Noninvasive Ventilation in Sleep Medicine and Pulmonary Critical Care

Critical Analysis of 2018-19 Clinical Trials

Antonio M. Esquinas
Editor-in-Chief

Giuseppe Fiorentino
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Correction to: Skin Injuries Associated with Noninvasive Mechanical Ventilation: Evidence-Based Synthesis. C1

Part I

Pulmonary (Non-critical Care)

Giuseppe Fiorentino

1 Noninvasive Mechanical Ventilation Physiology and Ventilatory Management in Morbidly Obese Patients

Guniz M. Koksal and Cigdem Akyol Beyoglu

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Abbreviations

AVAPS	Average volume-assured pressure support ventilation
BiPAP	Bi-level airway pressure
BMI	Body mass index
CPAP	Continuous positive airway pressure
ERV	Expiratory reserve volume
FRC	Functional residual capacity
HFNC	High-flow nasal cannula
NIV	Noninvasive ventilation
OHS	Obesity hypoventilation syndrome
$PaCO_2$	Partial carbon dioxide pressure
PaO_2	Partial oxygen pressure
SBD	Sleep breathing disease
TLV	Total lung volume
TLC	Total lung capacity
VtPS	Volume-targeted pressure support ventilation

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1.1 Introduction

Obesity is the disease of our age. When the body mass index (BMI) exceeds 40 kg/m^2, it is called morbid obesity. Morbid obesity is a disease that can be seen in as high as 2–8% of the population [1]. Morbid obesity affects the cardiovascular and respiratory systems. Left ventricular

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dilatation occurs directly without ventricular hypertrophy. Therefore, morbidly obese patients cannot tolerate dehydration and cannot tolerate volume loading and tachycardia in cases such as sepsis and septic shock. Pulmonary edema and heart failure may develop during volume loading. Pulmonary pressures are already high. Serious changes occur in respiratory systems of morbidly obese patients [2]. There is an excess weight on the thorax that has a mass effect. This reduces thoracic compliance and therefore the lung parenchyma cannot expand. Expiratory reserve volume (ERV) and total lung capacity (TLV) decrease due to decreased functional residual capacity (FRC) in morbidly obese patients. In these patients, the lung volumes will decrease in supine position due to upward movement of the diaphragm muscle. Air confinement results in intrinsic PEEP (auto-PEEP) and expiratory pressure increase. This increases work of breathing. In addition, the increase in soft tissue in the upper airways will increase the airway resistance contributing to increase in work of breathing [1, 2]. After a while, arterial carbon dioxide partial pressure ($PaCO_2$) increases. Of the morbidly obese patients, 26% have metabolic syndrome, and 1.4–7% have diabetes mellitus and cardiovascular system diseases. In addition sleep disorders (SBD) such as obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS) develop in these patients. These diseases cause acute respiratory insufficiency on chronic state. Deteriorating lung mechanics may cause postoperative respiratory insufficiency in patients who have to undergo surgery. Lung infections are also frequently seen. Morbidly obese patients may suffer fatigue due to increased respiratory activity in the respiratory muscles even when carbon dioxide levels are normal. For all these reasons, morbidly obese patients are prone to respiratory support in a period of their lives [1, 2]. It would not be enough to apply oxygen to these patients. The excess weight on thorax creates obstruction on closed airways and lungs. In the first step, noninvasive mechanical ventilation (NIV) may be performed. In patients with sleep disorders, NIV should be administered overnight without interruption. If hypercarbia develops, it is necessary to switch to NIV applications during the day. An average of 6–8 h of NIV administration during the day will provide relief in morbidly obese patients. NIV is a reliable application for obese and morbidly obese patients. By NIV application, complications of intubation and invasive mechanical ventilation are avoided (such as difficult airway, pneumonia, baro-volutrauma, and difficult weaning). Various modes of NIV such as CPAP, BiPAP, volume- or pressure-targeted pressure support, or pressure support modes may be used with appropriate interfaces (nasal cannula, nasal, and oronasal fullface mask or helmet) [3, 4]. The face masks must be compatible and comfortable. Oronasal masks should be preferred for acute respiratory failure. The objective is to keep the airways open, and the SpO_2 is 90% or above, and the pH is 7.35 or higher. Before starting NIV application, morbidly obese patients should have cardiac examination. ECG and ECO examinations should be performed. SpO_2, transcutaneous carbon dioxide analyzer may be used during NIV administration. In addition, the patient's consciousness, respiratory frequency, and respiratory depth-pattern should also be followed, and arterial blood gas analysis should be performed. Depending on the patient's need, oxygen can also be added to the treatment to support SpO_2 90% or above. Tidal volumes should be adjusted to the ideal weight in morbidly obese patients. NIV applications may also be performed in operating rooms, emergency services, and treatment rooms in addition to intensive care units [5].

1.2 "Continuous Positive Airway Pressure" (CPAP)

CPAP can be applied in two different ways: as a CPAP ventilator or as a "Boussignac" type. The Boussignac-type CPAP has been in use since 1974. At the end of the interfacial mask, there is an apparatus that will continuously generate positive pressure on the airways. If desired, oxygen may be added to the same location as the

intermediate hose. The airflow generated by the compressed air is used. The application of CPAP improves FRC and lung compliance and therefore corrects oxygenation. CPAP reduces breathing work by decreasing airway obstruction. It has been shown that hypoxemic non-hypercarbic respiratory insufficiency due to primary acute lung injury decreases the incidence of intubation and provides clinical recovery. The de Boussignac, CPAP system, which provides gas flow using pressure regulator, is avant-garde because it is easy, cheap, and available everywhere. The average gas flow of 15 l/min creates a pressure of 10 cmH_2O in the CPAP assembly. It has also been shown that CPAP application does not cause anastomotic leak in patients with morbid obesity following surgery [6, 7].

1.3 "Bi-level Airway Pressure" (BiPAP)

In the acute phase of chronic hypercapnic respiratory failure in morbidly obese patients and sometimes by using CPAP in OHS, alveolar hypoventilation cannot be eliminated. Therefore, two different positive pressure levels (BiPAP) may be required for inspiration and expiration in airways. The operating principle of BiPAP is similar to "pressure support" ventilation but not exactly the same. Two different positive pressures provide both the upper airways and alveoli open in spontaneous breathing. The patient's tolerance is easier than CPAP. In BiPAP, it is recommended that the initial parameters must be 8–10 cmH_2O for inspiratory positive pressure (IPAP) and 4–6 cmH_2O for expiratory positive pressure (EPAP). The IPAP level should be administered to keep patient's SpO_2 90% or above, and the EPAP level should be increased to the level where the patient's snoring and apnea disappear. Although some clinicians suggest 30 cmH_2O IPAP level, it is generally sufficient to have a maximum of 20 cmH_2O IPAP pressures. The higher IPAP-level requirements should alert the clinician about the deterioration of the patient's general condition. It is necessary to be ready for intubation and invasive mechanical ventilation. These levels are particularly relevant for OHS patients. Lower IPAP and EPAP levels will be sufficient in other patients [8].

1.4 "Volume-Targeted Pressure Support Ventilation" (VtPS)

Tidal volumes are not guaranteed when applying BiPAP or pressure support to morbidly obese patients. The immediate changes in the patient's ventilator mismatches cause a fall in the tidal volumes and the respiratory frequency increase (to keep the minute ventilation constant). This causes an increase of breathing work. After a while, alveolar hypoventilation develops. In VtPS mode, the ventilator inspires the patient to the set fixed volume target in each respiratory cycle. Especially in morbidly obese patients with sleep disorders and OHS, it is very important to be able to guarantee tidal volume. VtPS is a hybrid mode. It uses pressure support and volume ventilation together. The ventilator measures the tidal volume of the patient during spontaneous breathing under pressure support. If the target tidal volume is not reached, the tidal volume is completed with volume control [9].

1.5 "Average Volume-Assured Pressure Support Ventilation" (AVAPS)

AVAPS is very effective in preventing hypercarbia especially at night. Minute ventilation is supplied by ensuring a fixed tidal volume. An average of 7–8 ml/ideal weight tidal volumes are used in the ventilator. Parameter settings can be changed according to the ventilator response and tolerance of the patient in spontaneous breathing mode. IPAP may be applied a maximum of 30 cmH_2O, and EPAP may be applied a minimum of 4 cmH_2O pressure. Respiratory frequency is recommended to be set to 2–3 breaths/min. In controlled breaths of the ventilator, inspiratory time is set at 30–40% of one breath, whereas in patients with small airway obstruction, this rate is recommended to be 25–30% [10].

1.6 "High-Flow Nasal Cannula" (HFNC)

Morbidly obese patients may need oxygen therapy after bariatric surgery or in acute respiratory failure. Oxygen therapy may increase the oxygen partial pressure in the blood temporarily, but it cannot prevent the development of atelectasis and hypercarbia. Ventilator-patient mismatches are frequently seen in morbidly obese patients during NIV administration. Noninvasive mechanical ventilation by HFNC applications with nasal cannula and heated and humidified high oxygen flow is more easily tolerated by the patients. In particular, if the patient is incompatible with the ventilator, it can be easily applied in the early postoperative period. Although NIV has been shown not to cause anastomotic leakage in the early postoperative period, however, the surgical team still worries that the NIV may cause leakage.

As a result, the HFNC increases the lung volume at the end of the expiratory by applying a small positive pressure to the airways at adjustable FiO_2 levels. Also, the high flow washes carbon dioxide in the nasopharyngeal dead space and increases excretion of carbon dioxide [11, 12].

1.7 Final Conclusions

Learning Points

- Morbid obesity is the disease of our age.
- Morbid obesity may cause serious respiratory and cardiovascular diseases.
- These patients may require NIV after a period of their lives.
- NIV application should be observed closely.

Critical Points

- Tidal volumes should be adjusted according to ideal weight in morbidly obese patients.
- "High-flow oxygen therapy" is a new research area in morbidly obese patients.
- Sleep breathing disease should be always kept in mind in morbidly obese patients.

1.8 Key Summary

NIV is a reliable application for obese and morbidly obese patients. Complications of intubation and invasive mechanical ventilation are avoided (such as difficult airway, pneumonia, barovolutrauma, and difficult weaning). Patients may be administered CPAP, BiPAP, volume- or pressure-targeted pressure support, or pressure support by using appropriate interfaces (nasal cannula, nasal, and oronasal fullface masks or helmet) to apply NIV. In morbidly obese patients, it has been shown that CPAP application does not cause anastomotic leak after surgery in patients with respiratory failure. In the acute phase of chronic hypercapnic respiratory failure in morbidly obese patients and sometimes in case of using a CPAP in OHS, alveolar hypoventilation cannot be eliminated. Therefore, two different positive pressure levels (BiPAP) may be required for inspiration and expiration in airways. We cannot guarantee tidal volumes when applying BiPAP or pressure support mode to morbidly obese patients. In VtPS mode, the ventilator guarantees a fixed tidal volume in each respiratory cycle by using pressure support or volume-controlled mode. Especially in morbidly obese patients with sleep disorders and OHS, it is very important to be able to guarantee tidal volume. AVAPS is very effective at preventing hypercarbia especially at night. The minute ventilation is tried to be achieved by fixing the tidal volume. Noninvasive mechanical ventilation by HFNC applications with nasal cannula and heated and humidified high oxygen flow is more easily tolerated by the patients. In particular, if the patient is incompatible with the ventilator, it can be easily applied in the early postoperative period.

References

1. Ofstad AP, Sommer C, Birkeland KI, Bjørgaas MR, Gran JM, Gulseth HL, Johansen OE. Comparison of the associations between non-traditional and traditional indices of adiposity and cardiovascular mortality: an observational study of one million person-years of follow-up. Int J Obes (Lond). 2019;

https://doi.org/10.1038/s41366-019-0353-9. [Epub ahead of print].
2. Chacon MM, Cheruku SR, Neuburger PJ, Lester L, Shillcutt SK. Perioperative care of the obese cardiac surgical patient. J Cardiothorac Vasc Anesth. 2018;32(4):1911–21. https://doi.org/10.1053/j.jvca.2017.12.025. Epub 2017 Dec 13.
3. Carron M, Zarantonello F, Iepparіello G, Ori C. Obesity and perioperative noninvasive ventilation in bariatric surgery. Minerva Chir. 2017;72(3):248–64. https://doi.org/10.23736/S0026-4733.17.07310-2.
4. Sequeira TCA, BaHammam AS, Esquinas AM. Noninvasive ventilation in the critically ill patient with obesity hypoventilation syndrome: a review. J Intensive Care Med. 2017;32(7):421–8. https://doi.org/10.1177/0885066616663179. Epub 2016 Aug 15.
5. Nicolini A, Ferrando M, Solidoro P, Di Marco F, Facchini F, Braido F. Non-invasive ventilation in acute respiratory failure of patients with obesity hypoventilation syndrome. Minerva Med. 2018;109(6 Suppl 1):1–5. https://doi.org/10.23736/S0026-4806.18.05921-9.
6. Nicolini A, Lemyze M, Esquinas A, Barlascini C, Cavalleri MA. Predictors of noninvasive ventilation failure in critically ill obese patients: a brief narrative review. Adv Respir Med. 2017;85(5):264–70. https://doi.org/10.5603/ARM.a2017.0044. Epub 2017 Oct 30.
7. de Raaff CAL, Kalff MC, Coblijn UK, de Vries CEE, de Vries N, Bonjer HJ, van Wagensveld BA. Influence of continuous positive airway pressure on postoperative leakage in bariatric surgery. Surg Obes Relat Dis. 2018;14(2):186–90. https://doi.org/10.1016/j.soard.2017.10.017. Epub 2017 Oct 27.
8. Stéphan F, Bérard L, Rézaiguia-Delclaux S, Amaru P, BiPOP Study Group. High-flow nasal cannula therapy versus intermittent noninvasive ventilation in obese subjects after cardiothoracic surgery. Respir Care. 2017;62(9):1193–202. https://doi.org/10.4187/respcare.05473. Epub 2017 Aug 1.
9. Tong S, Gower J, Morgan A, Gadbois K, Wisbach G. Noninvasive positive pressure ventilation in the immediate post-bariatric surgery care of patients with obstructive sleep apnea: a systematic review. Surg Obes Relat Dis. 2017;13(7):1227–33. https://doi.org/10.1016/j.soard.2017.02.009. Epub 2017 Feb 20.
10. Briones-Claudett KH, Esquinas Rodriguez A, Briones-Claudett MH, Puga-Tejada M, Cabrera Baños MDP, Pazmiño Dueñas CR, Torres Herrera CI, Grunauer M. Use of noninvasive mechanical ventilation with pressure support guaranteed with average volume in de novo hypoxaemic respiratory failure. A pilot study. Anaesthesiol Intensive Ther. 2018;50(4):283–90. https://doi.org/10.5603/AIT.a2018.0036. Epub 2018 Oct 14.
11. Pilcher J, Richards M, Eastlake L, McKinstry SJ, Bardsley G, Jefferies S, Braithwaite I, Weatherall M, Beasley R. High flow or titrated oxygen for obese medical inpatients: a randomised crossover trial. Med J Aust. 2017;207(10):430–43.
12. Zhao H, Wang H, Sun F, Lyu S, An Y. High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to noninvasive mechanical ventilation on intubation rate: a systematic review and meta-analysis. Crit Care. 2017;21(1):184. https://doi.org/10.1186/s13054-017-1760-8.

2 Noninvasive Ventilation in Obesity Hypoventilation Syndrome. Short- and Long-Term Outcomes

Michalis Agrafiotis, Christos Karachristos, and Dimosthenis Fletsios

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2.1 Introduction

Obesity hypoventilation syndrome (OHS) is diagnosed based on the combination of a body mass index (BMI) ≥ 30 kg/m^2, daytime hypercapnia ($PaCO_2$ > 45 mmHg), and sleep-disordered breathing; other causes of hypoventilation should be excluded beforehand [1, 2]. The vast majority of OHS patients (90%) suffers from obstructive sleep apnea (OSA), defined according to an apnea-hypopnea index (AHI) ≥5 events/h, while the rest have nonobstructive sleep hypoventilation [3]. Based on pooled data, 8–11% and 18–31% of non-Asian patients with a BMI between 30 and 35 kg/m^2 and ≥40 kg/m^2, respectively, suffer from OHS; for East Asian populations, OHS prevalence might be even higher than non-Asians at a lower BMI range. The overall prevalence of OHS in adult non-Asian populations has been estimated in the range of 0.4–0.6% [1, 2]. OHS is commonly diagnosed between the fifth and sixth decade of age, usually as a result of an acute-on-chronic decompensation, and has been linked to increased healthcare resource utilization, including intensive care unit (ICU) admissions [4], and

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several comorbidities, mainly metabolic and cardiovascular [2]. Lifestyle modifications, bariatric surgery, and the application of positive airway pressure (PAP) therapy are the main treatment options for patients with OHS. PAP therapy is commonly administered noninvasively during sleep in the form of continuous positive airway pressure (CPAP), fixed bi-level PAP, or other noninvasive ventilation (NIV) modalities [1]. Several studies and a recent meta-analysis [5] have demonstrated that PAP therapy improves arterial blood gases, sleep hypoxemia, daytime sleepiness, sleep quality, health-related quality of life (HRQL), and survival; however, so far no advantage of fixed bi-level PAP, as opposed to CPAP therapy, has been established. In the rest of this chapter, a 2-year review of recent developments in the field of PAP therapy in OHS will be provided.

2.2 Search Methodology

We searched PubMed from January 2017 to April 2019 for original papers reporting on the use of PAP treatment in patients with OHS. For our search, we used the following Medical Subject Headings (MeSH) terms: "obesity hypoventilation syndrome" AND "noninvasive ventilation" and "obesity hypoventilation syndrome/therapy." We also conducted a basic word text search over the same time period using the following key string: "obesity hypoventilation syndrome OR Pickwick syndrome AND noninvasive ventilation OR noninvasive ventilation OR therapy." Out of 117 initially retrieved articles, 15 were considered eligible for inclusion (Fig. 2.1). Six articles evaluated CPAP and fixed bi-level PAP therapy for short- [6–9] and long-term outcomes [10, 11]; 4 reported on survival and its predictors for NIV-treated OHS patients as opposed to patients with other hypoventilation syndromes [12–15]; 3 reported on the application of PAP modes other than CPAP and fixed bi-level PAP [16–18]; and 2 investigated issues of NIV monitoring [19, 20].

