editor: Antonio M. Esquinas

Antonio M. Esquinas
Bushra Mina
Savino Spadaro
Daniela Perrotta
Francesco De Sanctis *Editors*

Pharmacology in Noninvasive Ventilation

Springer

Noninvasive Ventilation. The Essentials

Series Editor
Antonio M. Esquinas, Hospital Morales Meseguer
Murcia, Spain

Nowadays, Noninvasive Ventilation (NIV) is widely accepted in medical practice. This Series, titled "Noninvasive Ventilation: Clinical and Practice," is a culmination of extensive prior publications on the topic. It aims to define current clinical developments in NIV technologies, including equipment and ventilator modes, and provide practical recommendations primarily in Critical Care (CC), Pulmonary, Emergency, and Sleep Medicine.

Building on previous publications, a group of experienced Editors and top international contributors aim to present new books that take a multidisciplinary approach and provide a comprehensive overview of Non-invasive Ventilation. The main goals of this Series are as follows:

Establish a scientific reference for NIV clinical practice, covering pathophysiology, clinical indications, and evidence-based concepts.

Present significant advances in CC, pneumology, anesthesiology, sleep medicine, pediatrics, and healthcare organization in acute and chronic respiratory failure.

Analyze technological advancements and complementary procedures associated with NIV, such as aerosol therapy, humidification, and airway clearance, crucial for effective NIV techniques.

Serve as a valuable teaching reference for healthcare professionals, including residents, consultants, and allied healthcare professionals, as well as undergraduate and postgraduate students and fellowship participants.

The Series will produce focused thematic volumes, led by internationally recognized guest editors, providing comprehensive coverage of specific areas of NIV advancement in CC, emergency medicine, pulmonary, and sleep medicine.

Antonio M. Esquinas • Bushra Mina
Savino Spadaro • Daniela Perrotta
Francesco De Sanctis
Editors

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Springer

Editors
Antonio M. Esquinas
Intensive Care Unit
Hospital General Universitario Morales M
Murcia, Murcia, Spain

Savino Spadaro
Translational Medicine
University of Ferrara
Ferrara, Italy

Francesco De Sanctis
Anesthesiology and Pediatric Intensive Care
UOC ARCO Palidoro Bambino Gesù
Children's Hospital
Roma, Italy

Bushra Mina
Medicine, Pulmonary Critical Care Medicine
Northern Westchester Hospital
Mount Kisco, NY, USA

Daniela Perrotta
Anesthesiology and Pediatric Intensive Care
Bambino Gesù Children's Hospital
Roma, Italy

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Abbreviations

ACE inhibitors	Angiotensin converting enzyme inhibitors
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute respiratory distress syndrome
BiPAP	Bi-level positive airway pressure
BIS	Bispectral index
BVM	Bag-valve mask
BZDs	Benzodiazepines
CHF	Chronic heart failure
CNS	Central nervous system
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary edema
CPET	Cardiopulmonary exercise testing
CT	Computed tomography
CTPA	Computerized tomography pulmonary angiography
DLCO	Diffusing capacity for carbon monoxide
EtN_2	End-tidal nitrogen concentration
EtO_2	End-tidal oxygen concentration
FAO_2	Alveolar fraction of oxygen
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
FVC	Forced vital capacity
GABA	Gamma aminobutyric acid
GCS	Glasgow Coma Scale
HFNC	High-flow nasal cannula
HFpEF	Heart failure with preserved ejection fraction
iCPET	Invasive cardiopulmonary exercise testing
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
iNO	Inhaled nitric oxide
MAP	Mean arterial pressure
mMRC	modified Medical Research Council
NDMAD	N-desmethyl adinazolam

NIV	Noninvasive mechanical ventilation
NIV	Noninvasive ventilation
NMA	Network meta-analysis
NO	Nitric oxide
NPPV	Noninvasive positive pressure ventilation
NRM	Non-rebreathing mask
NTG	Nitroglycerin
NT-pro BNP	N-terminal pro-brain natriuretic peptide
P:F Ratio	PaO_2:FiO_2 Ratio
PaO_2	Partial pressure of arterial oxygen
PCWP	Pulmonary capillary wedge pressure
PEEP	Positive end expiratory pressure
PFT	Pulmonary function test
PND	Paroxysmal nocturnal dyspnea
PPHN	Persistent pulmonary hypertension of the newborn
PVR	Pulmonary vascular resistance
RARs	Rapidly adapting receptors
RAS	Reticular activating system
RASS	Richmond Agitation-Sedation scale
RCT	Randomized controlled trial
RSI	Rapid sequence induction
RSS	Ramsay scale
SAPS	Simplified Acute Physiology Score II
SARs	Slowly adapting receptors
SAS	Riker Sedation-Agitation scale
THRIVE	Transnasal humidified rapid insufflation ventilatory exchange

1 Noninvasive Ventilation and Pharmacology: Basic Physiological Interaction

Ketki Deotale, Subrata Singha, and Jitendra Kalabandhe

1.1 Introduction

In recent years, the use of noninvasive ventilation (NIV) to manage respiratory failure has dramatically expanded, as it offers less dependency on invasive mechanical ventilation (IMV) and its associated complications such as upper respiratory airway trauma and haemorrhage and the use of muscle relaxants and sedative drugs that have been proven to hurt clinical outcomes [1, 2]. Nevertheless, this widespread use of NIV has allowed us to determine its application's limits. Mask intolerance and agitation due to several factors such as anxiety, fear, pain, discomfort or claustrophobia may result in a patient's refusal of ongoing NIV, leading to its discontinuation and subsequent requirement for endotracheal intubation [3]. In this regard, NIV failure is defined as the need for endotracheal intubation and has a high failure rate (up to 40%) [4, 5]. Failure of NIV is a significant issue because it is related to adverse clinical outcomes, such as increased mortality and the prolongation of mechanical ventilation [6]. Therefore, increasing attention is now being paid to understanding the possible factors responsible for NIV intolerance to improve patient comfort during NIV.

According to Carlucci et al., the rate of NIV discontinuation associated with patient refusal was up to 22% [7]. The NIV interface tolerance, anchor system, ventilatory settings, humidification, noise, patient position, psychological distress, anxiety, fear, pain and type and severity of the respiratory failure contribute to NIV intolerance. The underlying disease, haemodynamic instability, neurological status deterioration and poor patient-ventilator synchrony are some factors that also contribute to NIV intolerance/deterioration. Various interventional strategies to improve patient's comfort and ensure the success of NIV include establishing a relationship

K. Deotale · S. Singha (✉) · J. Kalabandhe
Department of Anesthesia and Critical Care, AIIMS Raipur, Raipur, Chhattisgarh, India

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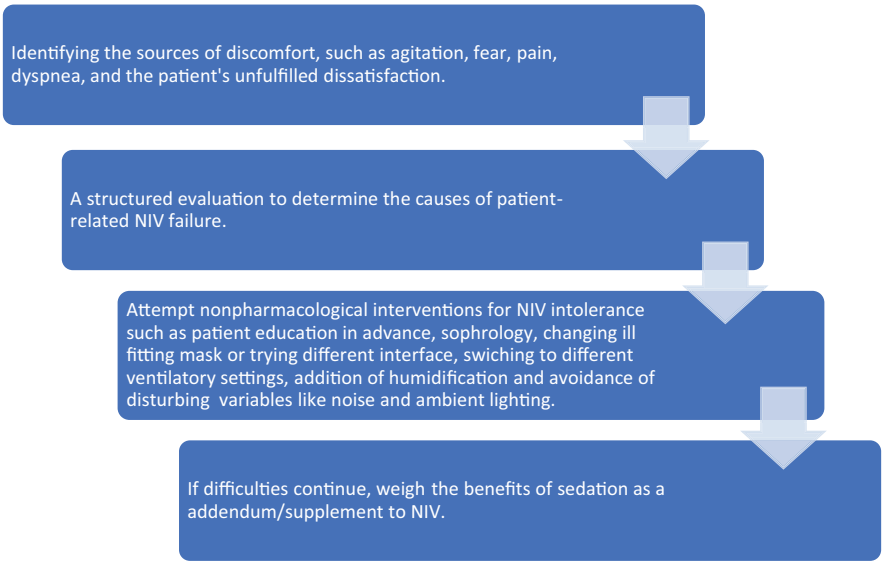

Fig. 1.1 Clinical rationale/approach for the use of sedation in NIV

of collaboration with the patient, switching to another interface, changing the ventilatory setting (PSV, NAVA or PAV) and progressively increasing inspiratory pressure (thereby giving time for the patient to adapt), adopting interface rotation strategy, adding adequate humidification and controlling disturbing factors such as noise [8] (Fig. 1.1). Pharmacological measures, including analgo-sedative medications, can be a valuable option to avoid intubation when the above-listed non-pharmacological strategies prove unsuccessful.

1.1.1 Is It Necessary to Use Sedation During NIV? What Does the Literature Say?

Sedation and analgesia can alleviate psychological distress and pain, improving NIV tolerance. Due to lack of evidence, sedation practices widely differ within and among specialities and geographic regions, and the physician's clinical experience determines agent selection [9]. In 2015, an ancillary study conducted by Muriel et al. [10], using data from a prospective, international, multicentre observational trial of mechanically ventilated patients conducted in 322 ICUs from 30 countries [11], analysed the impact of analgesia and sedation on the risk of NIV failure. Patients who received at least 2 h of NIV as first-line ventilatory support at ICU admission were selected. They reported that about 19.6% of patients (162/842) received analgesia or sedation during NPPV; 8 patients received analgesia, 44 patients received sedation and 33 patients received both. Using a marginal structural model analysis, they observed no deleterious effect on NIV outcome when sedation

or analgesia was used as a single agent; however, their simultaneous use was significantly associated with NIV failure, ICU mortality and 28-day mortality. The study did, however, have certain limitations.