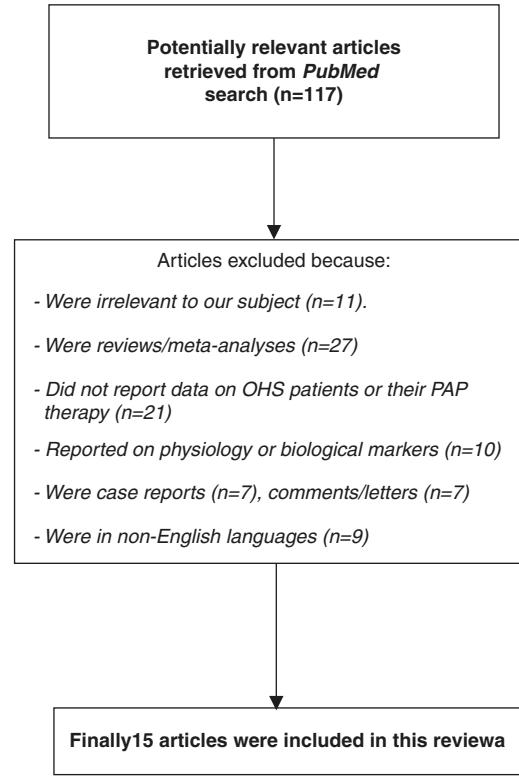

Fig. 2.1 Flowchart of article selection process

2.3 Effect of PAP Therapy on Outcomes

2.3.1 Short-Term Outcomes (Table 2.1)

Howard et al. [6] conducted a single-center, randomized, double-blind, parallel, 3-month trial to compare the effectiveness of fixed pressure CPAP (n = 31) vs. spontaneous-timed (ST) bi-level PAP (n = 29) in the management of patients with OHS; severe nocturnal hypoventilation was not an exclusion criterion. The primary outcome consisted of treatment failure (i.e., any hospital admission, a rise in $PaCO_2$ > 10 mmHg, or failure of $PaCO_2$ to fall <60 mmHg) or nonadherence (use for <2 h per night for at least two consecutive follow-up visits). Secondary outcomes were appraised at enrollment and at 3 months and included sleepiness (Epworth sleepiness scale, ESS), HRQL (Medical Outcomes

Table 2.1 Studies evaluating PAP therapy for short-term outcomes

	Author name/ year/[ref]	Type of study	Population/ number of patients	PAP treatment	Follow-up	Outcomes
1	Howard/2017/ [6]	Randomized controlled trial	OHS with OSA: 60	CPAP: 31 Bi-level PAP: 29	3 months	• No difference between CPAP and the bi-level PAP in the rates of treatment failure (13.3 vs. 14) and in nonadherence (10 vs. 14.8%) • Comparable improvements between CPAP and bi-level PAP in ESS, SF-36, SRI, cardiovascular risk factors, respiratory muscle pressures, and physical activity
2	Orfanos/2017/ [7]	Prospective crossover trial	OHS with OSA: 15	Bi-level PAP switched to CPAP	>1 month	• No difference in gas exchange variables and machine software data between CPAP and bi-level PAP • 80% of the patients preferred CPAP
3	Corral/2017/[9]	Randomized controlled trial	OHS with severe OSA: 221	Lifestyle modifications: 70 CPAP: 80 Bi-level PAP: 71	2 months	• Only bi-level PAP improved PASP (−6.4 mmHg), left ventricular mass index (−5.7 g/ m^2), and 6-MWD (32 m) • Only PAP therapy improved ESS and polysomnographic variables
4	Onofri/2018/[8]	Prospective cohort	OHS: 14	Bi-level PAP: 12 Volume-assured: 2	3 months	• PAP therapy improved respiratory drive, but not TAPSE, PASP, SGRQ, and MRC • The "symptoms and sleep" SRI subscale was improved

Note. For abbreviations see main text

Study Short-Form Health Survey, SF-36; Severe Respiratory Insufficiency Questionnaire, SRI), cardiovascular risk factors (blood lipids, hemoglobin A1C, and C-reactive protein), respiratory muscle pressures, and physical activity. During the 3-month follow-up period, 1 patient dropped out from the CPAP arm and 2 patients from the bi-level PAP arm. This study observed no significant difference in the rates of treatment failure between the CPAP arm and the bi-level PAP arm (13.3 vs. 14.8%, respectively) and in nonadherence (10 vs. 14.8%, respectively); a trend for an elevated $PaCO_2$ (>45 mmHg) was, however, more evident in the CPAP group initially but was less clear at the end of the study. Comparable improvements were also noted in HRQL, cardiovascular indices, physical activity, and lung function tests. A high initial $PaCO_2$ (>62 mmHg) was the only risk factor associated with persistent ventilatory failure at 3 months. This study has also been included in the previously mentioned meta-analysis [5].

Orfanos et al. [7] conducted a prospective trial to validate the feasibility and effectiveness of a protocol for switching OHS patients from bi-level PAP to CPAP. Patients were recruited if NIV settings were optimized, and they had been clinically stable at NIV for >2 months. HRQL (SRI), sleepiness (ESS), sleep quality (Pittsburgh Sleep Quality Index, PSQI), morning arterial blood gases, overnight oximetry, transcutaneous capnography readings, and the machine's report

for patient compliance data, leaks, and AHI were assessed at enrollment and at the end of the study period. Following baseline evaluation, NIV was withdrawn for a week, and pulmonary function tests, as well as overnight polygraphy (PG), were conducted at the end of this 7-day period. Then patients were switched to CPAP at a pressure of 2 cmH_2O above their previous end-expiratory positive airway pressure (EPAP). Follow-up evaluation was performed after >1 month of CPAP treatment. Out of 22 patients initially enrolled, 15 completed the study. Dropout reasons included denial to undergo PG, presence of obstructive lung disease, and an AHI <15 events/h. Switching to CPAP was not associated with significant differences in gas exchange variables and machine report data. ESS significantly improved after CPAP treatment (4.29 vs. 8.21), although SRI and PSQI scores remained unchanged. Nevertheless, 12 patients (80%) favored CPAP over NIV for their treatment.

The Spanish Sleep Network [9] compared the impact of CPAP, bi-level PAP, and lifestyle modifications on various echocardiographic parameters of patients with OHS and severe OSA (AHI > 30 events/h) in the context of a multicenter randomized controlled trial on OHS respiratory treatment. This study allocated 221 OHS patients to lifestyle modifications only (control group, $n = 70$), lifestyle modifications plus CPAP ($n = 80$), and lifestyle modifications plus bi-level PAP ($n = 71$). At baseline pulmonary arterial hypertension, defined as pulmonary artery systolic pressure (PASP) >40 mmHg, was observed in 55% of the patients, while 51% had left ventricular hypertrophy (left ventricle mass index ≥115 g/m^2 in men and ≥95 g/m^2 in women). Dropout rates did not differ across the three groups. At the end of the 2-month study period, a significant decrease in PASP (−6.4 mmHg) and left ventricle mass index (−5.7 g/m^2) was observed only in the bi-level PAP group; the benefit in pulmonary hemodynamic profile was, however, more prominent in patients with pulmonary hypertension at baseline. In addition, bi-level PAP and CPAP were more effective than lifestyle modifications in improving sleepiness (ESS) and polysomnographic variables, while only bi-level PAP effected an improvement (32 m) in 6-minute walking distance (6-MWD).

Onofri et al. [8] prospectively investigated the impact of NIV initiation on cardiac and respiratory parameters, breathlessness, and HRQL of patients with OHS. Improvements in neural respiratory drive (NRD) assessed by parasternal electromyography (EMG_{para}) and pulmonary hemodynamics, assessed by tricuspid annular plane systolic excursion (TAPSE), were the primary outcomes. Neural respiratory drive index (NRDI) was calculated as the product of EMG_{para} (%max) (percentage of mean EMG_{para} divided by its maximum value) multiplied by respiratory rate. Breathlessness was assessed by the MRC scale and HRQL by the St George's Respiratory Questionnaire (SGRQ) and SRI. This study enrolled 14 patients who were studied at baseline (before NIV) and at day 1, 6 weeks, and 3 months post-NIV; bi-level ST ($n = 12$) and volume-assured ($n = 2$) ventilation were the prescribed modes. NIV significantly improved NRDI, EMG_{para} (%max), and raw EMG_{para} at all post-NIV time points. However, no significant differences were noted between baseline and 3 months in TAPSE (24.6 vs. 23.4 mm) and PASP (36.7 vs. 44.5 mmHg). MRC and SGRQ did not change, but the "symptoms and sleep" SRI subscale was significantly improved.

2.3.2 Long-Term Outcomes (Table 2.2)

Bouloukaki et al. [10] conducted a single-center, prospective, observational, clinical study to investigate the effects of compliance to PAP therapy on survival and functional outcomes of patients with OHS for a follow-up period of >2 years. All enrolled patients ($n = 252$) were treated with either fixed CPAP/auto-CPAP ($n = 84$, 37.3%) or fixed bi-level PAP ($n = 141$, 62.6%) titrated during an in-laboratory night according to a standard protocol. Daytime sleepiness (ESS), HRQL (SF-36), depressive symptoms (Beck Depression Inventory, BDI), arterial blood gases, and patient adherence data comprised the appraised variables. OSA severity

Table 2.2 Studies evaluating PAP therapy for long-term outcomes

	Author name/year/[ref]	Type of study	Population/number of patients	PAP treatment	Follow-up	Outcomes
1	Bouloukaki/2018/[10]	Prospective observational	OHS and OSA: 225	CPAP: 84 Bi-level PAP: 141	>2 years	• PAP improved blood gases, ES, SF-36, and BDI • High adherence (≥6 h/day) was associated with better improvement in blood gases and SF-36 • Survival was better for high vs. low PAP adherence (8.7 vs. 2.5%) • No difference in outcomes between CPAP and bi-level PAP
2	Masa/2019/[11]	Randomized controlled trial	OHS and severe OSA: 215	CPAP: 115 Bi-level PAP: 100	3 years	• No difference between CPAP and bi-level PAP in mean hospitalization days per patient-year (1.63 vs.1.44) • No difference between CPAP and bi-level PAP incidence of cardiovascular events (15 vs. 18%) and in mortality (15 vs. 18%) • Comparable improvements in arterial blood gases, blood pressure, spirometry, FOSQ, SF-36, MRC dyspnea scale, and ESS • Higher adherence linked to better survival and reduced complications

Note. For abbreviations see text

was categorized as mild (5 < AHI < 15 events/h), moderate (15 < AHI < 30 events/h), or severe (AHI ≥ 30 events/h); eventually data were available for at the end of the follow-up period for 225 patients. Significant improvements were noted in arterial blood gases in all OSA subgroups. PAP adherence and baseline $PaCO_2$ independently predicted improvement in $PaCO_2$, while the changes in PaO_2 and HCO_3^- were only predicted by their respective baseline values. At the end of the study period, 18% of the patients had persistent daytime hypercapnia ($PaCO_2$ > 45 mmHg); these patients were more likely to suffer from moderate or severe OSA, while their average PAP use was significantly lower as opposed to patients whose $PaCO_2$ normalized (5.7 vs. 6.7 h/night). PAP therapy also effected improvements in ESS, SF-36, and BDI for all OSA subgroups. However, while the change in ESS was independently predicted only by its baseline value, the respective predictors for BDI included baseline BDI, SF-36, and awake transcutaneous $PaCO_2$ ($tcPaCO_2$); baseline SF-36 and PAP use were the only independent predictors of SF-36 improvement. When patients were divided according to the hours of PAP use, those who used PAP ≥ 6 h/night experienced greater improvements in arterial blood gases and SF-36. However, the percentage of patients who achieved a normal $PaCO_2$ (<45 mmHg) at the end of the follow-up period did not differ significantly between the ≥6 h/night and the <6 h/night adherence subgroups (76 vs. 71%). Eleven out of the 252 patients (5%) deceased, with the majority of them (9 patients) belonging to the moderate-severe OSA subgroup. Baseline $PaCO_2$ and percentage of time spent with a SpO_2 < 90%

were correlated with increased mortality, while survival was significantly better in patients with a PAP use ≥6 h/night, as opposed to those with lower PAP use (8.7 vs. 2.5%). In addition, although patients who were prescribed bi-level PAP had greater PAP adherence and improvement in BDI score, no difference in mortality and other outcomes was noted between the CPAP and bi-level PAP subgroup.

The Spanish Sleep Network [11] performed a multicenter, open-label, randomized, controlled trial to assess the impact of CPAP vs. bi-level PAP on long-term outcomes of OHS patients. This study enrolled 215 patients with OHS and severe OSA (AHI ≥ 30 events/h), of which 115 were allocated to the CPAP arm and 100 to the bi-level PAP arm, for a follow-up period of 3 years. No significant difference was noted between the CPAP and the bi-level PAP arm in the mean hospitalization days per patient-year (1.63 vs.1.44), which was the primary outcome. Similar rates were also observed in the incidence of cardiovascular events (15 vs. 18%) and in mortality (15 vs. 18%). Cardiovascular events were the main cause of death with no difference between the two arms (56 vs. 54%). Blood pressure, spirometric indices, and arterial blood gases significantly improved, albeit with no difference between the two study groups; 6-MWD was not influenced by either treatment. HRQL was assessed by the Functional Outcomes of Sleep Questionnaire (FOSQ), SF-36, and a visual analogical well-being scale; both therapies effected significant improvements in these indices, but again no difference was noted between the two arms. Daytime sleepiness (ESS) also improved similarly in both arms, while the incidence of significant breathlessness, as assessed by the Medical Research Council (MRC) scale (≥2), had significantly decreased by the end of the study period from 54 to 29% in the CPAP arm and from 63 to 27% in the bi-level PAP arm, again with no difference between the two therapies. Patients with a higher adherence had lower rates of hospitalization, emergency department visits, ICU admissions, and mortality. In addition, CPAP treatment was associated with a lower cost.

2.4 Survival and Its Predictors in OHS Patients Under Treatment with NIV (Table 2.3)

Gouda et al. [12] reported retrospectively on the outcomes of West Ireland patients under prescription of domiciliary NIV for a follow-up period of 10 years. Their database consisted of 161 patients with various hypoventilation syndromes, including 76 with chronic obstructive pulmonary disease (COPD, 48%), 50 with OHS (31%), 21 with neuromuscular disease (NMD, 12%), and 14 with restrictive thoracic disease (RTD, 9%). Bi-level PAP modes were prescribed to all but 2 patients, and at the end of the follow-up period, complete survival data were available for 141 patients (87.5%). Patients with RTD had the best mean survival post-NIV (7.3 years), followed by patients with OHS (5.5 years), COPD (3.03 years), and NMD (2.5 years). At the first year, the best survival rates were observed in OHS (100%) and RTD (90.9%) patients, followed by COPD (87.3%) and NMD (72.2%) patients. Five years after NIV initiation, survival rates were still higher for OHS and RTD (80 and 83.3%, respectively), followed by COPD (64.3%) and NMD (28.6%). Based on a survey of 60 patients (all disease types represented), self-perceived quality-of-life was improved in 91.6% of patients treated with NIV.

Blankenburg et al. [13] prospectively recruited patients with COPD ($n = 51$) and OHS ($n = 34$) and chronic hypercapnic respiratory failure to evaluate the impact of high-intensity NIV on respiratory parameters, physical function, and survival for a follow-up period of 4 years. All patients were clinically stable, had received previous NIV treatment, and became adjusted to high-intensity NIV during a period of hospitalization. Assisted pressure-controlled and pressure-support ventilation were the applied modes; target inspiratory pressure was set to ≥20 cmH_2O aiming to achieve a tidal volume >0.8 L with a backup rate of 2 breaths above the patient's native rate, for a total duration of daily ventilation ≥12 h/day. High-intensity NIV was considered successful when spontaneous $PaCO_2$ reached normal values or had dropped by at least 7.5 mmHg.

Table 2.3 Survival of OHS patients treated with NIV as opposed to patients with other hypoventilation syndromes

	Author name/year/ [ref]	Type of study	Types of diseases/number of patients	Type of treatment	Follow-up	Survival	Predictors of survival for OHS patients
1	Gouda/2017/ [12]	Retrospective cohort	COPD: 76 OHS: 50 NMD: 21 RTD: 14	Bi-level PAP	10 years	*5-year survival rate (%)* RTD: 83.3 OHS: 80 COPD: 64.3 NMD: 28.6	Not specified
2	Blankenburg/2017/ [13]	Prospective cohort	COPD: 51 OHS: 34	High-intensity bi-level PAP	4 years	*4-year survival rate (%)* OHS: 68 COPD: 26	Not specified
3	Tan/2018/[14]	Retrospective cohort	Motor neuron disease: 93 Pulmonary disease: 60 NMCW: 51 OHS: 36	Bi-level PAP	>10 years	*5-year survival rate (%)* OHS: 77 NMCW: 69 Pulmonary disease: 48 Motor neuron disease: 7	Age FEV1
4	Markussen/2019/ [15]	Prospective cohort	NMD: 48 OHS: 32 COPD: 24 RTD: 8	Not specified	Up to 80 months	*6-year survival rate (%)* RTD: 75 OHS: 69 NMD: 54 COPD: 25	SRI did not predict survival

Note. For abbreviations see main text

Comparable improvements were noted in both groups with normocapnia achieved on discharge in 70.6 and 61.8% of COPD and OHS patients, respectively. In addition, mean $PaCO_2$ significantly dropped by 13 mmHg in COPD and by 11 mmHg in OHS. Significant increases were also noted in 6-MWD for both COPD and OHS (78 m and 42 m, respectively). Survival rates for COPD patients were 83, 73, 55, and 26% at the first, second, third, and fourth year, respectively. Survival rates for OHS patients were 85 and 72% at the first and second year and 68% in the third and fourth year. Average NIV use did not differ between the COPD and OHS (5.6 vs. 5.2 h/day).

A single-center retrospective study by Tan et al. [14] investigated survival rates and predictors for patients with chronic hypoventilation syndromes treated with long-term home mechanical ventilation (HMV). This study involved 240 home-ventilated patients including 93 patients with motor neuron disease (39%), 60 patients with pulmonary diseases (25%), 51 patients with other neuromuscular and chest wall diseases (NMCW, 21%), and 36 patients with OHS (15%); only 2 patients (1 with pulmonary disease and 1 with NMCW) received tracheostomy ventilation. Patients were started on HMV between January 2005 and December 2010 and were followed up to 1 June 2016. The highest median duration of survival from HMV initiation was achieved by OHS patients (>11.5 years), followed by NMCW patients (9.9 years), pulmonary disease patients (4.2 years), and motor neuron disease patients (1 year). The respective 5-year survival rates were

77, 69, 48, and 7%. On multivariate analysis, age was an independent predictor of death in all but the motor neuron disease group. In addition, FEV1 predicted mortality in OHS, oxygen therapy and obesity in pulmonary disease, and cardiovascular disease in motor neuron disease.

Markussen et al. [15] prospectively investigated the impact of HRQL, assessed by the SRI questionnaire, on the mortality of patients treated with HMV. This study recruited 122 patients, including 48 with NMD (43%), 24 with COPD (21%), 32 with OHS (29%), and 8 with RTD (7%); only 9 patients (8%, all with NMD) received tracheostomy ventilation. During the 80-month follow-up period, 52 patients (46%) deceased. Mortality rates were the highest for COPD (18 patients, 75%), followed by NMD (22 patients, 46%), OHS (10 patients, 31%), and RTD (2 patients, 25%). With respect to the whole population of patients, the SRI sum score and its "physical functioning," "psychological well-being," and "social functioning" subscores were significantly associated with improved mortality after adjusting for covariates. In addition, several SRI subscores were associated with improved mortality after adjustment in patients with NMD, COPD, and RTD; however, after adjustment, neither SRI sum score nor its subscores were found to predict survival in patients with OHS.

2.5 Application of PAP Modes Other than CPAP and Fixed Bi-Level PAP

McArdle et al. [16] conducted a single-center, randomized, crossover, noninferiority trial to compare fixed EPAP vs. auto-EPAP in patients with various chronic hypoventilation syndromes and OSA (AHI > 5 events/h). This study enrolled 25 patients, including 11 patients with OHS, 9 patients with COPD, and 5 patients with NMD. NIV was provided in the ST, intelligent volume-assured pressure-support mode (iVAPS, ResMed, Australia), and all patients were clinically stable on NIV for ≥3 months. At baseline, all patients underwent polysomnography to optimize fixed EPAP and other ventilatory settings. Subsequently, patients were randomized to be studied by polysomnography on two separate nights using auto-EPAP on day 1 and fixed EPAP on day 2 (n = 11) and vice versa (n = 14). No significant difference was observed in mean AHI between fixed EPAP and auto-EPAP, while OSA was adequately controlled in both arms with minimal residual events. No significant differences were also observed in sleep architecture, overnight gas exchange variables, and self-reported sleep quality, comfort and preference.

Baiamonte et al. [17] reported retrospectively on the efficacy of auto-bi-level PAP in 356 patients with OSA, including 80 patients with COPD (overlap syndrome) and 34 patients with OHS. Initially, all patients underwent home titration using auto-CPAP devices for 2–4 nights. Fixed CPAP was then applied based on the machine software data, and its efficacy was evaluated using overnight oximetry and arterial blood gases. If CPAP titration was unsuccessful or not tolerated (88 patients, 26 with overlap syndrome, 29 with OHS), an auto-bi-level PAP machine (Auto25, ResMed, Australia; Biflex, Respironics, USA; Tivan, Lowenstein Medical Inc., Germany) was tried using the same protocol; EPAP was set to the level established by the CPAP trial. Auto-bi-level PAP was prescribed if tolerance was good and obstructive events and hypoventilation were abolished; for the rest of the patients, other NIV modes were tried. All patients were re-evaluated at 1–3 months and every 6 months thereafter based on the machine software data (residual AHI, leaks, mean daily use), overnight oximetry, and arterial blood gases. Causes of CPAP failure varied, with the persistence of breathing disorders being significantly more common in OHS and overlap patients while intolerance rates were higher in the OSA-only subgroup. Auto-bi-level PAP was successfully applied to 70 out of the 88 patients (79.5%) who failed CPAP. The combined success rate of CPAP and auto-bi-level PAP superseded 90% in patients with OSA-only and overlap syndrome but was significantly lower (76%) in OHS patients. Independent predictors of CPAP or auto-bi-level PAP failure were a high body mass index (>40 kg/m^2) and a high time spent with a SpO_2 < 90% (>20% for CPAP and >42% for auto-bi-level PAP).

Zou et al. [18] recruited 23 OHS patients with moderate and severe OSA in a crossover study which aimed to compare the efficacies of fixed bi-level PAP and auto-trilevel PAP (Prisma25ST, Lowenstein Medical, Inc., Germany). Auto-trilevel PAP aims to improve patient tolerance by applying two different EPAP levels during expiration, a lower at the early phase of expiration and a higher at the latter portion when obstructive events are likely to be more pronounced. Initially, all patients underwent EPAP and inspiratory positive airway pressure (IPAP) titration, while end-tidal CO_2 ($ETCO_2$) was monitored to effect a value <45 mmHg with the lowest IPAP. Subsequently, three different PAP modes were applied to each patient with an interval of two nights between each study: (1) mode 1, in which a fixed EPAP was set to abolish snoring; (2) mode 2, in which a fixed EPAP was set at a pressure 3 cmH_2O higher than mode 1; and (3) mode 3 in which auto-trilevel PAP was applied with the lowest EPAP level set according to mode 1. IPAP was set based on the initial titration night in all modes. All modes effected remarkable improvement in AHI (mean value before NIV 41.2 events/h); however, although no difference in mean AHI was noted between mode 2 (2.7 events/h) and mode 3 (3.3 events/h), both were significantly higher than mean AHI in mode 1 (6.1 events/h). A similar pattern of improvement was also noted in obstructive events and in the minimum SpO_2 overnight value; significant decreases in central events were also observed but did not differ across the three modes. In addition, early morning $PaCO_2$ was significantly improved by all modes (mean value before NIV 57.3 mmHg); however, $PaCO_2$ values post-NIV did not differ between mode 1 and 3 (41.8 vs. 42.3 mmHg), although they were both significantly higher compared to mode 2 (48.9 mmHg). Improvements in arousal index and sleep efficiency were effected by all three treatments with significant differences across the three modes; however, mode 3 achieved the greatest effect. The percentages of N1+N2 and N3 sleep also increased with best values recorded for mode 2 and mode 3 as opposed to mode 1; REM sleep percentages improved too but did not differ across the three modes. Daytime sleepiness (ESS, mean value before NIV 16.3) also decreased post-NIV for all three modes although mode 3 achieved the greatest improvement as opposed to mode 2 and mode 1 (4.9 vs. 7.9 vs. 7.2, respectively).

2.6 Monitoring of OHS Patients Under NIV

Alvarez et al. [19] compared the reliability of ventilator built-in software (BIS) to standard respiratory PG in the scoring of respiratory events in patients with OHS. This study evaluated data from 24 stable OHS patients under treatment with NIV at the ST mode (VPAP ST, ResMed, Australia). All patients were studied at home during a full night under NIV; respiratory PG was simultaneously performed with airflow data obtained from a pneumotachograph set between the circuit and the mask. Software data were downloaded using the ResLink module (ResMed, Australia), and an automated event/h index, including apneas and hypopneas (E_{AUT}), was calculated. In addition, a manual analysis of software (E_{BIS}) and PG data (E_{PG}) by two experienced operators was also performed. Based on a cutoff value of 10 events/h, PG, BIS manual analysis, and automated analysis identified "abnormal" recordings in 5 (19%), 3 (11%), and 3 (11%) patients, respectively. Agreement between operators was "good" for software data scoring (kappa 0.71) and "excellent" for PG scoring (kappa 0.84); however automatic analysis yielded a significantly lower EI than both manual analyses. Bland-Altman comparison of E_{PG} to E_{BIS} yielded a small bias (0.6 events/h) albeit with wide limits of agreement (−6.2 to 7.5 events/h); the comparison of E_{PG} and E_{BIS} to E_{AUT} yielded higher biases (3.3 and 2.7 events/h, respectively), again with wide limits of agreement (−1.9 to 8.6 and −6.2 to 11.7 events/h, respectively).

Aarasted et al. [20] reported on the frequency and types of abnormal respiratory events in 67 stable patients receiving treatment with NIV for various hypoventilation syndromes including 16 with OHS, 26 with NMD, 10 with RTD, and 5 with congenital central hypoventilation

syndrome (CHS). These events included high unintentional leaks, apneas and hypopneas, desynchronization (delayed or ineffective triggering), auto-triggering, and double triggering. All patients were studied by attended sleep PG, while SpO_2 and $tcPaCO_2$ readings were used for nocturnal gas exchange monitoring. Total desynchronization index (TDI) was calculated as the number of desynchronization events divided by the total recording time (TRT); patient-ventilator asynchrony index (PVAI) was calculated as the sum of the number of desynchronization, auto-triggering, and double triggering events divided by TRT. The percentage of TRT occupied by asynchronies (PVA%) was also calculated. While periods with high unintentional leaks were rarely observed, discrete events were common, with mean AHI being significantly higher in OHS (4.5 events/h), NMD (2.7 events/h), and CHS (3.8 events/h) as opposed to RTD (0.8 events/h); however, no differences in mean AHI were observed between OHS, NMD, and CHS. Obstructive hypopneas associated with desaturation were the most common respiratory events. PVAI ranged between 0 and 25.4 events/h (median 2.1 events/h) and PVA% between 0 and 45% (median 2%) with no significant differences across the individual subgroups. A PVA% > 10% and a PVI > 5 events/h were observed in 2 and 6 out of the 16 OHS patients, respectively. No correlation was found between abnormal respiratory events and persistent nocturnal hypercapnia (time with a $tcPaCO_2$ > 50 or >55 mmHg or mean $tcPaCO_2$ value). Time spent with a SpO_2 < 90% was significantly, albeit weakly, correlated with PAVI, PVA%, and TDI.

2.7 Key Points

- PAP therapy improves diurnal and nocturnal gas exchange variables, dyspnea, quality of sleep, HRQL, and survival in patients with OHS. PAP therapy also improves echocardiographic variables at least in the short term.
- Increased PAP adherence is associated with favorable prognosis.
- CPAP is no inferior to fixed bi-level PAP in the management of OHS. The potential role of alternative PAP modalities requires further evidence.
- OHS patients under treatment with NIV have among the higher survival rates when compared to other NIV-treated patients with various hypoventilation syndromes.
- Residual respiratory events and patient-ventilator asynchrony are not uncommon in patients with OHS.

References

1. Masa JF, Pépin J-L, Borel J-C, Mokhlesi B, Murphy PB, Sánchez-Quiroga MÁ. Obesity hypoventilation syndrome. Eur Respir Rev. 2019;28 https://doi.org/10.1183/16000617.0097-2018.
2. Balachandran JS, Masa JF, Mokhlesi B. Obesity hypoventilation syndrome epidemiology and diagnosis. Sleep Med Clin. 2014;9:341–7.
3. Mokhlesi B, Kryger MH, Grunstein RR. Assessment and management of patients with obesity hypoventilation syndrome. Proc Am Thorac Soc. 2008;5:218–25.
4. Marik PE, Desai H. Characteristics of patients with the "malignant obesity hypoventilation syndrome" admitted to an ICU. J Intensive Care Med. 2013;28:124–30.
5. Royer CP, Schweiger C, Manica D, Rabaioli L, Guerra V, Sbruzzi G. Efficacy of bilevel ventilatory support in the treatment of stable patients with obesity hypoventilation syndrome: systematic review and meta-analysis. Sleep Med. 2019;53:153–64.
6. Howard ME, Piper AJ, Stevens B, Holland AE, Yee BJ, Dabscheck E, et al. A randomized controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax. 2017;72:437–44.
7. Orfanos S, Jaffuel D, Perrin C, Molinari N, Chanez P, Palot A. Switch of noninvasive ventilation (NIV) to continuous positive airway pressure (CPAP) in patients with obesity hypoventilation syndrome: a pilot study. BMC Pulm Med. 2017;17:50.
8. Onofri A, Patout M, Kaltsakas G, Lhuillier E, Mushemi-Blake S, Arbane G, et al. Neural respiratory drive and cardiac function in patients with obesity hypoventilation syndrome following initiation of non-invasive ventilation. J Thorac Dis. 2018;10:S135–43.
9. Corral J, Mogollon MV, Sánchez-Quiroga M-Á, Gómez de Terreros J, Romero A, Caballero C, et al. Echocardiographic changes with non-invasive ventilation and CPAP in obesity hypoventilation syndrome. Thorax. 2018;73:361–8.
10. Bouloukaki I, Mermigkis C, Michelakis S, Moniaki V, Mauroudi E, Tzanakis N, et al. The association between adherence to positive airway pressure ther-

apy and long-term outcomes in patients with obesity hypoventilation syndrome: a prospective observational study. J Clin Sleep Med. 2018;14:1539–50.
11. Masa JF, Mokhlesi B, Benítez I, Gomez de Terreros FJ, Sánchez-Quiroga MÁ, Romero A, et al. Long-term clinical effectiveness of continuous positive airway pressure therapy versus non-invasive ventilation therapy in patients with obesity hypoventilation syndrome: a multicentre, open-label, randomized controlled trial. Lancet Lond Engl. 2019; https://doi.org/10.1016/S0140-6736(18)32978-7.
12. Gouda P, Chua J, Langan D, Hannon T, Scott A, O'Regan A. A decade of domiciliary non-invasive ventilation in the west of Ireland. Ir J Med Sci. 2017;186:505–10.
13. Blankenburg T, Benthin C, Pohl S, Bramer A, Kalbitz F, Lautenschläger C, et al. Survival of hypercapnic patients with COPD and obesity hypoventilation syndrome treated with high-intensity non invasive ventilation in the daily routine care. Open Respir Med J. 2017;11:31–40.
14. Tan GP, McArdle N, Dhaliwal SS, Douglas J, Rea CS, Singh B. Patterns of use, survival and prognostic factors in patients receiving home mechanical ventilation in Western Australia: a single center historical cohort study. Chron Respir Dis. 2018;15:356–64.
15. Markussen H, Lehmann S, Nilsen RM, Natvig GK. Health-related quality of life as predictor for mortality in patients treated with long-term mechanical ventilation. BMC Pulm Med. 2019;19:13.
16. McArdle N, Rea C, King S, Maddison K, Ramanan D, Ketheeswaran S, et al. Treating chronic hypoventilation with automatic adjustable versus fixed EPAP Intelligent Volume-Assured Positive Airway Pressure Support (iVAPS): a randomized controlled trial. Sleep. 2017;40 https://doi.org/10.1093/sleep/zsx136.
17. Baiamonte P, Mazzuca E, Gruttad'Auria CI, Castrogiovanni A, Marino C, Lo Nardo D, et al. Use of autobilevel ventilation in patients with obstructive sleep apnea: an observational study. J Sleep Res. 2018;27:e12680.
18. Zou C, Sheng W, Huai D, Cao J, Su M, Ning D, et al. Comparison between auto-trilevel and bilevel positive airway pressure ventilation for treatment of patients with concurrent obesity hypoventilation syndrome and obstructive sleep apnea syndrome. Sleep Breath. 2018;23(3):735–40. https://doi.org/10.1007/s11325-018-1750-3.
19. Fernandez Alvarez R, Rabec C, Rubinos Cuadrado G, Cascon Hernandez JA, Rodriguez P, Georges M, et al. Monitoring noninvasive ventilation in patients with obesity hypoventilation syndrome: comparison between ventilator built-in software and respiratory polygraphy. Respiration. 2017;93:162–9.
20. Aarrestad S, Qvarfort M, Kleiven AL, Tollefsen E, Skjønsberg OH, Janssens J-P. Sleep-related respiratory events during non-invasive ventilation of patients with chronic hypoventilation. Respir Med. 2017;132:210–6.

Noninvasive Ventilation in COPD

3

Jakob Wittenstein

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Abbreviations

AECOPD	Acute exacerbation of COPD
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	End-expiratory positive airway pressure
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
NIV	Noninvasive ventilation
$PaCO_2$	Arterial partial carbon dioxide pressure
PaO_2	Arterial partial oxygen pressure

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3.1 Introduction

Chronic obstructive pulmonary disease (COPD) remains a common cause of morbidity and mortality worldwide. While COPD is mainly a chronic disease, a substantial number of patients suffer from exacerbations [1]. Patients with COPD and respiratory failure, whether acute (AECOPD, acute exacerbation of COPD) or chronic, have a poorer prognosis compared with patients without respiratory failure. Noninvasive ventilation (NIV) has been shown to be a useful tool in both the acute hospital (AECOPD) and chronic home care setting

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(severe stable hypercapnic COPD). Today, NIV is the gold standard therapy for AECOPD patients. When used properly, mortality and intubation rates are reduced compared with standard therapy [2].

Furthermore, NIV can be used in the ambulant setting in the form of home NIV in stable hypercapnic COPD. Even though the mechanisms are not completely clear, the intermittent off-loading of the respiratory muscles with NIV in patients with chronic hypercapnic failure may be part of the explanation of the beneficial effects of NIV in these patients [2]. Recently, a randomised trial showed that home NIV compared with long-term oxygen therapy only can improve the outcome [3].

3.2 Methodology

A systematic electronic literature search was performed using the PubMed database from January 2017 up to March 2019 including clinical trials, meta-analysis and review articles in the English language. A combination of the following entry terms "noninvasive ventilation", "NIV", "continuous positive airway pressure (CPAP)" and "chronic obstructive pulmonary disease (COPD)" was used.

3.3 Home Noninvasive Ventilation

Home NIV can be used in COPD patients with concomitant chronic hypercapnic respiratory failure to correct nocturnal hypoventilation and improve sleep quality, quality of life and survival [4]. Today NIV is used in nearly one-third of COPD patients considered to have a poor life expectancy and can thereby contribute to symptom relief without adding to the care burden [2]. Principles are overnight placement, allowing the respiratory muscles to recover so that better respiratory function can be achieved during the day. The quality of home NIV should be monitored in order to assess the effectiveness of ventilation and adherence to therapy, resolve potential adverse effects, reinforce patient knowledge, provide maintenance of the equipment and readjust the ventilator settings according to the changing condition of the patient. Ventilator data can show unintentional leaks, upper airway obstruction and patient-ventilator asynchrony. Furthermore, nocturnal oximetry and capnography can be used to assess the impact of NIV on gas exchange [4]. Respiratory work is physiologically increased during sleep and can lead to severe alterations in COPD patients, especially by raising sleep hypoventilation. Impaired sleep and the increase of respiratory work may be one of the major triggers of diurnal events like hypoventilation, exacerbation and even mortality [5]. Indications for home NIV are chronic respiratory insufficiency with $PaCO_2$ (arterial partial carbon dioxide pressure) > 7 kPa and resting dyspnoea, stress intolerance and central nervous restrictions due to hypercapnia despite the exhaustion of all conservative measures including long-term oxygen therapy [6]. This should be kept in mind, as patient selection seems to be one of the most important determinants of success [2].

Home NIV today is also known under the term high-intensity NIV. Originally, it was described for COPD patients in 2009 and refers to a specific ventilatory approach whereby NIV settings are aimed at achieving the lowest $PaCO_2$ values possible [7]. Nevertheless, optimal goals according to which home NIV should be titrated are missing, as we lack knowledge about mechanisms of how NIV improves outcomes [8]. High-intensity NIV has been shown to improve outcomes in stable hypercapnic COPD patients [9, 10]. Duivermann and colleagues showed in a small crossover trial (n = 10) that high-intensity NIV might provide optimal unloading of respiratory muscles, without undue increases in patient-ventilator asynchrony [9]. A randomised clinical trial (n = 116) by Murphy et al. tested the effect of home NIV plus oxygen on time to readmission or death in patients with persistent hypercapnia after an acute COPD exacerbation (see also Table 3.1) [3]. COPD patients with a $PaCO_2$ above 7 kPa at 2–4 weeks after acute NIV use were included in the trial. Patients received moderate to high levels of airway pressure with a median inspiratory airway pressure (IPAP) of 24 cmH_2O, median end-expiratory airway pressure (EPAP) of 4 cmH_2O and

Table 3.1 Summary of best clinical trials and meta-analysis

Trial	Patient	Intervention	Comparison	Outcome	Author
Home NIV (RCT)	COPD patients with a $PaCO_2$ above 7 kPa at 2–4 weeks after acute NIV cessation (n = 116)	Home NIV (IPAP = 24 cmH_2O, EPAP = 4 cmH_2O, for 7.6 h/night) + oxygen therapy	Oxygen therapy only	Increased time to hospital readmission or death	Murphy et al. [3]
NIV in AECOPD (meta-analysis)	Acute respiratory failure due to AECOPD (n = 1264)	NIV + usual care	Usual care alone	Reduced mortality, risk of needing endotracheal intubation and hospital length of stay	Osadnik et al. [22]
Weaning from NIV (RCT)	After recovery from AECOPD tolerating 4 h of unassisted breathing	Three additional nights of NIV	Direct NIV discontinuation	No benefits	Sellares et al. [25]

RCT randomised controlled trial, *COPD* chronic obstructive pulmonary disease, *AECOPD* acute exacerbation of COPD, *$PaCO_2$* arterial partial carbon dioxide pressure, *NIV* noninvasive ventilation, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure

oxygen therapy delivered at 1 L/min, compared with the standard treatment group receiving oxygen therapy alone at a flow rate of 1 L/min. The median time on the ventilator was 7.6 h per night at 12 months. The median time to readmission or death was 4.3 months in the NIV group compared with 1.4 months in the oxygen alone group. Therefore, NIV was clinically effective in increasing the time to hospital readmission or death. However, all-cause mortality was not different between the two groups. This provides the clinical rationale to screen patients in the recovery phase for persistent hypercapnia following a life-threatening exacerbation of COPD requiring acute NIV. In COPD patients who have a $PaCO_2$ above 7 kPa and a PaO_2 (arterial partial oxygen pressure) below 8 kPa, home NIV should be added to long-term oxygen therapy to increase the time to hospital readmission and reduce exacerbation rate [11]. The study by Murphy et al. was also an important landmark in the NIV field, as this important benefit was achieved not only through adequate ventilatory settings but also through very careful patient selection [12]. Duivermann and colleges point out that several good-quality RCTs have shown that if adequate ventilatory settings are applied, aimed at a substantial reduction in $PaCO_2$, chronic NIV improves outcomes in patients with severe chronic hypercapnic respiratory failure [12].