Another cross-sectional Web-based survey conducted by Devlin et al. identified that sedation was used in only ≤25% of patients receiving NIV [9]. Matsumoto et al. retrospectively evaluated the role of sedation in agitated patients treated with NIV after an episode of acute respiratory failure. Of the 155 of 3506 patients who received NIV, only 3.4% (81 patients with non-intubation code [DNI] and 39 non-DNI) were sedated intermittently or by continuous infusion. Risperidone or haloperidol for intermittent use and dexmedetomidine, midazolam or propofol for constant information were titrated as per RASS scores. The authors concluded that sedation is potentially helpful in avoiding NIV failure in both groups of patients (DNI and non-DNI) [12]. Several other observational studies and RCTs have also compared the efficacy and safety of sedatives during NIV, which will be discussed later in this chapter.

1.1.2 The Goal of Sedation in ICU Settings and During NIV or Does NIV Have an Impact on Sedation Goals?

The goals of sedation in the intensive care unit (ICU) are to ensure analgesia and comfort, preserve natural sleep cycles and avoid disturbances such as ambient light and noise in a cooperative patient. Haemodynamic stability, preservation of metabolic homeostasis, muscular relaxation, preservation of diaphragmatic function, attenuation of the stress/immune response and the programmed withdrawal from sedation are also some of the goals which should not be different during NIV. Nonetheless, if NIV is being considered while progressing from intermittent mandatory ventilation to spontaneous breathing, there should be a gradual reduction in the use of sedation.

While using sedation during NIV, firstly, we should avoid deep sedation and the respiratory depressant effects of various sedatives. Secondly, untoward effects of sedative drugs resulting in impairment of the upper airway should be considered, especially in patients with obstructive sleep apnoea [13].

1.2 Effects of Pharmacological Interventions on Physiology of NIV

The level of acceptance and compliance with NIV depends on sedation, as cooperation can't be expected from an insensate/deeply sedated patient or an agitated, anxious and disoriented patient. Hence, a sedation regime that brings the patient to calm, alert cooperation is demanded. However, considering the following physiological aspects in play, pharmacological intervention should be regarded as the last stage after the causal evaluation of NIV intolerance (Fig. 1.1).

1.2.1 Is Sedation an Element/Component in the Success or Failure of NIV?

1.2.1.1 NIV Affects the Ventilatory Control Centre (VCC)

A cluster of neurons in the brainstem known as the ventilatory control centre (VCC) controls the ventilatory pattern (tidal volume, frequency and inspiratory/expiratory ratio). As it facilitates gas exchange and unloads muscles, NIV significantly impacts the brainstem's VCC. The VCC contains an intrinsic rhythm generator that receives inputs from chemoreceptors (i.e. PO_2, PCO_2 and pH receptors) in the great arteries and the fourth ventricle of the brain, as well as from mechanoreceptors (i.e. stretch and irritation receptors) in the thorax and ventilatory muscles. The VCC's output regulates the intensity and timing of ventilatory and inspiratory muscle contractions. Cortical inputs (e.g. pain, anxiety, stress, the presence of an artificial airway and various central nervous system injuries) can also impact this pattern (loop gain), usually boosting overall ventilatory drive. Drugs like sedatives and opioids, as well as many other central nervous system ailments, can suppress the total ventilatory drive [14]. A patient's sleep status can also influence these responses.

1.2.1.2 Sleep Status

Sleep quality and regular sleep patterns are believed to affect the restoration of health in ICU settings. A study concluded that early sleep disturbances illustrated by an abnormal electroencephalographic way, disruption of the circadian sleep cycle and decreased rapid eye movement sleep have been associated with late NIV failure in elderly patients with acute hypercapnic respiratory failure [15]. Neurophysiological features of intravenous anaesthetic drugs and their relationships to rest have been studied in detail. Still, investigations of the differential effects of sedatives on electrophysiological dimensions of sleep are some areas/points to ponder. Under these pretences, measures to alter the environment, such as minimising noise, ambient lighting and other disturbances, should be considered before using sedatives.

1.2.1.3 Patient-Ventilator Asynchrony and Sedation

Data obtained from a small cohort of 48 patients undergoing chronic NIV at home detected an increased incidence of ineffective efforts (IE) during sleep compared to an awake state. Consequently, these observations can be hypothetically considered in the ICU setting involving NIV and sedation.