Zhou et al. could show that 3-month use of standard long-term oxygen therapy plus home NIV (5 h daily, mean IPAP 17.8 cmH_2O and mean EPAP 4.2 cmH_2O) in hypercapnic COPD patients (n = 115) could reduce the $PaCO_2$ and improve exercise tolerance [13].

A meta-analysis of seven studies with 810 patients in total showed that long-term home NIV decreases the $PaCO_2$ of stable hypercapnic COPD patients with respiratory failure, while outcome parameters and mortality were not different compared with the no home NIV groups [14]. Home NIV may theoretically adversely affect cardiac function. However, Duivermann and colleagues showed in a small crossover trial (n = 14; severe stable COPD patients) that long-term NIV with adequate IPAP to improve gas exchange and health-related quality of life did not have an overall adverse effect on cardiac performance [10].

A rather new alternative to home NIV might be high-flow oxygen therapy. Nevertheless, evidence is weak, with some promising results from small clinical trials [15, 16]. For high-flow oxygen therapy, see also Chap. 31.

3.3.1 How to Use Home NIV

Home NIV should be started in an appropriate environment, and the patient should be given some background information about the procedure (see also Fig. 3.1). For home NIV it can be recommended to start with daytime practice sessions using a spontaneous-timed mode with IPAP levels of 12–18 cmH_2O, a low EPAP (4–5 cmH_2O) and a low backup respiratory rate (10/min) [8]. The mask should be known to the patient and fit well. Under strict monitoring of gas exchange, IPAP can be increased in order to reach normocapnia. The ratio of inspiratory to expiratory time should be at least 1:2 preferably longer. Inspiratory oxygen fraction can be titrated according to peripheral oxygen saturation (>88%) [10].

3.4 NIV in Acute Exacerbations of COPD

In patients with AECOPD, early use of NIV can reduce intubation risk and complications such as ventilator-associated pneumonia and reduce mortality [17, 18]. Possible explanations for the positive effects are recruitment of collapsed alveoli, improved ventilation-perfusion matching with consecutive improved oxygenation and respiratory acidosis and a decreased work of breathing [19]. A guideline by the European Respiratory

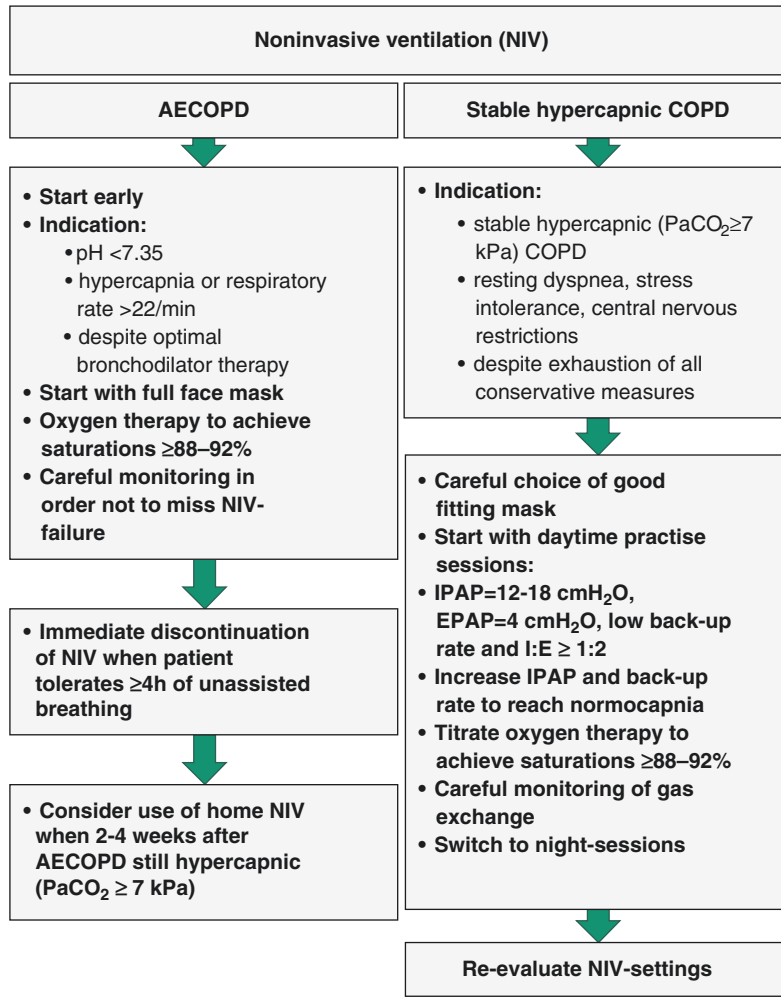

Fig. 3.1 Noninvasive ventilation in acute and stable hypercapnic COPD. *COPD* chronic obstructive pulmonary disease, *AECOPD* acute exacerbation of COPD, $PaCO_2$ arterial partial carbon dioxide pressure, *NIV* noninvasive ventilation, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure, *I:E* inspiratory to expiratory time

Society and American Thoracic Society published 2017 points out that NIV reduces the need for intubation, mortality, complications of therapy and length of both hospital stay and ICU (intensive care unit) stay in patients with acute or acute-on-chronic respiratory failure due to a COPD exacerbation with no reports of adverse consequences [20]. The established criteria for patient selection includes persistent acidosis (pH < 7.35), hypercapnia ($PaCO_2$ > 6.5 kPa) or tachypnoea (respiratory rate >22/min) despite optimal bronchodilator and controlled oxygen therapy [21]. Furthermore, a full-face mask should be the first type of interface used; oxygen therapy should be used to achieve a target saturation of 88–92% [21].

A systematic Cochrane review points out that the use of NIV in patients admitted with AECOPD decreased the risk of mortality by 46% with a number needed to treat for an additional beneficial outcome (NNTB) of 12 and decreased the risk of needing endotracheal intubation by 65%, with a NNTB of 5 (see also Table 3.1) [22]. As the application of NIV is relatively simple and well tolerated by most patients [23], it is an indispensable tool in the treatment of AECOPD. Nevertheless, NIV failure has to be recognised early in order not to slow down necessary therapy escalation (see also Chap. 31), as NIV failure rate is still high [2].

A rather new form of NIV uses helium instead of air. Helium has a lower density than air. Thereby density-dependent components of airway resistance within bronchi with increased resistance can be reduced, as it is the case in AECOPD. Furthermore, this might result in a lower work of breathing and improved respiratory parameters [24]. Abroug and colleagues compared in a meta-analysis a mixture of helium and oxygen (He/O_2) with an air-oxygen mixture (air/O_2) [17]. The authors did not find a significant difference in the rate of NIV failure when using He/O_2 mixture compared with air/O_2. However, He/O_2 significantly reduced the length of ICU stay and the rate of NIV-associated complications [17]. Nevertheless, in conclusion, there is not enough evidence to recommend the systematic use of He/O_2 in all AECOPD patients.

The question of when to stop NIV in AECOPD patients has long been unanswered. Recently Sellares and colleagues assessed whether prolongation of nocturnal NIV after recovery from acute hypercapnic respiratory failure for COPD patients with NIV could prevent subsequent relapse of respiratory failure (see also Table 3.1) [25]. When patients tolerated unassisted breathing for 4 h, they either received three additional nights of NIV ($n = 61$) or direct NIV discontinuation ($n = 59$). The prolongation of NIV was not beneficial, and the authors, therefore, conclude that NIV can be directly discontinued when the acute episode is resolved and patients tolerate unassisted breathing [25]. Nevertheless, further trials are needed to answer the question with greater certainty.

3.5 Conclusion

1. Learning Points
   - Nocturnal home NIV can increase time to hospital readmission or death in stable hypercapnic COPD patients.
   - Home NIV settings should be titrated to the patient's gas exchange.
   - In AECOPD patients, NIV should be used early, as it reduces mortality and decreases the need for endotracheal intubation.
   - When patients tolerate unassisted breathing for more than 4 h after AEOCPD, NIV can be discontinued directly.
   - New modalities like high-flow oxygen and helium oxygen mix instead of air oxygen mix have shown some promising results; nevertheless, the evidence is weak.
2. Critical Points
   - Patients for home NIV have to be selected carefully, as selection seems to be an important determinant of success.
   - Careful monitoring of NIV is crucial in order not to miss NIV failure in AECOPD patients and to optimise NIV settings in stable hypercapnic COPD patients.
3. Key Summary

   In the last 2 years, important clinical trials and meta-analysis on NIV in COPD patients

have been published. Today there is new evidence that when the right patients are selected, home NIV in stable hypercapnic COPD can reduce hospital readmission rate. In AECOPD NIV not only improves patients outcome but also reduces mortality, with a small number needed to treat (NNTB = 5). After an AECOPD episode, NIV might be stopped as soon as the patient tolerates more than 4 h of unassisted breathing. In all cases, a precise monitoring is necessary, in order to achieve the greatest possible positive effects with NIV.

References

1. Viniol C, Vogelmeier CF. Exacerbations of COPD. Eur Respir Rev. 2018;27(147). pii: 170103.
2. Shah NM, D'Cruz RF, Murphy PB. Update: noninvasive ventilation in chronic obstructive pulmonary disease. J Thor Dis. 2018;10(Suppl 1):S71–s9.
3. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. JAMA. 2017;317(21):2177–86.
4. Arnal JM, Texereau J, Garnero A. Practical insight to monitor home NIV in COPD patients. COPD. 2017;14(4):401–10.
5. Grassion L, Gonzalez-Bermejo J. Sleep and mechanical ventilation in stable COPD patients. COPD. 2017;14(4):411–7.
6. Storre JH, Callegari J, Magnet FS, Schwarz SB, Duiverman ML, Wijkstra PJ, et al. Home noninvasive ventilatory support for patients with chronic obstructive pulmonary disease: patient selection and perspectives. Int J Chron Obstruct Pulmon Dis. 2018;13:753–60.
7. Schwarz SB, Magnet FS, Windisch W. Why high-intensity NPPV is favourable to low-intensity NPPV: clinical and physiological reasons. COPD. 2017;14(4):389–95.
8. van der Leest S, Duiverman ML. High-intensity noninvasive ventilation in stable hypercapnic COPD: evidence of efficacy and practical advice. Respirology. 2019;24(4):318–28.
9. Duiverman ML, Huberts AS, van Eykern LA, Bladder G, Wijkstra PJ. Respiratory muscle activity and patient-ventilator asynchrony during different settings of noninvasive ventilation in stable hypercapnic COPD: does high inspiratory pressure lead to respiratory muscle unloading? Int J Chronic Obstruct Pulmon Dis. 2017;12:243–57.
10. Duiverman ML, Maagh P, Magnet FS, Schmoor C, Arellano-Maric MP, Meissner A, et al. Impact of high-intensity-NIV on the heart in stable COPD: a randomised cross-over pilot study. Respir Res. 2017;18(1):76.
11. Suh ES, Murphy PB, Hart N. Home mechanical ventilation for chronic obstructive pulmonary disease: What next after the HOT-HMV trial? Respirology. 2019;24(8):732–9.
12. Duiverman ML. Noninvasive ventilation in stable hypercapnic COPD: what is the evidence? ERJ Open Res. 2018;4(2). pii: 00012-2018.
13. Zhou L, Li X, Guan L, Chen J, Guo B, Wu W, et al. Home noninvasive positive pressure ventilation with built-in software in stable hypercapnic COPD: a short-term prospective, multicenter, randomized, controlled trial. Int J Chronic Obstruct Pulmon Dis. 2017;12:1279–86.
14. Liao H, Pei W, Li H, Luo Y, Wang K, Li R, et al. Efficacy of long-term noninvasive positive pressure ventilation in stable hypercapnic COPD patients with respiratory failure: a meta-analysis of randomized controlled trials. Int J Chronic Obstruct Pulmon Dis. 2017;12:2977–85.
15. Ceriana P, Vitacca M, Carlucci A, Paneroni M, Pisani L, Nava S. Changes of respiratory mechanics in COPD patients from stable state to acute exacerbations with respiratory failure. COPD. 2017;14(2):150–5.
16. Braunlich J, Mauersberger F, Wirtz H. Effectiveness of nasal highflow in hypercapnic COPD patients is flow and leakage dependent. BMC Pulmon Med. 2018;18(1):14.
17. Abroug F, Ouanes-Besbes L, Hammouda Z, Benabidallah S, Dachraoui F, Ouanes I, et al. Noninvasive ventilation with helium-oxygen mixture in hypercapnic COPD exacerbation: aggregate meta-analysis of randomized controlled trials. Ann Intensive Care. 2017;7(1):59.
18. Kondo Y, Kumasawa J, Kawaguchi A, Seo R, Nango E, Hashimoto S. Effects of non-invasive ventilation in patients with acute respiratory failure excluding post-extubation respiratory failure, cardiogenic pulmonary edema and exacerbation of COPD: a systematic review and meta-analysis. J Anesth. 2017;31(5):714–25.
19. Kim DK, Lee J, Park JH, Yoo KH. What can we apply to manage acute exacerbation of chronic obstructive pulmonary disease with acute respiratory failure? Tuberc Respir Dis. 2018;81(2):99–105.
20. Wedzicha JA, Miravitlles M, Hurst JR, Calverley PM, Albert RK, Anzueto A, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J. 2017;49(3). pii: 1600791.
21. Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl):2.
22. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respira-

tory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;(7):Cd004104.
23. Esquinas AM, Benhamou MO, Glossop AJ, Mina B. Noninvasive mechanical ventilation in acute ventilatory failure: rationale and current applications. Sleep Med Clin. 2017;12(4):597–606.
24. Jolliet P, Ouanes-Besbes L, Abroug F, Ben Khelil J, Besbes M, Garnero A, et al. A multicenter randomized trial assessing the efficacy of helium/oxygen in severe exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2017;195(7):871–80.
25. Sellares J, Ferrer M, Anton A, Loureiro H, Bencosme C, Alonso R, et al. Discontinuing noninvasive ventilation in severe chronic obstructive pulmonary disease exacerbations: a randomised controlled trial. Eur Respir J. 2017;50(1). pii: 1601448.

4 Noninvasive Ventilation for Cystic Fibrosis

Carlotta Biglia, Roberta Di Tria, and Barbara Messore

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Abbreviations

ARF	Acute respiratory failure
ATS	American Thoracic Society
BTS	British Thoracic Society
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
EPAP	Expiratory positive airway pressure
ERS	European Respiratory Society
HFNC	High-flow nasal cannula
IMV	Invasive mechanical ventilation
IPAP	Inspiratory positive airway pressure
NICE	National Institute for Health and Care Excellence
NIV	Noninvasive ventilation
PEEP	Positive end-expiratory pressure
ppFEV1	Percentage predicted forced expiratory volume in one second
PPV	Positive pressure ventilation
PSV	Pressure support ventilation
$PtcCO_2$	Transcutaneous carbon dioxide
Pts	Patients

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QoL	Quality of life
RCTs	Randomized clinical trials
REM	Rapid eye movement
SaO_2	Saturation of haemoglobin with oxygen using pulse oximetry
UK	United Kingdom

4.1 Introduction

Cystic fibrosis (CF) is the most common autosomal recessive disorder in the Caucasian population due to defective function of the CFTR (cystic fibrosis transmembrane conductance regulator) protein—a transmembrane apical channel whose task is to balance transcellular transport of electrolytes (mainly chloride and bicarbonate ions) and fluids with the consequent pathologic inspissation of extracellular fluids and exocrine glandular secretions. CFTR is expressed in the respiratory tract, pancreas, gastroenteric tract, liver, genito-urinary tract, bone and sweats glands. Thousands of mutations with different impact on CFTR protein function are recognized, and so even if CF is a monogenic disease, it can be heterogeneous in clinical expression with variability in severity, rate of progression and organ involvement. CF is a multisystemic disease in which the respiratory system is affected in the majority of patients and is responsible of morbidity and of death in young adults affected.

Respiratory system involvement occurs early; impairment is progressive with recurrent infectious and inflammatory processes of varying intensity, bronchial hypersecretion of thick mucus that plugs airways, inflammation of the bronchi wall with thickening of the same, bronchiectasis and a progressive airflow obstruction with an increase of intrinsic positive end-expiratory pressure (PEEP). Mucus plugs may determine segmental or lobar atelectasis with consequent possible evolution in parenchymal carnification and fibrosis [1].

CF lung disease has unique physiopathological features due to a mix of obstructive and restrictive functional defect and the presence of tenacious secretions.

In CF the respiratory work is increased by the structural bronchi and lung parenchymal alterations described above, to which sequelae of chronic infection and weakness of the respiratory muscles have to be added. Systemic inflammation, oxidative stress and malnutrition may further worsen functional capacity.

Ventilation is a fragile balance between the nervous system, which interacts with the respiratory muscles, and respiratory work (Fig. 4.1). As respiratory work increases, there is an increase in the central drive, which is not sufficient to avoid alveolar hypoventilation; moreover, mucus plugs in the peripheral airways can give rise to atelectasis and gas exchange impairment. In addition to chronic damage, CF patients experience acute exacerbations that further increase the respiratory work bringing to respiratory failure [2]. Ventilation in CF during sleep deserves a separate discussion (Fig. 4.1).

Different studies, even if few compared to the literature concerning pathologies such as chronic obstructive pulmonary disease (COPD), have shown how the application of noninvasive ventilation (NIV) in CF can lighten the respiratory work by compensating or preventing respiratory failure [3–6].

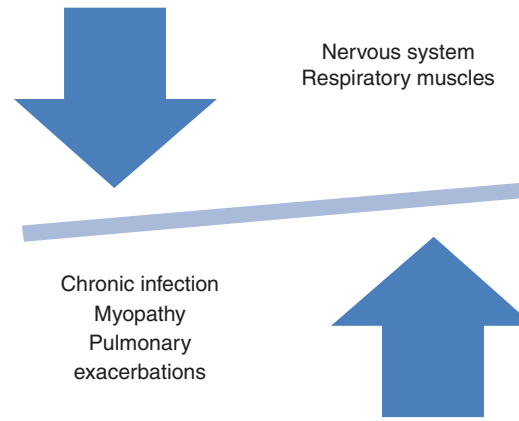

Fig. 4.1 Balance between respiratory work and the ability of respiratory muscles. Structural alterations due to bronchiectasis and mucoid impacts, increased catabolism and energetic demand due to chronic infection and exacerbations resulting in increased respiratory work, not adequately compensated from the increase of the nervous drive, determine the onset of respiratory failure

NIV has been used for CF patients since the early 1990s when it was described as a holding measure for the lung transplant waiting list, but other indications exist for considering NIV in CF care:

- Hypercapnic acute and chronic respiratory failure
- Sleep disorders
- As an adjunct to physiotherapy for secretion airways clearances

4.2 Bibliography Research

To address the innovations in the last 2 years in the role of NIV in CF, we have undertaken an analysis of publications on this topic that were featured in PubMed and Embase using "cystic fibrosis" as primary keyword and "noninvasive ventilation", "respiratory failure or insufficiency", "sleep disorders" and "hypercapnic" as secondary keywords, selecting period from January 2017 to March 2019.

The search selected only "few" publications: a Cochrane review edited in 2017 that has included seven clinical trials, a large retrospective analysis published in 2018 on NIV utilization in CF based on United Kingdom (UK) CF patient registry database in the period 2007–2015 and only one randomized crossover physiological study comparing high-flow nasal cannula (HFNC) versus NIV in severe CF adult patients (Table 4.1).

The 2017 Cochrane review on NIV in CF [6]—which analysed 191 mixed adult and paediatric CF patients ventilated for several indications (with different inclusion criteria in any trial)—is limited by small sample sizes of adult only trials, sparse reporting of physiological variables, heterogeneous inclusion of varying degrees of disease severity and intervention period too short to observe significant changes. This review includes ten trials. Seven short-term trials showed that NIV can improve a range of breathing and gas exchange measures and ease sputum clearance; one evaluated a 2-week intervention; one evaluated a 6-week

Table 4.1 An Analysis of publications in the role of NIV in CF in 2017–2019

Year of publication	Authors, title, journal	Type of study	Results	Conclusions	Comments
2017	Moran F. et al,, Noninvasive ventilation for cystic fibrosis *Cochrane Database of Systematic Reviews*	RCTs comparing a form of pressure preset or volume preset NIV to no NIV used for airway clearance or during sleep or exercise in people with acute or chronic respiratory failure in CF	Ten trials, total pts 191 The goals of trials are airway clearance may be easier with NIV and improvement in lung clearance index, QoL and CO_2 levels They showed it is effective, safe and acceptable, but no clear differences between NIV and oxygen or room air. There is a significant improvement in exercise on NIV	NIV improves the physiological markers of early respiratory failure following a single nocturnal treatment session, with improvements in exercise tolerance, selected aspects of QoL and nocturnal CO_2 levels when used over a longer period. Nocturnal respiratory support with NIV has important implications for CF patients and advanced lung disease and may attenuate the early effects and progression of respiratory failure	Intervention period length may be too short to observe significant changes Different inclusion criteria for any trial

(continued)

Table 4.1 (continued)

Year of publication	Authors, title, journal	Type of study	Results	Conclusions	Comments
2018	Olga Archangelidi et al., Noninvasive ventilation and clinical outcomes in cystic fibrosis: Findings from the UK CF registry, *Journal of Cystic Fibrosis*	Retrospective-observational study	Total pts: 1107 Rise ppFEV1 in children : 0.70 (95% CI: −0.83, 2.24) Rise ppFEV1 in adults with a low ppFEV1 (<40): 2.60 (95% CI: 0.93, 4.27) NIV initiation is associated with an increased risk of death/transplant in both children (HR = 2.47; 95% CI: 1.20–5.08) and adults (HR = 1.96; 95% CI: 1.63–2.36), but effect was attenuated in children with low ppFEV1 (<40)	NIV use in CF improves spirometric values but does not benefit survival	Date of NIV use initiation is not specified in the UK CF registry. This did not allow to distinguish short-term NIV use that followed an acute exacerbation event with subsequent lung function recovery There are no data on arterial blood gas measurements, and we were not able to capture ventilator settings, dose, duration or adherence, precluding any firm conclusions about the consistency and duration of NIV use
2018	Sklar MC et al., High-flow nasal oxygen versus noninvasive ventilation in adult patients with cystic fibrosis: a randomized crossover physiological study. *Annals Intensive Care*	Physiological prospective randomized crossover study	Total pts 15 HFNC, reduced respiratory rate (by 3 breaths/min, $p = 0.01$) and minute ventilation (by 2 L/min, $p = 0.01$). Patients also took slightly larger tidal volumes with HFNC compared to NIV ($p = 0.02$) MAP increased from baseline with NIV compared to HFNC ($p \leq 0.01$). No differences were found for heart rate, SaO_2, $PtcCO_2$ or dyspnoea	In adult CF patients stabilized after indication for ventilatory support, HFNC and NIV have similar effects on diaphragmatic work per breath, but HFNC confers additional physiological benefits by decreasing respiratory rate and minute ventilation	Few patients No placebo, but each participant is his/her own control Time of treatments is only 30 min
2019	Christopher S. King et al., Critical Care of the Adult Patient With Cystic Fibrosis, *Chest*	Systematic review		NIV should be initiated early in the course of acute hypercapnia	

intervention; and one evaluated a 3-month intervention. When used with oxygen, NIV may improve gas exchange during sleep more than oxygen therapy alone. Some evidence has been found to support the use of NIV in addition to other airway clearance methods in CF. Reviewers were not able to find any evidence that NIV improves life expectancy in CF, and data were insufficient to show whether NIV should be used in exercise training in severe disease.

4.3 What Do the Guidelines Say About CF and NIV?

No indications on NIV in CF are reported in the ERS/ATS 2017 clinical practice guidelines [7], while the National Institute for Health and Care Excellence (NICE) guidelines stated only indications for utilization of NIV for clearance of respiratory secretions [8]; the British Thoracic Society (BTS) 2017 guidelines state that, as in COPD, NIV in CF has a role in acute exacerbation with respiratory acidosis stressing that differently from COPD, there are no clinical trials on NIV versus IMV (invasive mechanical ventilation) [9]. BTS guidelines refer to two retrospective studies [9]. In the first multicenter study, 42 adult patients were enrolled in 60 ICUs for acute respiratory failure. NIV has proven to be superior to IMV in terms of therapeutic success and mortality [10]. In the second, a monocentric study of 30 adult patients indicated IMV as the first choice in case of respiratory failure due to pneumothorax or haemoptysis [11].

4.3.1 NIV in Acute and Chronic Respiratory Failure

We can observe in clinical practice two typical clinical scenarios. In the first one, the patient is in the end-stage of CF respiratory disease: ppFEV1 should be <30 associated with daytime hypercapnia, and the only chance is represented by lung transplant. In this case, NIV can represent a "bridge to transplantation", improving gas exchange during wakefulness, sleep, exercise and physiotherapy preserving respiratory muscle performance. This leads to an improvement in the quality of life and in some cases a lower decline in lung function and a better post-transplant outcome [12, 13].

We can also observe a patient with a moderate lung disease, which presents a severe CF exacerbation (increased sputum production and purulence, loss of appetite, weight loss, fatigue, lung function decline and occasionally fever, chest pain, shortness of breath and haemoptysis), that requires hospitalization. In this case there is an "extraordinary" overload of muscular work accompanied by an increase in peripheral mucoid impacts which damage alveolar gas exchange. The result can be an acute respiratory failure with hypoxemia and hypercapnia [1, 2, 14].

It has been suggested that a concomitant metabolic alkalosis contributes to hypercapnic respiratory failure in exacerbations of CF; as a consequence of the abnormal electrolyte transport CF patients less frequently exhibit acidosis than COPD [15].

No randomized controlled studies are available comparing NIV to invasive ventilation in patients with CF due to ethical reasons. All investigations are observational trials, showing that NIV may be useful when used early during an acute respiratory exacerbation [2].

Moreover, there are very few randomized clinical trials on NIV in CF due to the limited numbers of patients, mainly treated in CF centre and not in pulmonary departments with special interest and skills in NIV, to the extremely variable clinical manifestations and respiratory disease being modified by type of bacterial infection, nutritional status and other possible respiratory and systemic CF complications (pneumothorax, parenchymal atelectasis and fibrotic consolidation, diabetes, osteoporosis). Most of the experience is based on retrospective analysis on practice in a single centre or on data from national registry [12].

4.4 NIV and Sleep Disorders

Most studies report disturbed sleep in more than 50% of patients, such as sleep-onset insomnia, frequent awakenings, night cough, snoring, excessive daytime sleepiness, headaches, anxiety, restless leg syndrome and even in the absence of gas exchange abnormalities. The presence of cough, for example, resulting in fragmented sleep may result in an alteration in the physiological progression to rapid eye movement (REM) sleep [16–18].

The headache, however, can be the result of a nocturnal hypoventilation with hypoxemia that generally precedes diurnal hypoxemia. In this regard, there is no consensus either on the definition of nocturnal desaturation or on the timing of oxygen supplementation. Consensus guideline in adult CF patients recommends supplemental oxygen if SaO_2 is less than 88–90% for 10% of the total sleep time [19]. Nocturnal hypoxemia is more present in adult patients with lower ppFEV1 and with a resting awake oxygen SaO_2 of 93–94% and occurs primarily during REM sleep, becoming a risk factor for developing pulmonary hypertension [20].

Supplement oxygen via nasal cannula represents the first- line treatment. Finally, the nocturnal oxygen desaturations occur during CF pulmonary exacerbations. In this case it can be reversible with adequate therapy [21].

Studies carried out to examine the quality of sleep in adult patients with CF have shown that the following abnormalities are present: lower sleep efficiency, less REM sleep and increased arousal index. Pulmonary exacerbations are associated with more wakefulness after sleep onset, less REM sleep and hypoxemia [17, 18]. The frequency of obstructive sleep apnoea is high among CF patients, and it is associated with lower nocturnal oxygen saturations [23].

It is good to note that although many patients report poor quality of sleep, polysomnographic tracings do not always show an alteration of sleep architecture compared to healthy controls. Nevertheless, the quality of sleep would seem to be related to ppFEV1 and the degree of nocturnal desaturation. However, studies on the oxygen supplementation o PPV in hypoxemic CF patients have not shown a clear and significant difference on the modification of sleep architecture, but it is evident that patients who present daytime hypercapnia certainly have nocturnal hypercapnia. In such cases the preferred treatment is the NIV [16, 22].

4.5 NIV and Airway Clearance Physiotherapy

NIV can be used as an adjunct to physiotherapy; moreover, it may be a useful adjunct to other airway clearance techniques particularly in people who have difficulty expectorating sputum [6, 8].

In a single physiotherapy session, the use of NIV led to easier airway clearance in participants with stable moderate to severe disease, and most participants preferred to use NIV for airway clearance [6].

Treatment, but no evidence, found that NIV increases sputum expectoration or improves lung function. There is some evidence that the introduction of NIV to airway clearance preserved muscle strength and improved expiratory muscle strength. In terms of airway clearance over a longer period of time, e.g., among people hospitalized for an acute exacerbation, the use of NIV as an adjunct to the airway clearance regimen offers no clear benefit compared to no NIV [6].

Studies that assess the impact of NIV associated to a pulmonary rehabilitation program on longer, functional capacity, health gains, physical conditioning and functionality scale should be encouraged [6].

4.6 How to Ventilate Patients with CF?

Pressure-targeted ventilatory mode (or pressure support ventilation, PSV) is preferred, avoiding the barotrauma that in the volume-targeted mode would be more likely. In clinical practice,

patients are also better suited to this type of ventilation. However, it is necessary to have accuracy in setting the sensitivity of the trigger to avoid patient-ventilator desynchronies. One must consider that the CF patients have an intrinsic PEEP similar to COPD, so it is to be considered PEEP $\geq$ 5 cmH_2O. A good alternative should be represented by bi-level positive pressure ventilation (PPV). It is a combination of PS and PEEP: you can set two different levels of expiratory positive airway pressure (EPAP) and inspiratory positive airway pressure (IPAP). The patient breathes spontaneously with a continuous positive pressure in the airways and with the support of IPAP [1, 2, 24].

The active humidification both in acute and chronic ventilation is very important because CF patients have viscous and tenacious secretions. Regardless of the mode of ventilation you decide to use, remember that the setting of the ventilator parameters is essential depending on the patient's clinical status (exacerbation, domiciliary chronic ventilatory support, end of life support).

No evidence was found of pathogenic microbial contamination of NIV devices used by CF patients [25].

Contraindications for using NIV in CF are severe respiratory acidosis, mental obnubilation, pneumothorax and massive haemoptysis [14].

4.7 Possible Alternative to NIV

In recent years the use of high-flow nasal cannula (HFNC) has also expanded in CF, although there are still no clinical studies on this topic. The clinical practice shows us that its use is effective and safe in those patients with diurnal hypercapnia to postpone the use of the NIV, when possible, or when NIV is contraindicated, for example, pneumothorax or massive haemoptysis.

In 2018 a physiological randomized crossover study of high-flow nasal oxygen cannula versus NIV in 15 adult patients showed that in CF patients with acute exacerbation requiring ventilator support HFNC with oxygen (a heated humidified, high-flow oxygen delivery system) was not inferior to NIV with respect to diaphragmatic work in CF patients with advanced respiratory disease who had an indication for ventilator support. These preliminary physiologic data limited to an observation of 30 min suggest that HFNC may confer physiological benefits by decreasing respiratory rate and constitute an interesting alternative to NIV [14, 15].

4.8 The Ongoing Clinical Trials (from linicaltrial.gov) on NIV in CF

- One interventional trial is ongoing about the efficacy of NIV during hospital admission for an acute exacerbation complicated by respiratory failure, in patients for which long-term use is not yet indicated (NCT02234401) [26].
- One interventional trial is ongoing to compare efficacy and comfort, in patients requiring ventilatory support, between NIV and high-flow nasal oxygen cannula (HFN), that is a relatively new system providing heated and humidified, high-flow (50 L/min) oxygen, through the nostrils (NCT02262871) [26].
- One interventional, randomized, open-label, crossover study is ongoing to compare NIV and oxygen supplementation safety, during physical training (NCT02684552) [26].

4.9 Conclusions

Learning Points

- NIV has a role in CF in:
  - Correcting hypoxemia and/or hypercapnia both in acute and chronic respiratory failure
  - Improving tidal volume and alveolar recruitment to avoid atelectasis
  - Decreasing fatigue and the work of breathing, improving exercise tolerance
  - Improving quality of sleep and nocturnal gas exchange
  - Palliative treatment of dyspnoea
  - Physiotherapy for airway clearance

Critical Points

– It is necessary to conduct observational and prospective multicentric studies with defined inclusion criteria and unique outcomes to better define the real role of NIV even if ethical considerations and the number of patients limit the possibility of studies.
– It is still to be analysed if chronic use of NIV might impact on pulmonary exacerbations, disease progression and quality of life.
– It is still to be analysed, and it is difficult to define CF patients who might benefit to a larger extent from NIV.
– HFNC with or without oxygen supplementation has an emergent role in the treatment of respiratory failure even with hypercapnia in various respiratory diseases, but they must still be assessed in CF.

Key Summary

• CF patients are now living longer, and there is expectation that young ones reach adulthood with good lung function. NIV use in adult patients is increasing, although the timing and indication in clinical practice appears to be variable. Possible reasons include the lack of validated criteria to start NIV, controversies regarding the optimal ventilatory settings, no evidence of long-term efficacy and poor acceptance by some patients (Table 4.2).

Table 4.2 Conclusions/future prospective

• There is a lack of evidence for the use of NIV in CF, and there is not a consensus for its beginning or role in exacerbations
• NIV is indicated in the end of disease, as bridge for transplantation or as palliative use for dyspnoea
• NIV improves stress tolerance and is also a good therapeutic option for physiotherapy
• NIV can improve the quality of sleep and its physiology in patients opportunely selected
• It is necessary to conduct observational and prospective multicentric studies with defined inclusion criteria and unique outcomes to better define the real role of NIV
• HFNC has an emergent role in the treatment of hypercapnia in various respiratory diseases, and it must still be assessed and studied in CF

References

1. Bright-Thomas RJ, Johnson SC. What is the role of noninvasive ventilation in cystic fibrosis? Curr Opin Pulm Med. 2014;20(6):618–22.
2. Faroux B. Why, when and how to propose noninvasive ventilation in cystic fibrosis? Minerva Anestesiol. 2011;77(11):1108–14.
3. Fauroux B, Pigeot J, Isabey D, Harf A, Clément A, Lofaso F. In vivo physiological comparison of two ventilators used for domiciliary ventilation in children with cystic fibrosis. Crit Care Med. 2001;29:2097–105.
4. Fauroux B, Louis B, Hart N, Essouri S, Leroux K, Clement A, et al. The effect of back-up rate during non-invasive ventilation in young patients with cystic fibrosis. Intensive Care Med. 2004;30:673–81.
5. Fauroux B, Nicot F, Essouri S, Hart N, Polkey MI, Clément A, et al. Setting of pressure support in young patients with cystic fibrosis. Eur Respir J. 2004;24:624–30.
6. Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. Cochrane Database Syst Rev. 2017;(2):CD002769.
7. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi P, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;31:50(2).
8. Walshaw MJ. Cystic fibrosis: diagnosis and management - NICE guideline 78. Paediatr Respir Rev. 2019;31:12–4.
9. Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, Church AC, Creagh-Brown B, Dodd JW, Felton T, Foëx B, Mansfield L, McDonnell L, Parker R, Patterson CM, Sovani M, Thomas L, BTS Standards of Care Committee Member, British Thoracic Society/Intensive Care Society Acute Hypercapnic Respiratory Failure Guideline Development Group, On behalf of the British Thoracic Society Standards of Care Committee. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl 2):ii1–35.
10. Texereau J, Jamal D, Choukroun G, et al. Determinants of mortality for adults with cystic fibrosis admitted in Intensive Care Unit: a multicenter study. Respir Res. 2006;7:14.
11. Jones A, Bilton D, Evans TW, Finney SJ. Predictors of outcome in patients with cystic fibrosis requiring endotracheal intubation. Respirology. 2013;18(4):630–36.
12. Archangelidi O, Carr SB, Simmonds NJ, Bilton D, Banya W, Cullinan P, CF-EpiNet. Non-invasive ventilation and clinical outcomes in cystic fibrosis: Findings from the UK CF registry. J Cyst Fibros. 2018. pii: S1569-1993(18)30934-2.

13. Madden BP, Kariyawasam H, Siddiqi AJ, Machin A, Pryor JA, Hodson ME. Noninvasive ventilation in cystic fibrosis patients with acute or chronic respiratory failure. Eur Respir J. 2002;19(2):310–3.
14. King CS, Brown AW, Aryal S, Ahmad K, Donaldson S. Critical care of the adult patient with cystic fibrosis. Chest. 2019;155(1):202–14.
15. Sklar MC, Dres M, Rittayamai N, West B, Grieco DL, Telias I, Junhasavasdikul D, Rauseo M, Pham T, Madotto F, Campbell C, Tullis E, Brochard L. High-flow nasal oxygen versus noninvasive ventilation in adult patients with cystic fibrosis: a randomized crossover physiological study. Ann Intensive Care. 2018;8(1):85.
16. Katz ES. Cystic fibrosis and sleep. Clin Chest Med. 2014;35(3):495–504.
17. Naqvi SK, Sotelo C, Murry L, Simakajornboon N. Sleep architecture in children and adolescents with cystic fibrosis and the association with severity of lung disease. Sleep Breath. 2008;12:77–83.
18. Spier S, Rivlin J, Hughes D, Levison H. The effect of oxygen on sleep, blood gases, and ventilation in cystic fibrosis. Am Rev Respir Dis. 1984;129:712–8.
19. Yankaskas JR, Marshall BC, Sufian B, et al. Cystic fibrosis adult care: consensus conference report. Chest. 2004;125:1S–39S.
20. De Castro-Silva C, de Bruin VM, Cavalcante AG, Bittencourt LR, de Bruin PF. Nocturnal hypoxia and sleep disturbances in cystic fibrosis. Pediatr Pulmonol. 2009;44:1143–50.
21. Dobbin CJ, Bartlett D, Melehan K, et al. The effect of infective exacerbations on sleep and neurobehavioral function in cystic fibrosis. Am J Respir Crit Care Med. 2005;172:99–104.
22. Paiva R, Krivec U, Aubertin G, Cohen E, Clément A, Fauroux B. Carbon dioxide monitoring during long-term noninvasive respiratory support in children. Intensive Care Med. 2009;35:1068–74.
23. Shakkottai A, O'Brien LM, Nasr SZ, Chervin RD. Sleep disturbances and their impact in pediatric cystic fibrosis. Sleep Med Rev. 2018;42:100–10.
24. Caronia CG, Silver P, Nimkoff L, Gorvoy J, Quinn C, Sagy M. Use of bilevel positive airway pressure (BIPAP) in end-stage patients with cystic fibrosis awaiting lung transplantation. Clin Pediatr. 1998;37:555–9.
25. Mutagi A, Nash EF, Cameron S, Abbott G, Agostini P, Whitehouse JL, Honeybourne D, Boxall E. Microbial contamination of noninvasive ventilation devices used by adults with cystic fibrosis. J Hosp Infect. 2012;81:104–8.
26. www.clinicaltrials.gov.