A clinical challenge with NIV (and invasive ventilation) occurs with minimal ventilator settings but a vigorous patient effort resulting in potentially harmful transpulmonary pressures and volumes. In these scenarios, reversible causes of a robust inspiratory action such as pain, acidosis and anxiety must be addressed. However, beyond that, managing such patients without any apparent reason becomes an issue/difficult [16]. Some authors suggest that an inappropriate, excessive respiratory drive should be blunted with sedatives or opioids to prevent self-induced lung injury. On the contrary, others believe that self-induced lung injury is controversial and that sedative drugs should be avoided to ease the ventilator withdrawal process.

1.2.1.4 Respiratory Drive and Timing

Sedation and analgesia have different depressive effects on respiratory function depending on the drug's choice and dose, its sedative or analgesic effects and the recipient's sensitivity and metabolic capacity. Two classes of drugs have been used most frequently in some studies examining the clinical use of sedatives in patients receiving NIV or, more accurately, in patients failing NIV for interface intolerance: both GABAergic agonists such as midazolam or propofol and opiates such as morphine or remifentanil may blunt the respiratory centre's output. The electrical activity of the diaphragm (EAdi) can be considered a direct measure of respiratory drive and timing close to assessing respiratory centres, which permits a better understanding of patient-ventilator interaction. By implementing EAdi monitoring, it was proven that propofol substantially interferes with patient-ventilator synchrony in pressure support ventilation (PSV) at doses inducing deep sedation during MIV [17]. Propofol decreased neural drive and effort during PSV and neurally adjusted ventilator assistance (NAVA) while preserving the respiratory timing.

On the contrary, a reduction of the respiratory drive was not seen during continuous infusion of opioids. Still, detrimental effects on respiratory timing were observed when airway occlusion pressure was at 0.1 s (P 0.1) (surrogate of EAdi) [18, 19] or even when EAdi was measured directly [20]. Even though these results were obtained during invasive ventilation, they suggest caution when using the same sedation strategies and dosages during NIV, especially in light of the lack of data on other sedation side effects, particularly haemodynamic instability, which may be a severe problem in COPD patients who are typically older and have significant comorbidities such as cor pulmonale or other cardiovascular diseases.

1.2.1.5 Underlying Disease

It should be noted that the likelihood of NIV success seems to be related to the underlying disease in patients with hypoxic respiratory failure rather than to the degree of hypoxia. For example, acute respiratory distress syndrome or community-acquired pneumonia forewarns NIV failure, as does the lack of oxygenation improvement after an hour on NPPV. There is no substantial evidence that sedation will be beneficial in these situations where the response rate to NIV is intrinsically poor. On the contrary, initiating sedation in these situations may lead to failure of NIV due to underlying pathology and thus ultimately delaying MIV when necessary.

Also, sedation does not avert any of the contraindications to NIV [21]. Nava and Ceriana [22] divided NIV failure into three groups, namely, immediate (< 1 h after initiation), early (1–48 h) and late (>48 h), and identified predictors of failure for each time segment. Factors responsible for immediate NIV failure included "intolerance, agitation and patient-ventilator asynchrony", for which "judicious sedation" is recommended but not described in detail.

1.2.1.6 Experienced Staff

Patient acceptance and compliance are the critical factors for the success of NIV, and staff proficiency and competence play a vital role in achieving that. The NIV training and experience of the clinician team partly determine whether the patient

will succeed with NPPV or, instead, require intubation. Greater clinician-team NPPV experience and expertise are associated with a higher percentage of patients achieving NIV than a less-experienced clinician team [22].

Intensivists and nurses in ICUs are well-versed in administering sedatives and analgesics. Because of the varying sensitivities and rates of metabolism among patients, dosing these medicines can be complex. As a precaution, sedation and analgesia should be delivered by trained personnel at the minimal doses necessary to build tolerance while avoiding oversedation. This should be done in an environment where ECG and oximetry tracings can be examined constantly, at the very least. Several sedation scales are available to help guarantee that the dose of sedation is kept to a minimum, but their use requires experienced personnel.

1.2.2 Specific Situations Where Sedation During NIV Is Beneficial

Specific guidelines for NIV [2] acknowledge indications for which there is compelling or even persuasive (Grade 2B or better) evidence for the benefit of sedation during NIV is relatively small and may be summarised as follows:

Acute respiratory failure in the forms of:

- Exacerbation of chronic obstructive pulmonary disease (acute-on-chronic) with acidotic and hypercapnic components
- Acute respiratory failure in immunocompromised patients
- Respiratory failure that is secondary to cardiogenic pulmonary oedema not arising from shock or acute coronary syndrome

As an adjunct to extubation (in higher centres) for:

- Patients with COPD
- Patients who are at a high risk of recurrent respiratory failure

Most candidates for sedation during NIV are expected to come from these categories and share some presenting features. As seen earlier, discomfort, anxiety, agitation, pain, dyspnoea, delirium and the disappointed expectations of the patient are pivotal in many cases to failure of NIV and hence also to the decision to use sedation in NIV.