5 High-Intensity Noninvasive Ventilation in Stable Hypercapnic COPD

Antonello Nicolini, Josef Lucazovitch, and Stephan Walterspacher

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5.1 Background

Patients with chronic obstructive pulmonary disease (COPD) who develop hypercapnic respiratory failure have more severe illness and an increased risk for exacerbations, hospitalization, and mortality [1]. Mechanical ventilation in chronic hypercapnic respiratory failure aims at the unloading of the respiratory muscles, which leads to at least a reduction (ideally the normalization) of PCO_2 during the day, improved clinical symptoms, quality of life, life expectancy, and reduction of exacerbations [2].

Noninvasive ventilation (NIV) is used to improve gas exchange by increasing tidal volume and producing positive airway pressure, relieving respiratory muscle fatigue and improving respiratory center's sensitivity to carbon dioxide (CO_2) [3]. Application of NIV in acute hypercapnic respiratory failure is nowadays considered a gold standard and recommended in national and international guidelines [4]. It has been suggested that frequent and persistent hypercapnic exacerbators benefit most from long-term NIV [5]. Earlier NIV studies in COPD patients not aiming at maximally reducing CO_2 levels (applying inspiratory positive airway pressures (IPAP) ranging from 12 to 18 cmH_2O) have not shown beneficial effects in survival, respiratory

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function, or exacerbation rates [6, 7]. Over the past decade, it has been shown that NIV may lead to a substantial improvement of elevated PCO_2 levels when ventilator pressure settings are markedly increased [8] and therefore alveolar ventilation is increased. The concept of this so-called "high-intensity" NIV (Hi-NIV) has been developed to describe an approach with increased inspiratory pressure levels together with an increased backup rate [3, 8] with the goal of the normalization of PCO_2. Hi-NIV in a larger multicentered randomized controlled trial has shown to increase with 12–33% the 1-year survival in chronic hypercapnic COPD patients [9, 10]. Furthermore, high-intensity NIV in chronic hypercapnic COPD patients has been shown to markedly increase health-related quality of life [11].

There is a persuasive argument that targeting CO_2 control rather than simply reducing muscle effort might yield in better long-term outcomes [3, 4].

5.2 Physiological Changes During High-Intensity NIV

The development of hypercapnic respiratory failure in patients with COPD is mainly related to the occurrence of alveolar hypoventilation caused by a marked increase in the ratio of dead space volume (VD) to tidal volume (VT). This is a consequence of the reduced VT that occurs as failing patient develops a rapid shallow breathing pattern and increased VD that results from a severe ventilation/perfusion inhomogeneity [12].

Hi-NIV helps reverse this process by augmenting VT and reducing the ventilation/perfusion mismatch. Hi-NIV increasing VT decreases $PaCO_2$.This ventilatory setting acts mostly as a semi-controlled ventilation and induces positive pleural pressure swings during inspiration. This increased pleural pressure, and decreasing the venous return leads to a decreased right atrial preload and lowered cardiac output [12]. Figures 5.1 and 5.2 show the most important

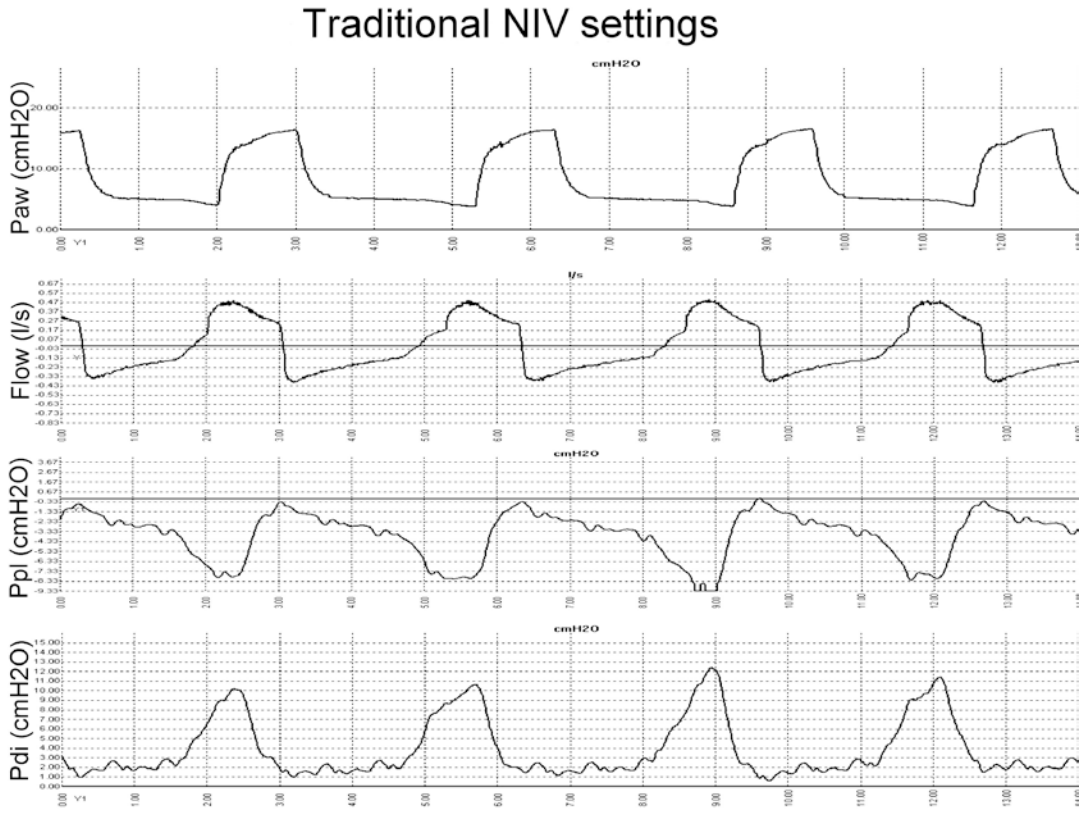

Fig. 5.1 Respiratory mechanical parameters during traditional NIV (*Paw* airway pressure, *Flow* respiratory flow, *Ppl* pleural pressure, *Pdi* transdiaphragmatic pressure)

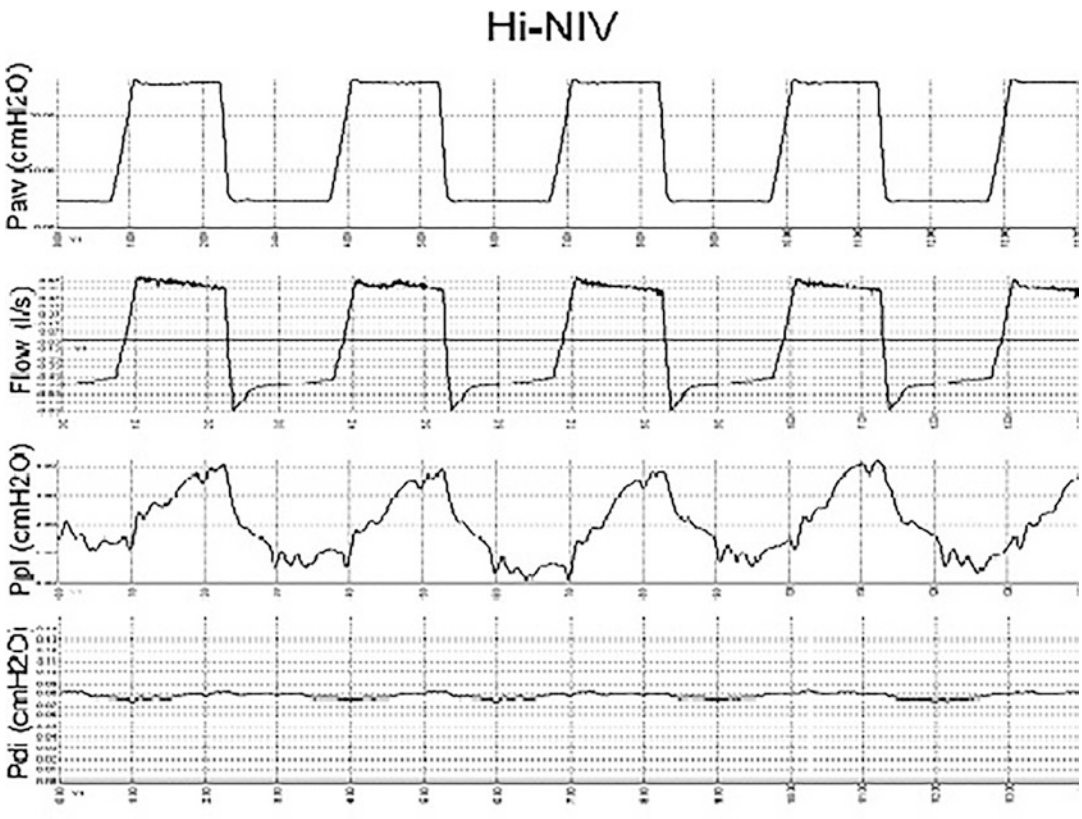

Fig. 5.2 Respiratory mechanical parameters during Hi-NIV

respiratory mechanical parameter traces during traditional and Hi-NIV settings. It can be seen that during Hi-NIV, the pleural pressure (Ppl) trace becomes positive and the transdiaphragmatic pressure (Pdi) trace becomes practically flat, suggesting a controlled ventilation. Long-term Hi-NIV in COPD patients did not yield adverse effects on cardiac performance; however, it must be applied carefully in patients with preexisting cardiovascular diseases, because the application of higher pressure may lead to a reduced cardiac output [12]. It has been thought that the combination of a higher respiratory rate exceeding the spontaneous breathing rate may be as important in unloading the respiratory muscles as an increased driving range (difference between IPAP and PEEP). Conversely, Murphy et al. have shown that there was no additional benefit for nighttime ventilator adherence or on efficacy of ventilation, sleep quality, and health-related quality of life after the addition of a high backup rate to high-pressure NIV. These data might suggest that it is the high-pressure component of the high-intensity NIV that has the most important therapeutic role in the management of hypercapnic respiratory failure [13].

5.3 Basic Assessment of a Patient with Chronic Hypercapnia in COPD

A thorough general and disease-specific assessment of the medical history and the associated respiratory failure as well as physical examination is obligate. Nicotine abstinence before NIV initiation is strongly recommended. The follow-

ing (technical) tests are also essential according to the German guidelines [2]:

- Electrocardiogram (ECG)
- Diurnal and nocturnal BGA under room-air conditions or, in the case of long-term oxygen therapy, with the prescribed oxygen flow rate
- Lung function tests (spirometry, whole-body plethysmography, respiratory muscle function tests, if applicable [e.g., P0.1, PImax])
- Basic laboratory tests
- Chest X-ray, with consultation of earlier X-ray images if necessary
- Polygraphy (polysomnography, if necessary)
- Exercise testing (e.g., 6-min walking test)

5.4 Ventilator Settings in High-Intensity NIV

In order to optimize alveolar ventilation, an assist/controlled mode is used, preferably in a pressure-limited mode [10]. Three major targets for the ventilatory adjustment are described to achieve normocapnia: the driving range, respiratory rate, and pressure increment [10, 14]. However, it is still subject of debate whether an increased respiratory rate significantly adds to the goal of normalization of PCO_2 or whether the increased respiratory rate or increased inspiratory pressure is the main factor for reducing hypercapnia [13]. Establishing NIV in a naive patient and lowering PCO_2 levels may take several days, and enough time for adaptation has to be given [2].

A practical approach is recommended. The initial settings consist of a low backup rate (i.e., 12 breaths/min) and trigger threshold with avoidance of auto-triggering. The pressure increment should be set at 0.9–1 s.

These settings are used in conjunction with modest IPAP levels (i.e., between 12 and 16 cmH_2O) and the low positive end-expiratory pressure (PEEP) levels (i.e., 5–7 cmH_2O). Subsequently, IPAP is carefully increased up to the point where normocapnia is achieved or no longer tolerated by the patient [1, 10, 14]. Moreover, the respiratory rate is increased beyond the spontaneous rate to establish a semi-controlled ventilation, while PEEP may be increased in order to avoid dynamic hyperinflation. Patient-ventilator synchrony can be optimized by optimizing the inspiratory/expiratory (*I*/*E*) rate with very short inspiration time (*I*/*E* > 1:2) [1, 10].

NIV is primarily established during daytime with the main aim of establishing mask tolerance [1, 10]. Once daytime NIV is tolerated, the nocturnal NIV may be tried. In general, NIV application in daytime is as feasible as during night; however, nocturnal NIV is recommended since higher PCO_2 levels occur during night [15].

Generally nasal masks, oronasal masks, face masks, mouth masks, and mouthpieces are available as patient-ventilator interfaces. Nasal masks provide greater patient comfort; however, oral leakage at higher pressure levels is common and may lead to less optimal control of hypercapnia. A great concern about high-intensity NIV is the increased risk of leakage and consequently patient-ventilator asynchronies. However, it has been demonstrated that triggering asynchronies also occur during low-intensity settings [11]. In real-life studies, it has been shown that oronasal masks are predominantly used for Hi-NIV in chronic hypercapnic COPD patients [16] and that sleep quality is not negatively affected by Hi-NIV [14].

Supplemental humidification is not generally required for NIV. The need for humidification is based on the patient's symptoms. Passive humidification with a heat and moisture exchanger may lead to an increased dead space which negatively affects ventilatory function and gas exchange [17]. Active humidification using a pass-over humidifier system is recommended, if airway dryness persists [10, 14].

5.5 Conclusions

The novel approach of high-intensity NIV is so far the most effective way of NIV application in order to improve lung function, health-related quality of life, and survival in patients with chronic hypercapnic COPD.

References

1. Marchetti MWN, Czysz A, Hill N, Sciurba F, Strollo P, Criner GJ. High intensity non-invasive positive pressure ventilation (HINPPV) for stable hypercapnic chronic obstructive pulmonary disease (COPD) patients. Chronic Obstr Pulm Dis. 2015;2:313–20.
2. Windisch W, Geiseler J, Simon K, Walterspacher S, Dreher M. German national guideline for treating chronic respiratory failure with invasive and non-invasive ventilation: revised edition 2017 - part 1. Respiration. 2018;96(1):66–97.
3. Liao H, Pei W, Li H, Luo Y, Wang K, Li R, et al. Efficacy of long-term noninvasive positive pressure ventilation in stable hypercapnic COPD patients with respiratory failure. A meta-analysis of randomized controlled trials. In J Chron Obstruct Puml Dis. 2017;12:2977–85.
4. Rochwerg B, Brochard L, Elliott MW, Dean H, Nicholas H, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1602426. https://doi.org/10.1183/13993003.02426-2016.
5. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. JAMA. 2017;317:2177–86.
6. Clini E, Sturani C, Rossi A, et al. The Italian Multicentre Study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J. 2002;20:529–38.
7. Casanova C, Celli BR, Tost L, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest. 2000;20:156–63.
8. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD : a randomized crossover trial. Thorax. 2010;65:303–10.
9. Kohnlein T, Windisch W, Kohler D, Drabik A, Geiseler J, Harti S, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med. 2014;2:698–705.
10. Windisch W, Haenel M, Storre JH, Dreher M. High-intensity non-invasive positive ventilation for stable hypercapnic COPD. Int J Med Sci. 2009;6:72–6.
11. Windisch W. Impact of home mechanical ventilation on health-related quality of life. Eur Respir J. 2008;32(5):1328–36. https://doi.org/10.1183/09031936.00066407.
12. Lukacsovits J, Carlucci A, Hill N, Ceriana P, Pisani L, Schreiber A, et al. Physiological changes during low- and high-intensity ventilation. Eur Respir J. 2012;39:869–75.
13. Murphy PB, Brignall K, Moxham J, Polkey MI, Davidson AC, Hart N. High pressure versus high intensity noninvasive ventilation in stable chronic obstructive pulmonary disease: a randomized crossover trial. Int J Chron Obstruct Pulm Dis. 2012;7:811–8.
14. Dreher M, Ekkernkamp E, Walterspacher S, Walker D, Schmoor C, Storre JH, Windisch W. Noninvasive ventilation in COPD: impact on inspiratory pressure levels on sleep quality. Chest. 2011;140:939–45.
15. Schönhofer B, Geibel M, Sonneborn M, Haidl P, Köhler D. Daytime mechanical ventilation in chronic respiratory insufficiency. Eur Respir J. 1997;10:2840–6.
16. Callegari J, Magnet FS, Taubner S, Berger M, Schwarz SB, Windisch W, Storre JH. Interfaces and ventilator settings for long-term noninvasive ventilation in COPD patients. Int J Chron Obstruct Pulmon Dis. 2017;12:1883–9. https://doi.org/10.2147/COPD.S132170.
17. Jaber S, Chanques G, Matecki S, Ramonatxo M, Souche B, Perrigault PF, Eledjam JJ. Comparison of the effects of heat and moisture exchangers and heated humidifiers on ventilation and gas exchange during non-invasive ventilation. Intensive Care Med. 2002;28:1590–4.

Alternative Positive and Negative Noninvasive Ventilation

6

Umberto Vincenzi

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6.1 Introduction

It can be said that the first real mechanical ventilator was presented on September 13, 1864, when an American researcher, Alfred F. Jones, patented his "depurator" (Patented No. 44,168).

This machine had the shape of a large container. The patient was seated inside it, with the exclusion of the head, and had to undergo the action of cyclical depressions to facilitate breathing.

However, it was only after more than 60 years (1928) that Philip Drinker and Dr. Louis Agassiz Shaw presented the first "iron lung," with an electric motor, which was widely used throughout the world.

This machine, equipped with a cylindrical container in which the patient's body had to be housed in the supine position, managed to ventilate the patient in a noninvasive manner. It was a great success, especially among patients with polio, not only in the acute phase but also in the chronic phase.

But it was the vastness of patients affected by the polio epidemic in Copenhagen in 1950 and the relative lack of negative pressure ventilators that dictated the need to intervene with intubation and manual artificial ventilation.

The latter was soon replaced by positive pressure machines that followed the "spiro-pulsator," the first positive pressure ventilator presented by Clarence Crafoord, a surgeon at the Stockholm Sabbatsberg Hospital, at the American Association for Thoracic Surgery in 1939.