1.2.2.1 Agitation and Delirium

Patients already agitated before tracheal extubation are the first group to consider. Managing agitated and restless patients presenting with severe respiratory distress can be challenging. Failure of compliance with NIV calls for unwanted endotracheal intubation. Administration of a sedative drug should be preceded by a thorough evaluation of the causes of anxiety. Anxiety caused by a decrease or change in sedative regimen is diagnosed after all other stress causes have been excluded.

Some prospective observational studies reported the efficacy of sedatives for agitated patients with acute respiratory failure undergoing NIV [23–27]. The effects of delirium in NIV patients require immediate care. A comprehensive study indicated a high prevalence of fever in NIV patients (37%), connected to a significantly higher chance of failure. The evidence on which these conclusions were founded, on the other hand, was labelled as poor quality [28]. There is currently weak evidence for dexmedetomidine use in delirium management.

1.2.2.2 Dyspnoea

The second group of patients could well be those who are dyspnoeic and apprehensive, with dyspnoea being related to extubation delays. In a report published by the American Thoracic Society, dyspnoea's neuro(patho)physiology and clinical features were explored in depth [29]. Dyspnoea was characterised based on the quality of the dyspnoea experience, the stimuli that elicited it and the afferent neural pathways that mediate it.

It's important to emphasise that dyspnoea has an affective component that may be distinguished from the sensory dimension and modulated independently [30]. This highlights the necessity of recognising and evaluating the anxiety element of dyspnoea. The patient's participation is required, and any existing sedation regimen must be modified to meet that requirement. Single-item evaluations of severity of discomfort or unpleasantness, as well as multi-item scales of emotional responses such as anxiety, can be used to explore the affective dimension of dyspnoea.

As a result, sedation may be beneficial in cases where NIV is recommended, and meticulous examination indicates anxiety, dyspnoea with a high affective dimension or delirium as roadblock/hurdle to successful implementation.

1.2.3 Analgesics and Sedatives Are Preferably Used During NIV

When the non-pharmacological strategies have failed, analgo-sedation schemes can be employed to manage agitation during NIV. Given the pathophysiology of an NIV failure, the selection of sedative drug depends upon three factors: the upper airway patency, respiratory depression and the affective aspect of dyspnoea.

Agitation can be due to fear, anxiety, pain, lack of sleep, fever and hypoxia. To counteract musculoskeletal pain and subsequent stiffening of the chest wall and diaphragm, analgesic drugs such as acetaminophen, nonsteroidal anti-inflammatory drugs or opioid can be administered [31]. Physicians can choose sedative drugs when the cause for agitation is anxiety or intolerance. The rate of NIV failure could be reduced by implying a sedation strategy [32].

Irrespective of the sedation plan adopted, sedation assessment is vital during NIV through subjective scales like RASS (Richmond agitation-sedation scale) [12] or tools like the bi-spectral index and entropy. A sedation assessment at regular time intervals allows to achieve the desired sedation target and avert oversedation [33].

1.2.3.1 Opioids

Opioids are the most commonly used analgesic/sedative during NIV. Physicians efficiently use this drug class because of its combined effect of analgesia and sedation, especially if the cause of an NIV intolerance is unclear. Despite being an excellent analgesic, opioids as a single sedative agent should be restricted due to their respiratory depressive effect, which is undesirable in patients receiving partial ventilatory support like NIV. Opioids such as morphine, fentanyl, remifentanil and sufentanil have been studied over the past two decades to facilitate NIV tolerance.

Opioids provide analgesia by mainly activating μ1-receptor and its mild effect on μ2- and δ-receptors which, on the other hand, are also involved in respiratory drive depression. Fentanyl and morphine provide adequate analgesia at the cost of the reduced respiratory drive as they act on all receptor subtypes. Further, after a long-term continuous infusion, they also risk accumulation exacerbating respiratory depression. However, the literature shows one study depicting that intravenous morphine infusion improved NIV compliance in a case of acute pulmonary oedema caused by heart failure [34]. Sufentanil, a synthetic opioid acting specifically on μ1-receptors, proves interesting for continuous infusion in ICU patients as its context-sensitivity half-life is seven times lower than fentanyl, reducing the risk of accumulation. One pilot study suggested continuous infusion of sufentanil at 0.2–0.3 μg/kg/h resulting in awake sedation without any adverse effects in critically ill patients on partial respiratory support [19].

Two European studies have demonstrated the curative use of remifentanil for NIV intolerance in respiratory failure and rendered its use safe and effective during NIV [27, 35]. A recent cohort study by Hao et al. revealed that remifentanil and dexmedetomidine have similar efficacy in managing moderate to severe NIV intolerance [36].