Extrathoracic negative mechanical ventilation (NPV), due to its noninvasive characteristics, continued to be used in many intensive respiratory therapy centers until the early 2000s, when noninvasive positive pressure ventilation (NPPV)

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took over because they were smaller and cheaper and less nursing was required.

In recent years, however, interest in negative ventilation has increased given the possibility, which was previously denied, of coordinating the ventilatory cycle to the patient, through the use of simple flow sensors connected via the nasal route, and also to find out why, in patients to be referred for periods of prolonged ventilation, with intermittent positive pressure ventilation, there emerged problems created by the interfaces on the skin of the face.

Many articles concerning the various modes of mechanical ventilation are present in the scientific literature, but only a few directly compare negative pressure mechanical ventilation with positive pressure mechanical ventilation in the treatment of patients suffering from acute, chronic, or chronic acute respiratory diseases [1–3] or in neuromuscular patients [4]. Other articles compare external negative mechanical ventilation with positive pressure mechanical ventilation in surgery [5]. Further articles investigate the possibility of using both methods simultaneously but with the use of a continuous external negative pressure [6, 7].

The purpose of this article is to find out what has emerged in recent years by comparing the two noninvasive methods of mechanical ventilation with both negative pressure and positive pressure.

6.2 New Research

Double-Synchronized Noninvasive-Assisted Ventilation (DNIV or NPPV + NPV Ventilation).

A new mode in noninvasive ventilation, in my opinion, was conceived in Italy by our study group that, after requesting specific technological changes on ventilators supplied by the DIMA company (Italy), synchronized the action of the two machines, the first (Luna ventilator) with intermittent positive pressure delivery, through the face mask, inside the airways (NPPV) and the other (Pegaso ventilator), extrathoracic agent (NPV), with external negative pressure supply through the cuirass [8].

The study was based on the need to treat elderly patients with COPD and severe acute respiratory failure, with a mechanical ventilation mode that maintained its noninvasive characteristics but was more effective without increasing the risks for patients.

The severity of the patients subjected to this study was confirmed by mean initial pH values (=7.31 ± 0.05); high average values of $PaCO_2$ (=85.01 ± 12.25); average FEV1 values (=50% ± 5% of the theoretical); average FVC values (=73% ± 6% of the theoretical); and average values of the FEV1/FVC ratio (=67.5 ± 3 of the theoretical). Furthermore, it must be considered that the average age of the patients (6 males and 2 females) was decidedly high (=74 ± 8.6 years).

The combined action of the two ventilators was tested, in a respiratory intensive care unit of Foggia, on 8 patients suffering from severe COPD and exacerbated hypoxemic and hypercapnic respiratory failure (ARF). This mode of double ventilation was compared, on different days and at random, with the other two ventilation modes (NPPV mode and NPV), used separately and supplied by the same machines.

In addition to the anthropometric, clinical, and functional characteristics, blood gas and clinical variations were measured at the beginning and after an hour of treatment with the three modes of mechanical ventilation, i.e., with the NPPV and NPV separately and with the combined NPPV + ventilation NPV.

Studying the variations of the averages with the *t*-student statistical test, some very interesting results were found.

In fact, by setting the time values measured at the beginning and after 1 h of ventilatory treatment as T0 and T1, it was found that the pH had undergone an important and very significant variation, in an improvement sense, with double ventilation (NPPV + NPV).

With it, in fact, there were increases in pH values from 7.31 to 7.42 (p = 0.0008), while with positive pressure ventilation only (NPPV) the improvements were not significant (pH = 7, 38 to T0 vs. pH = 7.40 at T1 with p = NS) and equally with only negative pressure (pH = 7.36 at T0 vs. pH = 7.40 at T1 with p = NS).

Even the $PaCO_2$ values showed a clear improvement with double ventilation compared to the other two modes of mechanical ventilation.

In fact, with double ventilation, the $PaCO_2$ values decreased significantly ($PaCO_2$ = 85.01 mmHg at T0 vs. =61.93 mmHg at T1 with $p = 0.002$), while a lower significance was found with the positive pressure ventilation alone ($PaCO_2$ = 72.05 mmHg at T0 vs. = 66.81 mmHg at T1 with $p = 0.02$) and no significance with negative pressure ventilation alone ($PaCO_2$ = 71.90 mmHg at T0 vs. =71.53 mmHg at T1 with p = NS).

The variations of the PaO_2/FiO_2 ratio were also studied in the three modes of mechanical ventilation. With double ventilation (NPPV + NPV), clear improvements were found, although not statistically significant (PaO_2/FiO_2 = 354.62 mmHg vs. 488.75 mmHg with p = NS), with NPPV the improvements recorded were minimal (PaO_2/FiO_2 = 337.12 mmHg vs. 352.62 mmHg with p = NS), and with NPV there were no improvements (PaO_2/FiO_2 = 346.75 mmHg vs. 327.87 mmHg with p = NS).

In any case, it must be taken into account that the statistical results, although very evident, were conditioned by the small number of patients studied. The considerations to be made regarding the technical and mechanical ventilation aspects were determined by the double ventilation (NPPV + NPV), compared to the single two-ventilation modalities considered separately (NPPV or NPV), but also the clinical results found on the patients.

In the latter case, there was good tolerability, and none of the patients showed respiratory difficulties, intolerance to single ventilatory methods, or collateral disorders.

As for the equipment used, it must be remembered that every pulmonary ventilator has, inside it, sensors that allow the machine to interface with the patient and, therefore, to recognize the beginning and end of the ventilatory act, the pressure, and the flows and volumes reached during this act. However, the real difficulty in being able to use two ventilators simultaneously was the need to make them both perfectly synchronized with the patient to be subjected to double mechanical ventilation.

This was solved very well by the engineers of the DIMA company (Italy) to whom the technical problem was placed.

With the modifications made, the positive pressure ventilator (NPPV) was synchronized with the other extrathoracic negative pressure ventilator (NPV), detecting the start and end of the patient's inspiratory act in the form; it provided, in a combined and contemporary way, inside and outside the patient's chest, pressures suitable for assisting the entire ventilatory cycle. Continuous detection of the main ventilatory parameters (volumes, flows, pressures, and ventilatory frequency) allowed optimal control and monitoring of this double lung ventilation.

In this way, the positive pressure ventilator acted as a "master" and the extrathoracic negative pressure ventilator as a "server." Both determined a double mode of noninvasive-assisted mechanical ventilation (double noninvasive ventilation or NPPV + NPV ventilation).

The reason for the use of two pulmonary ventilators instead of one, based on the study of ventilation mechanics, is to be found in the need to be able to increase transpulmonary pressure (PL = Pawo − Ppl) in patients affected by severe respiratory failure without increasing airway pressure and thus avoiding the possible barotrauma during NPPV.

This mechanism can be explained by recalling some principles of ventilatory mechanics.

In fact, if we have the respiratory motion formula in mind:

$$\mathrm{Prs} = \left(\mathrm{Ers} \times \Delta V\right) + \left(\mathrm{Raw} \times V'\right) + \mathrm{Pin} \quad (6.1)$$

considering the negligible inertial pressure (Pin), we know that the pressure (Prs) that moves the entire respiratory system is the sum of the transpulmonary pressure (PL) and the pressure that moves the rib cage (Pcw):

$$\mathrm{Prs} = \mathrm{PL} + \mathrm{Pcw} \quad (6.2)$$

At this point it is possible to think that the positive pressure ventilator acts initially and

mainly on the airways and consequently on the transpulmonary pressure (PL), while the other ventilator, at negative pressure, acts initially on the thoracic cage, on the pleura, and consequently on transpulmonary pressure.

Furthermore, considering that the total elastance of the respiratory system (Ers) is the sum of pulmonary elastance (EL) and that of the rib cage (Ecw):

$$\mathrm{Ers} = \mathrm{EL} + \mathrm{Ecw} \tag{6.3}$$

we can rewrite the (6.1) in the following formula:

$$\begin{aligned}\mathrm{Prs} = \mathrm{PL} + \mathrm{Pcw} = &\left(\left(\mathrm{EL} + \mathrm{Ecw}\right)\Delta V\right) \\ &+ \left(\mathrm{Raw} \bullet V'\right) + \mathrm{Pin}\end{aligned} \tag{6.4}$$

Now we can also think that the two ventilators must overcome, in a prevalent way, the first, the pulmonary one (EL), and the second, the elastation of the rib cage (Ecw).

Both ventilators, synchronically, place their force of action on two diametrically opposite parts of the thorax: the airways, then the lung parenchyma, and the pleural space the first (NPPV); the thoracic cage, then the pleural space, and the pulmonary parenchyma the second (NPV).

However, it must be considered that the NPPV increases the pressure inside the airways and at the alveolar level, while the NPV, being a negative pressure, tends to lower the same pressures. Therefore the combined use of both ventilators means that the increase in airway pressure created by the NPPV is counterbalanced by the action of the NPPV.

Furthermore, both ventilators act, with summation action, on the transpulmonary pressure (PL = Pawo − Ppl), the only real pressure responsible for lung expansion, so the result is increased efficacy.

In practice there has been an overall increase in the ventilatory action and a failure to increase the pressures in the airways and the alveoli.

All this is what occurred in the Italian study reported above.

Continuous Noninvasive Negative Ventilation (CENPV) Combined with Intermittent Invasive Positive Ventilation (IMV).

A particular combination of negative and positive pressure is one in which continuous noninvasive negative ventilation (CENPV) is associated with an intermittent invasive ventilation (IMV) by intubation in subjects with ARDS.

Following the works published, in 2003, by the Italian group of Gattinoni [9] and in 2012 by Chierichetti [10]., the results of the application of a continuous negative pressure were studied alone or in addition to the intermittent positive pressure ventilation. In recent years, some interesting studies have been highlighted that have addressed this ventilatory mode in various areas.

The first interesting study, published as a case report, was proposed by Konstantinos Raymondos, who had previously compared, albeit at different times, the action of CENPV toward CPPV in the treatment of patients with ARDS [11].

This author [7], in a patient suffering from ARDS arisen after a surgical drainage of a tonsillar and peritonsillar abscess, following a first failed attempt of only invasive ventilation by tracheostomy (PEEP of 15 cmH_2O + pressure support with total pressure values in the airways that also reached 85 cmH_2O), was able to combine, simultaneously, a continuous external negative pressure (CENPV) ventilation with invasive positive pressure ventilation. For negative pressure a tank respirator was used, applying chamber pressures of −33 cmH_2O at inspiration and −15 cmH_2O at expiration; for positive pressure, a conventional intensive care ventilator was used with PEEP of 8 cmH_2O applying tidal volumes of 6–8 ml/kg predicted bodyweight.

The same patient, with double ventilation, had a rapid improvement so much so that it was possible to discharge him.

In this case it should be emphasized that the noninvasive negative pressure ventilation in a tank that contained the entire body of the patient could be associated with an invasive positive pressure ventilation via tracheostomy.

Continuous Abdominal Negative Ventilation (CNAP) Combined with Invasive Positive Pressure Ventilation.

Some researchers at the University of Toronto [12] have created a prototype that, through the administration of a continuous negative pressure at the abdominal level (CNAP), gave the possibility to increase oxygenation to pigs, affected by artificially induced ARDS and subjected to invasive mechanical ventilation by intubation.

Another study, conducted by Yushida et al. [13], also carried out on pigs with artificially induced ARDS, compared the action of continuous negative pressure applied on the abdomen (CNAP) with the prone position during mechanical pressure-controlled ventilation whose settings were VT of 5–6 ml/kg, titrated rate (20–30/min), targeting $PaCO_2$ < 60 mmHg, inspiratory-to-expiratory ratio of 1:2, pressure trigger of −2 cmH_2O, and FIO_2 of 1.0.

The objective was to evaluate lung recruitment capacities and changes in pleural pressure by comparing the two methods. The results showed that the CNAP reduced the vertical gradient of Ppl in the dependent lung, but not in the nondependent lung. The CNAP in the supine position, compared to the prone position without CNAP, was associated with a greater partial arterial pressure of oxygen, greater compliance, and greater homogeneity of ventilation. Moreover, CNAP seemed to offer physiological advantages compared to the prone position.

The same group of researchers carried out an experimental study [14] on anesthetized and intubated pigs, in which ARDS was artificially induced, and analyzed the positive effect of the application of a continuous negative abdominal pressure on the possibility of a progressive lung recruitment induced by PEEP.

Another work [15], conducted by the same authors on anesthetized, curarized, and ventilated pigs, showed how a continuous negative abdominal pressure, added to PEEP, reduced the ventilator-induced lung injury compared to the group in which only PEEP was used. There was also a significant increase in oxygenation (P = 0.005), better compliance (14.2 ± 3.0 vs. 10.3 ± 2.2 ml/cmH_2O, P = 0.049) with homogeneity of ventilation, a lower presence of pulmonary edema (≈10% less), and a lower expression of interleukin-6 (≈30% less).

6.3 Considerations

In recent years, more attention has been paid to noninvasive extrathoracic negative mechanical ventilation (NPV), largely abandoned in the last two decades given the greater lightness and ease of use by positive pressure ventilators acting directly on the airways.

The reason for this renewed attention is found, in part, in the numerous technological improvements made on negative pressure ventilators and in particular the possibility of synchronizing them to the patient through the use of flow sensors placed at the level of the nostrils or the upper airways (assisted and not only controlled ventilation), the reduced size and lightness of the armor plates (in plastic material) compared to those of the iron lungs, the ease of use even by nonmedical personnel, and also the significant reduction in purchase prices of these machines.

In more recent times, there has been an increased interest in extrathoracic negative ventilation when ventilatory assistance was required for very long periods of time, particularly in patients with neuromotor damage, when it was necessary to resort to noninvasive ventilatory support in patients to be subjected to operations on the upper airways or trachea, and when faced with patients who had objective difficulty in the positive pressure ventilatory treatment.

The new avenue of research, in my opinion, is the one that uses extra-mechanical negative mechanical ventilation in combination with intermittent positive pressure ventilation, resulting in a double noninvasive ventilation (DNIV or NPPV + NPV).

We found the first positive results of this new double ventilation in the work done by Italian researchers who, having to treat a group of

patients with COPD with severe respiratory insufficiency, used two ventilators, synchronized with each other, with a clear improvement after only 1 h of treatment.

Other work is being carried out in search of optimal and less risky ventilation in patients with ARDS. For now, except for an isolated case on a man, the studies are experimental and use animals (pigs); they combine the mode of ventilation and continuous negative pressure, at abdominal level, with normal invasive positive pressure ventilation by intubation or tracheostomy.

It is evident that the possibility of being able to act on the ventilation mechanics with two machines, an agent inside the airways and one outside the chest, shifts the balance of the intrathoracic pressures, recruits more lung tissue in the ventilation, improves the transpulmonary pressure, and reduces the risk of barotrauma. In my opinion, the future of double ventilation is all to be discovered, since studies are still only at the beginning and only concern isolated cases.

References

1. Corrado A, Confalonieri M, Marchese S, Mollica C, Villella G, Gorini M, Della Porta R. Iron lung vs mask ventilation in the treatment of acute on chronic respiratory failure in COPD Patients: a multicenter study. Chest. 2002;121(1):189–95.
2. Corrado A, Gorini M, Ginanni R, Pelagatti C, Villella G, Buoncristiano U, Guidi F, Pagni E, Peris A, De Paola E. Negative pressure ventilation versus conventional mechanical ventilation in the treatment of acute respiratory failure in COPD patients. Eur Respir J. 1998;12:519–25.
3. Raymondos K, Molitoris U, Capewell M, Sander B, Dieck T, Ahrens J, Christian Weilbach C, Knitsch W, Corrado A. Negative-versus positive-pressure ventilation in intubated patients with acute respiratory distress syndrome. Crit Care. 2012;16(2):R37.
4. Corrado A, Vianello A, et al. Non-invasive mechanical ventilation for the treatment of acute respiratory failure in neuromuscular diseases. Eur Respir J. 2000;16(Suppl. 31):542s.
5. Natalini G, Cavaliere S, Seramondi V, Foccoli P, Vitacca M, Ambrosino N, Candiani A. Negative pressure ventilation vs external high-frequency oscillation during rigid bronchoscopy. Chest. 2000;118:18–23.
6. Chaturvedi RK, Zidulka AA, Goldberg P, de Varennes B, Iqbal S, Rahme E, LachaPelle K. Use of negative extrathoracic pressure to improve hemodynamics after cardiac surgery. Ann Thorac Surg. 2008;85(4):1355–60.
7. Raymondos K, Ahrens J, Molitoris U. Combined negative- and positive-pressure ventilation for the treatment of ARDS. Case Rep Crit Care. 2015;2015:714902.
8. Carpagnano GE, Sabato R, Lacedonia D, Di Gioia R, Saliani V, Vincenzi U, Foschino-Barbaro MP. New non invasive ventilator strategy applied to COPD patients in acute ventilator failure. Pulm Pharmacol Ther. 2017;46:64–8.
9. Valenza F, Bottino N, Canavesi K, Lissoni A, Alongi S, Losappio S, Carlesso E, Gattinoni L. Intraabdominal pressure may be decreased non-invasively by continuous negative extra-abdominal pressure (NEXAP). Intensive Care Med. 2003;29(11):2063–7.
10. Chierichetti M, Engelberts D, El-Khuffash A, Babyn P, Post M, Kavanagh B. Continuous negative abdominal distension augments recruitment of atelectatic lung. Crit Care Med. 2012;40(6):1864–72.
11. Raymondos K, Molitoris U, Capewell M, Sander B, Dieck T, Ahrens J, Weilbach C, Knitsch W, Corrado A. Negative versus positive pressure ventilation in intubated patients with acute respiratory distress syndrome. Crit Care. 2012;16:R37.
12. Gordon A, Xin Jue Luo KA, Saab R, Engelberts D, Kavanagh B, Yoshida T, Looi T**.** A device for improving oxygenation in patients with acute respiratory distress syndrome. In: 2018 Design of medical devices conference, Minneapolis, 9–12 April 2018. ISBN: 978-0-7918-4078-8. https://doi.org/10.1115/DMD2018-6838.
13. Yoshida T, Engelberts D, Otulakowski G, Katira B, Ferguson ND, Brochard L, Amato MBP, Kavanagh BP. Continuous negative abdominal pressure: mechanism of action and comparison with prone position. J Appl Physiol. 2018;125:107–16.
14. Yoshida T, Engelberts D, Otulakowski G, Katira B, Post M, Ferguson ND, Brochard L, Amato MBP, Kavanagh BP. Continuous negative abdominal pressure recruits lungs at lower distending pressures. Am J Respir Crit Care Med. 2018 15;197(4):534–7.
15. Yoshida T, Engelberts D, Otulakowski G, Katira B, Post M, Ferguson ND, Brochard L, MBP A, Kavanagh BP. Continuous negative abdominal pressure reduces ventilator-induced lung injury in a porcine model. Anesthesiology. 2018;129(1):163–72.

7 What News in Noninvasive Ventilation in ALS/Motor Neuron Disease?

Fabrizio Rao and Montserrat Diaz-Abad

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7.1 Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disease of the motoneuron capable to affect both the first and second motoneuron, leading to progressive weakness of the muscles of the following districts: bulbar, spinal, thoracic, and abdominal. Cerebral functions involving oculomotor and sphincteric functions are usually saved. Cognitive disfunction occurs in about 20–50% of the cases, with about 15% of the affected patients developing frontotemporal dementia. Death usually occurs due to respiratory complications 2–4 years after the first symptoms [1]. The disease has a mean age onset of 43–52 years in familiar forms and of 58–63 years in sporadic forms [2]. Respiratory complications represent the major cause of death in ALS, mainly because of diaphragm weakness causing ventilatory failure and due to chest infections with bronchopneumonia and aspiration pneumonia [3]. Noninvasive ventilation (NIV) prolongs life and improves quality of life. Furthermore, it is effective in improving respiratory symptoms in advanced stages of the disease [4].