1.2.3.2 Benzodiazepines

Even though benzodiazepines are the most used sedative agent, they are barely studied for NIV tolerance. Benzodiazepines do not possess analgesic properties and also increase the risk of delirium; hence, they are avoided in elderly patients with agitation. However, a case report demonstrates the successful use of lorazepam during NIV in severe asthma exacerbation [37].

With the limited available data/with the scarce studies available, the risk-benefit aspect of benzodiazepines during NIV is not clear/defined yet. However, drugs such as midazolam can be opted for where anxiety is the apparent reason for NIV intolerance, provided facilities for close monitoring of respiratory parameters/status are available.

1.2.3.3 Propofol

Propofol seems an exciting option for sedation during NIV due to its rapid pharmacokinetics. However, propofol can adversely affect gas exchange, breathing patterns and respiratory drive in proportion to its infusion rate. It is also known to cause hypotension and apnoea. However, some studies demonstrate propofol as a potential safe agent when used with a target-controlled infusion during NIV [26, 38].

1.2.3.4 Dexmedetomidine

Among other sedative drugs, dexmedetomidine possesses the lowest risk of depression in the respiratory centres and does not affect the upper airway patency. Several studies show that dexmedetomidine can be safely used in paediatric patients with respiratory failure to facilitate NIV tolerance [39–42]. Although dexmedetomidine can cause bradycardia and hypotension, this drug has successfully improved patient-ventilator synchrony in patients with acute respiratory failure [23, 43]. It may also be a helpful sedative agent facilitating the induction of NPPV in patients with severe asthma [24]. Dexmedetomidine needs fewer dose adjustments than midazolam and is also superior for maintenance of sedation than benzodiazepines [44, 45]. However, in the literature, one study done by Devlin et al. (with a small sample size of 33) failed to show a beneficial effect of dexmedetomidine on NIV intolerance, although overall, we could say that dexmedetomidine is comparatively safe and probably effective during NIV.

1.2.3.5 Ketamine

Data are insufficient, but theoretically, ketamine is a good choice. Patients should go to their pleasant places in their minds. Ketamine provides analgesia, sedation and amnesia depending upon the dosing. As opposed to opioids, ketamine retains pharyngeal and laryngeal protective reflexes while preserving functional residual capacity, minute ventilation and tidal volume. It lowers airway resistance and increases lung compliance, so it is less likely to produce respiratory depression. Haemodynamically, ketamine increases heart rate and blood pressure due to its sympathomimetic effect, which may help manage respiratory failure in patients with hypotension [46]. However, ketamine can produce hypersalivation and emergence reactions, stimulating anxiety in a mentally unprepared patient. To date, very few case reports are available discussing the use of ketamine during NIV. Some case reports and small studies show the physiological benefits of ketamine in the setting of asthma. Despite insufficient evidence, Kiureghian et al. described the adjuvant use of NIV and intravenous ketamine to avoid MIV in a patient with severe exacerbation of asthma [47]. Verma et al. reported that a ketamine-induced dissociative state in patients with acute decompensated heart failure facilitated NIV management in an otherwise uncooperative patient allowing NIV to be effective [48]. In the future, extensive series and trials need to establish the use of ketamine-induced sedation in agitated, uncooperative patients to enable compliance with NIV and to compare ketamine with other sedatives during NIV for a better understanding. We suggest it should be used with caution in this subset of patients.

In the light of current evidence, given the paucity of well-controlled studies investigating the ICU sedation regimens during NIV, it is ambivalent about pointing to a single sedative agent optimal for every patient. Some important factors to be assessed before selecting an apt sedative agent are the cause of NIV intolerance, allergies, comorbidities and respiratory and haemodynamic status. Ideally, an agent should be able to resolve NIV intolerance without respiratory compromise.

1.3 Conclusion

While sedation is not mandatory, the present limited data suggests that sedation during NPPV is safe and feasible; a more widespread application should await the results of more extensive observational studies or randomised clinical trials. As emergency physicians, our goal should be to avoid intubating patients and to put them on mechanical ventilation when other options may be attempted. With the continued rise of NIV as a therapeutic tool, a more systematic approach to administering sedatives is required. Fresh research into prescribing patterns (and the reasoning underpinning them) is desirable: a study of the effects of switching sedatives would also be illuminating. Ways of sedation when NIV is delivered on standard wards are undocumented; this is another area that deserves more attention/subject to further studies (Table 1.1).

Table 1.1 Advantages and disadvantages of sedatives used during NIV

Drugs	Advantages	Disadvantages
Remifentanil	– Do not accumulate – Can be easily titrated – Hepatic of renal dysfunction do not alter its metabolism	– Nausea and vomiting – Chest wall rigidity
Propofol	– Favourable pharmacokinetic profile	– Hypotension and apnoea
Midazolam	– Good efficacy – Haemodynamic stability	– In critically ill patients who are obese, with low albumin levels, or have renal failure, accumulation can occur – Increased risk of delirium and agitation
Dexmedetomidine	– Provide anxiolysis, sedation and analgesia – No respiratory depression – Superior to midazolam for sedation with fewer dose adjustments	– Bradycardia and hypotension – Caution in haemodynamic instability
Ketamine	– Provides analgesia, sedation and amnesia – Produces less respiratory depression	– Hypersalivation and emergency reactions stimulating anxiety – Insufficient data for use during NIV

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Part I

Pharmacological Clinical Indications in Adults

2 Aerosol Therapy—Noninvasive Ventilation and Bronchodilators Pharmacology

Elisabetta Roma and Barbara Garabelli

What is inhalation therapy? In summary, it is the most effective way of administering drugs for most respiratory diseases.

The history of aerosol therapy dates back to 4000 years ago, when the leaves of *Atropa belladonna* and *Datura stramonium* were smoked in special pipes to relieve asthma attacks. It was only at the end of the nineteenth century that Sales created the first vaporizer for inhaling drugs, consisting of a large glass ampoule. In the mid-twentieth century, the first dry powder inhalers and then the first pre-dosed sprays were made.

The advantages of this route of administration can be summarized as follows:

(a) The drug is delivered directly to the target organ.
(b) Topical bioavailability of the drug.
(c) Systemic diffusion decreased.
(d) Need for lower dosages.
(e) Quick and powerful therapeutic action.
(f) Lower side effects compared to systemic administration.

The aerosol is a system consisting of multiple particles, solid or liquid, which are so small that they are stably suspended in a gaseous medium, generally air, but sometimes also oxygen.

Factors affecting the deposition of inhalant drugs are:

E. Roma (✉)
The NeMO Centre, Niguarda Hospital, Milan, Italy
e-mail: elisabetta.roma@centrocliniconemo.it

B. Garabelli
AOU Maggiore della Carità, University Hospital, Novara, Italy
e-mail: barbara.garabelli@maggioreosp.novara.it

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Table 2.1 Particle sizes of the aerosol that are able to reach each anatomical region

Nasal cavities, pharynx, larynx	Over 30 μm
Trachea	20–30 μm
Bronchi and lungs	10–20 μm
Terminal bronchioles	3–10 μm
Alveolar canals and pulmonary alveoli	<3 μm

Table 2.2 Inhalation devices available on the market

Pressurized metered-dose inhaler with valved holding chamber
Soft mist inhaler
Breath-actuated dry powder inhaler
Dry powder inhaler
Jet nebulizer
(a) Continuous-output
(b) Breath-enhanced
(c) Breath-actuated
Ultrasonic nebulizer
Vibrating mesh nebulizer

(a) Characteristics of the aerosol such as particle sizes (Table 2.1), supply pressure, propellants, humidity, and ambient temperature
(b) Characteristics of the patient (anthropometric, airway patency)

Bronchodilators, corticosteroids, antibiotics, prostaglandins, nitric oxide, anticoagulants, and heliox can be administered via inhalation. However, inhalation is most commonly used for bronchodilator administration.

There are different inhalation devices available on the market [1], which are summarized in Table 2.2.

Metered-dose inhalers (MDIs) contain definite total doses and provide a certain dose of the active agent in each puff. MDIs consist of a suspension or dispersion of one or more active ingredient in propellant or a mixture of propellants and solvent [2].

Propellant permits to generate the required pressure to split drug formulation into micron-sized droplet.

The accurate and repeatable dosing of MDIs minimizes errors in drug dosage.

At every depression of the MDI stem into the canister, a finite amount of drug is released at a certain velocity, generating a spray cloud.

A dry powder inhaler (DPI) is an inhalation device that delivers medication to the airways in the form of a dry powder.

The drug is available either in a capsule for manual loading or in a form contained inside the inhaler. Once loaded or actuated, the patient seals the mouthpiece

of the inhaler with his lips and takes a sharp, deep breath, holding the air for 5–10 s [2].

A soft mist inhaler (SMI) represents a new generation of inhalers; it is a multi-dose device without propellant. The drug is in liquid form (solution or suspension); the delivery of the dose produces slow-moving cloud with a spray time of 1.0–1.5 s which is inhaled by the patient [3]. The low aerosol speed can generate more than 60% of the fine particle fraction (≤5.0 μm) for the delivered bronchodilator independent of inspiratory effort.

Besides, the greater persistence of the cloud allows for better hand-breath coordination and less oropharyngeal deposition.

As regards nebulization, there are three different types of nebulizers on the market.

Jet nebulizers (JNs) force the diluted drug solution from the reservoir onto the baffles using a compressed gas (usually air or oxygen with a flow of 6–10 L/min).

Vibrating mesh nebulizers (VMNs) employ a vibrating mash or plate that generates an aerosol through numerous openings. These devices are portable and less noisy than jet nebulizers but need a battery or electricity to work. They have a negligible residual volume, so they don't need a big dilution of the drug and can ensure small administration times; besides, they are able to double or triple the percentage of drug delivered compared to jet nebulizers.

Given the lack of overheating of the dilution, the mesh nebulizers are particularly suitable for the delivery of proteins and peptides with minimal denaturing risk.

In ultrasonic nebulizers (UNs), an aerosol is produced by the vibration of a piezoelectric crystal. The particle size is influenced by the frequency and amplitude of vibration of the crystal. Most ultrasonic nebulizers guarantee high rates of nebulization in little time. Some critical aspects, such as their high cost, the production of aerosols of larger particles compared to jet nebulizers, the heating of the solution even by 10–15° during nebulization, and the danger they pose for some pharmaceutical preparations, did not allow ultrasonic nebulizers to become popular [4].

2.1 Aerosol Delivery During Mechanical Ventilation

Many factors influence aerosol delivery to the lungs during mechanical ventilation and are related to the drug, the device, the patient, the ventilator circuit, the artificial airways, and the ventilator settings.

JNs, VMNs, and pMDIs are the most commonly used aerosol devices during invasive mechanical ventilation. Literature have reported delivered drug doses of approximately 3–5% of the total administered dose for JNs, 17–35% for VMNs, and 10–20% for pMDIs with inline spacer, distal to an ETT [5].

Fang and colleagues used a commercial adaptor trying SMI use during mechanical ventilation and reported a total delivered dose with actuation during expiration which was threefold lower than that with the spontaneous model. The relatively low inhaled dose of aerosol from the SMI added to the volume loss from the circuit raised concerns whether adequate drug delivery can be assured to justify its use in mechanically ventilated patients [5].

With regard to aerosol delivery devices, it was initially believed that lung drug deposition during mechanical ventilation was better with the use of pressurized metered-dose inhalers (pMDIs) than with the use of conventional nebulizers. However, when the two types of devices are used correctly, the results are similar.

For instance, the use of a space chamber for the delivery of a pMDI during mechanical ventilation allows for four to six times greater pulmonary drug deposition compared to elbow or unidirectional adapters [6].

In fact, MDIs typically cause more aerosol deposition on the ETT than nebulizers do, decreasing the amount of drug delivered. Using a spacer and performing the administration during inspiration, possibly synchronizing puff delivery with the patient's spontaneous effort, can reduce the deposition on the ETT [7].

Clinical studies have shown that nebulizers and pMDIs have similar effects on lung function, both types of devices resulting in equivalent changes in FEV 1.

In general, pMDIs are more economical and pose a lower risk of nosocomial pneumonia.

Inhaled medications are the mainstay of therapy for many pediatric pulmonary diseases. These therapies are given to patients who receive different types of respiratory support. Improvements in survival and development of new technologies have also changed the prognosis of many pediatric pulmonary conditions [1].

COPD, asthma, and ventilator-dependent patients routinely receive treatment with inhaled bronchodilators, improving ventilatory parameters and patient-ventilator synchrony in cases of airway constriction. In fact, bronchodilators relax airway smooth muscles, reversing airway obstruction and preventing bronchoconstriction [8].

In the treatment of infections of the lower tract, the use of inhalation therapies such as short- or long-acting bronchodilators or corticosteroid drugs is common [9].

Bronchodilators are frequently used in ICU patients. The amount of bronchodilator that correctly deposits at its site of action depends on the amount of drug, inhaled mass, deposited mass, and particle size distribution.

Mechanical ventilation challenges both inhaled mass and lung deposition by specific features, such as a ventilatory circuit, an endotracheal tube, and ventilator settings [10].

In their review published in 2017, Dugernier et al. [11] evaluated studies that assessed in vivo lung delivery of inhaled drugs to invasively mechanically ventilated patients or animal models either as absolute drug concentrations or quantitative deposition relative to the nominal dose to provide current knowledge on whole lung deposition, examine the distribution and penetration of inhaled drugs into different regions of the respiratory tract, determine how the ventilator circuit and the artificial airways impact aerosol delivery, and discuss the administration techniques applied in these studies.

Drugs of interest were antibiotics (amikacin and amikacin sulfate, colistin or colistimethate sodium, ceftazidime, pentamidine, gentamycin, tobramycin, vancomycin, fosfomycin, imipenem, or teicoplanin), tracer labeled with technetium-99m, diethylenetriaminepentaacetic acid, pertechnetate, sulfur colloid, albumin or fenoterol, and bronchodilators (albuterol, fenoterol, or ipratropium bromide).