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7.2 Methodology

To assess recent research updates in the field of NIV in ALS, a systematic search was performed on the PubMed database using the terms noninvasive ventilation *and* amyotrophic lateral sclerosis

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for the time frame April 1, 2017, to March 31, 2019, registering 48 items. Results were grouped on the type of work (retrospective, observational, review, case report, survey, randomized trial, letter to editor). Additionally, three work areas were identified (early-onset NIV, ventilatory modality in NIV, monitoring of NIV therapy). The results of the most interesting publications were analyzed in and synthesized related to clinical applicability.

7.2.1 Early NIV Initiation

In the literature, there are some indications on the starting criteria for NIV in ALS [5] that identify in particular a forced vital capacity (FVC) of less than 80% predicted and in association with symptoms suggestive of nocturnal hypoventilation. In clinical practice, numerous experiences highlight how NIV is offered to patients only when FVC results are lower than 50% predicted or when orthopnea, symptoms associated with nocturnal hypoventilation, or diurnal hypercapnia is already present. The adherence to the French guidelines on the start of NIV was evaluated by the Gonzales-Bermejo group in an ALS referral center in 624 ALS patients [6]. There was good agreement with the indications set by the guidelines—568 patients (91%) met the NIV start criteria. However, NIV was only started in 70% of patients with orthopnea, in 74% of patients with symptoms related to nocturnal hypoventilation, and in 58% of patients with diurnal hypercapnia. These results highlighted how frequently NIV is delayed even when severe respiratory symptoms are present. While there was good overall adherence to national guidelines in this study, there was delay in the start of NIV in a significant number of patients, which was partly due to the difficulty in accessing periodic visits, the technical difficulty associated with performing pulmonary function tests (PFT) with worsening bulbar function, and the patient's difficulty in accepting the start of the NIV on the basis of instrumental functional impairment without clinical symptoms. The authors concluded that patients with ALS may be exposed to respiratory distress for too long before starting NIV, underlying the necessity of further studies to evaluate an earlier start of NIV.

Elamin et al. [7] evaluated the ability of PFT to predict disease progression by evaluating clinical ALS phenotypes at the time of NIV initiation: 137 patients (134 male) underwent FVC while sitting and supine. The rate of change (RoC) per FVC sitting and supine was calculated from the slope of the line derived from the measured FVC (% predicted) values on each measurement. The clinical phenotypes were defined as follows: 122 global phenotype (29 bulbar, 45 cervical, 48 lumbar), plus 12 flail phenotype and 3 primary lateral sclerosis (PLS). The primary outcome measure was tracheostomy-free survival. Eighty-nine patients underwent PTF at least twice with an average of four times and an average time between tests of approximately 4 months. The monthly average of RoC in sitting FVC was −0.04 L (% predicted −0.87). Similarly, the RoC in supine FVC was −0.03 L (% predicted −0.65). Patients with a global phenotype had a greater decline in RoC than those with flail phenotype or PLS. The authors also compared the RoC for 18 patients with global phenotypes before and after the introduction of NIV in average volume-assured pressure support (AVAPS) mode showing that pre-AVAPS versus post-AVAPS sitting FVC RoC was −2.86 and −0.91, respectively ($p = 0.16$). The results of this study, although statistically not significant, highlighted the utility of FVC rate of change as an independent predictor of survival in ALS and the importance of serial measurements of FVC. The most important data that emerges from this study is related to the fact that a slower RoC for the sitting/supine FVC of −0.91/−0.16 compared to rapid RoC of −1.19/−1.07 per month was associated with a better survival and a delay in the need for tracheostomy among patients with ALS. The authors concluded that an early start of NIV based on the decline of RoC rather than on the absolute value of FVC can slow down the deterioration of respiratory function in ALS patients.

Vitacca et al. [8] evaluated the impact of a very early NIV initiation program compared to current guidelines on survival and tracheostomy

time. In this pilot retrospective observational study, 194 patients suffering from ALS adapted to NIV were analyzed in three highly specialized Italian centers. The patients were arbitrarily divided into two groups based on the NIV start criterion: (1) later group (LG), with FVC <80% predicted, and (2) very early group (VEG), with FVC ≥ 80% predicted at the beginning of NIV, and were followed every 2–6 months for 36 months. At 3 years tracheostomy was required in 23.1% of patients in the VEG group versus 41.9% of the LG group ($P = 0.009$); in the non-bulbar subgroup (NB), tracheostomy was necessary in 11.1% of the VEG group versus 45% of the LG group. Furthermore, after 3 years of follow-up, VEG patients had a higher survival rate on NIV without tracheostomy in either the non-bulbar or bulbar subgroups. The authors hypothesized that the positive effect demonstrated in patients adapted very early to NIV may be due to the presence of the better state of neuromuscular junctions at the time of adaptation given the worst nutritional, neurological, and respiratory status of LG group patients at the time of NIV initiation. In addition, the more progressive increase in hours of ventilation during the night and on demand during the day may have improved adherence to the NIV of the VEG group allowing a more comfortable adaptation and greater confidence in the success of NIV by the patients. The strengths of the study in question are the large sample analyzed over a long period of time, the multidisciplinary experience of the three different centers, and the strong association between the very early beginning of the NIV and the low risk of failure of NIV itself (death or tracheostomy). On the other hand, the possible biases are the inclusion criteria for NIV in the VEG group linked to clinical medical judgment. These results are not easily generalized to all patients with ALS as this experience has been carried out in three highly specialized centers in neuromuscular diseases.

In their multicenter, prospective, randomized work, Bertella et al. [9] focused attention on the physical location of NIV initiation. Based on previous experiences that have shown that outpatient initiation of NIV is preferred by patients with ALS and their families [10, 11], the authors investigated whether NIV initiation carried out in an outpatient setting could be an effective alternative to in-hospital initiation in terms of better acceptance and adherence to NIV. The authors enrolled 50 consecutive patients in stable conditions without respiratory infections in the previous 3 months and residing within 40 km of the hospital and randomized them to an inpatient group (No. 25) or outpatient group (No. 25). No differences were found between the two groups in terms of rate of failure to accept NIV (20% in inpatient group vs. 24% in outpatient group) or in the rate of adherence failure (24% of inpatient vs. 32% of outpatient). The most important finding from the study is that outpatient initiation of NIV is no less effective than inpatient initiation in terms of acceptance and adherence to therapy. In addition, respiratory function changes, symptom control, and patient's and health staff satisfaction were similar in both groups. Furthermore, the hours of nighttime ventilation were greater in the outpatient group than in the inpatient group, at least in the first week of use of the NIV.

7.2.2 Ventilation Mode

In literature, different ventilation modalities in the ALS patient have been retrospectively analyzed, showing no significant differences between pressometric and volumetric modalities in terms of survival [12], even though the pressure modes are the most used [13]. The strongest indications remain for those related to the setting of a backup respiratory rate that seems to improve the management of NIV [14].

Nicholson et al. [15] retrospectively analyzed NIV device-recorded data of 271 patients with ALS in pressure support (PS) or in volume-assured pressure support (VAPS) modalities to evaluate the differences regarding target tidal volume (V_t) and ratio of respiratory rate to tidal volume (f/V_t), in addition to triggering and cycling ability. It is known in the literature that the breathing pattern of patients with ALS is abnormal, and in particular cases with severe disease show a shorter inspiratory time (T_i), reduced tidal volume

(V_t) and an increased f/V_t, indicative of rapid shallow breathing pattern [16]. The authors pointed out that, in their experience, VAPS achieved more reliable V_t than PS and is associated with the appearance of minimal rapid shallow breathing. Furthermore, there was no difference in compliance between the two ventilation modalities (NIV use per day 6.6 h/day for PS vs. 6.5 h/day for VAPS). Lastly, with respect to the PS modality, a decrease in spontaneously cycled breaths was demonstrated while triggering was less compromised. The authors concluded that V_t delivery was more reliable for VAPS mode compared with PS. The most significant finding that emerged from this work was that in the majority of patients with ALS in NIV, particularly in PS mode, there was a significant proportion of premature cycling. As a result, while ineffective efforts can be controlled by entering a backup frequency, the presence of premature cycling and the appearance of rapid shallow breathing could be reduced with the inclusion of a minimum inspiratory time in the ventilator settings. It is likely that the achievement of satisfactory lung volumes and a control of rapid shallow breathing could also be achieved with close monitoring and frequent changes in ventilator settings based on the respiratory changes associated with the disease.

A randomized crossover trial by Vrijsen et al. [17] compared gas exchange, sleep architecture, and patient-ventilator asynchrony (PVA) of two NIV PS modes: the spontaneous (S) mode and the spontaneous-timed (ST) mode. The results showed the absence of significant differences in the sleep architecture between S mode and ST mode, with significant differences noted in the minimum SpO_2 and $PtcCO_2$ values in favor of ST mode. Ineffective efforts were more frequent during S mode. However, it should be noted that 4 out of 13 (31%) patients were discharged in S mode due to better results in terms of sleep efficiency, gas exchange, and arousal index. The authors concluded that NIV treatment with ST mode improves gas exchange, PVA, and respiratory events compared to S mode. Thus starting the NIV in ST mode seems reasonable in ALS patients even if the decision on which modality to use should always be individualized.

7.2.3 Telemonitoring

Telemedicine can be used as an aid to diagnosis, symptom monitoring, and management as it allows the patient to transmit physiological data remotely. Although in limited numbers, some studies suggest benefits for the ALS patient. Selkirk et al. retrospectively analyzed the efficacy of telemonitoring of ALS patients on NIV by finding equivalent quality of care between conventional in-person consultation and video consultation, with no significant difference in survival time between the groups [18]. Ando H et al. [19] developed a 26-item self-report ALS OptNIVent question set for weekly remote monitoring of individuals on NIV to assess respiratory-related symptom changes and NIV-related issues, combined with oximetry and patient ventilation interaction data. The objectives were twofold: first to develop a specifically tailored question set for CarePortal, a remote monitoring system, and then to evaluate the usefulness of the questions as part of the telemonitoring care of ALS NIV users. The evaluation phase showed weekly telemonitoring through the CarePortal to be effective in prompting changes allowing optimization of the ventilatory support of patients with ALS in NIV, in terms of SpO_2 levels and ventilation.

7.3 Conclusion

In the last 2 years, the most significant research work focusing on patients with ALS on NIV therapy has shown that an early start of NIV can, in selected cases, increase survival and tracheostomy-free time. Another important factor that emerges from the literature is the importance of the FVC rate of change, which is more associated to the course of the disease than the absolute FVC, with patients with a lower rate of change having better survival. As a result, closer monitoring of FVC rate of change could make the start time of NIV more tailored to each patient. With regard to the NIV initiation settings, new research suggests to consider outpatient adaptation of NIV, which proved to be as effective as inpatient adaptation. Regarding the NIV modalities of the

ALS patient, the literature data indicate that the ST mode turns out to be the most suitable to begin adaptation compared to the S mode, but the decision must be individualized for each patient. Telemonitoring currently shows potential as an effective modality for following patient with ALS on NIV, allowing an individualized approach with early recognition of the worsening phases of the disease and optimization of ventilatory support.

Key Summary

- Early NIV initiation, taking into account rate of change (RoC) of FVC for each patient
- Outpatient adaptation of NIV, when possible
- ST mode with attention to premature cycling
- Telemonitoring in NIV patients, with early warning of respiratory worsening

References

1. Andersen PM, et al. EFNS Task Force on Management of Amyotrophic Lateral Sclerosis Guidelines for diagnosing and clinical care of patients and relatives. An evidence-based review with Good Practice Points. Eur J Neurol. 2005;12:921–38.
2. Haverkamp LJ, et al. Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. Brain. 1995;118:707–19.
3. Corcia P, et al. Causes of death in a post-mortem series of ALS patients. Amyotroph Lateral Scler. 2008;9(1):59–62.
4. Bourke SC, et al. Effect of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis : a randomized controlled trial. Lancet Neurol. 2006;5:140–7.
5. Andersen PM, et al. EFNS guidelines on Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNStask force. Eur J Neurol. 2012;19:360–75.
6. Georges M, et al. Initiation of non-invasive ventilation in amyotrophic lateral sclerosis and clinical practice guidelines: single-centre, retrospective, descriptive study in a national reference centre. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18:46–52.
7. Elamin EM, et al. Effect of early introduction of non-invasive positive pressure ventilation based on forced vital capacity rate of change: Variation across amyotrophic lateral sclerosis clinical phenotypes. Int J Clin Pract. 2019;73(1):e13257.
8. Vitacca M, et al. Impact of an early respiratory care programme with non-invasive ventilation in patients with amyotrophic lateral sclerosis. Eur J Neurol. 2018;25(3):556-e33.
9. Bertella E, et al. Early initiation of night-time NIV in an outpatient setting: a randomized non-inferiority study in ALS patients. Eur J Phys Rehabil Med. 2017;53(6):892–9.
10. Lloyd-Owen SJ, et al. Patterns of home mechanical ventilation use in Europe : results from the Eurovent Survey. Eur Respir J. 2005;25:1025–31.
11. Chatwin M, et al. Randomized trial of inpatient versus outpatient initiation of home mechanical ventilation in patients with nocturnal hypoventilation. Respir Medicine. 2008;102:1528–35.
12. Sancho J, et al. Non-invasive ventilation effectiveness and the effect of ventilatory mode on survival in ALS patients. Amyotroph Lateral Scler Frontotemporal Degener. 2014;15:55–61.
13. Janssens JP, et al. Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. Chest. 2003;123:67–79.
14. Berry RB, et al. Best clinical practices for the sleep center adjustment of noninvasive positive pressure ventilation in stable chronic alveolar hypoventilation syndromes. J Clin Sleep Med. 2010;6(5):491–509.
15. Nicholson TT. Respiratory pattern and tidal volumes differ for pressure support and volume-assured pressure support in amyotrophic lateral sclerosis. Ann Am Thorac Soc. 2017;14(7):1139–46.
16. Vitacca M, et al. Breathing pattern and respiratory mechanics in patients with amyotrophic lateral sclerosis. Eur Respir J. 1997;10:1614–21.
17. Vrijsen B, et al. Randomized cross-over trial of ventilator modes during non-invasive ventilation titration in amyotrophic lateral sclerosis. Respirology. 2017;22(6):1212–8.
18. Selkirk SM, et al. Delivering tertiary centre specialty care to ALS patients via telemedicine: a retrospective cohort analysis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18:324–32.
19. Ando H, et al. Incorporating self-reported questions for telemonitoring to optimize care of patients with MND on non-invasive ventilation (MND OptNIVent). Amyotroph Lateral Scler Frontotemporal Degener. 2019;20(5–6):336–47.

8 Noninvasive Ventilation in Neuromuscular Patient Non-ASL

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8.1 Background

Neuromuscular disorder (NMD) may result from metabolic injury or genetic abnormalities of the central or peripheral nervous system.

Neuromuscular disease is characterized by the development of respiratory muscle weakness (diaphragm and accessory muscles of respiration), hypotonia of bulbar muscles, sometimes anatomical abnormalities (scoliosis or rigid spine), heart diseases, and decreased central respiratory drive. These conditions lead to chronic progressive respiratory failure and increased risk of morbidity (pneumonia, atelectasis, etc.).

The onset of respiratory function impairment is different between many inherited neuromuscular diseases. NMD can be divided into slowly, variable, and rapidly progressive risk of respiratory failure [1]. There is no accepted definition of these subgroups; but understanding the speed of progression is important to choose the correct timing to start home mechanical noninvasive ventilation (NIV). Diseases with rapid progression are spinal muscular atrophy (SMA) type 1 (all children will develop respiratory failure by the age of 2 years unless treated), SMA type 2 (around 40% develop respiratory failure in childhood), X-linked myotubular myopathy, those with SMARD (SMA with respiratory distress) [2], Duchenne muscular dystrophy (DMD) (respiratory failure tends to follow loss of ambulation), and Becker muscular dystrophy, which despite looking like

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DMD is generally milder with a later onset and less severe muscle weakness; other rapidly progressive NMD is motor neuron disease/amyotrophic lateral sclerosis.

NMDs with variable progression are limb girdle muscular dystrophy, myopathies, nemaline myopathy, metabolic storage disease, and merosin negative congenital muscular dystrophy, while slowly progressive or nonprogressive are previous poliomyelitis, facioscapulohumeral muscular dystrophy, SMA type 3, myotonic dystrophy as myotonic dystrophy type 1 (DM1) [3], Emery-Dreifuss muscular dystrophy [4], central hypoventilation, and spinal cord injury [5].

However, in patient with variable, slowly progressive, or nonprogressive NMD, physiological changes, such as weight gain, chest infection, additional chronic cardiorespiratory pathology, or sleep-disordered breathing, may cause ventilatory failure, even if there isn't a disease progression [5].

In the last decades, noninvasive ventilation (NIV) [6, 7] has frequently been used as a respiratory support for NMD patients [8, 9], constituting around 10–51% of the overall indications for home mechanical ventilation [10, 11]. NIV in many NMD may change the natural history of the disease; for example, DMD patients now live longer (30 or 40 years old) than before the 1990s (median age at death of 18–20 years) [12]. NIV has also changed the life expectancy in type 1 SMA [13]. NIV may be used to palliate symptoms related to chronic hypoventilation and facilitate discharge to home [14].

Early NIV initiation may preserve muscle function, alter the natural progression of the disease [15], and reduce hospitalizations [16]. Furthermore, if home NIV is used combined to cough assistance, scoliosis surgery, steroid use, and cardiologic management, improvements in nutrition and gastrostomy feeding added to better outcomes in terms of reducing hospitalization, facilitating care at home, and increasing survival [17, 18].

The approach to NIV use in NMD has greatly changed over time, and this chapter aims to detail the latest updates focusing on the most important topics.

8.2 NIV Initiation

8.2.1 Respiratory Failure

In 1999, the Chest Consensus Conference report proposed, as a correct timing to NIV initiation for restrictive disease, the presence of symptoms suggestive of hypoventilation or sleep disorder (like fatigue, dyspnea, morning or continuous headaches, frequent nocturnal awakenings or difficult arousal, hypersomnolence, difficulty concentrating, awakenings with dyspnea and tachycardia, and frequent nightmares) and one of the following physiologic criteria: (a) awake arterial blood gas CO_2 levels > *o* = 45 mmHg, (b) oxygen saturation (SpO_2) of <88% for at least 5 consecutive minutes of nocturnal recording, and c) for progressive NMD, PImax ≤ 60 cmH_2O or FVC < 50% predicted performed in the upright or supine position [19].

Recently the usefulness of transcutaneous PCO_2 (Tc PCO_2) has been demonstrated to assess nocturnal hypoventilation in restrictive lung disorder studies as alternative to nocturnal pulse oximetry (NPO) [20].

Won et al. [21] demonstrated better sensibility of $TcCO_2$ than end-tidal carbon dioxide partial pressure (Pet CO_2) in monitoring during sleep for patients with NMD; using as hypoventilation criterion peak CO_2 > 49 mmHg ($TcCO_2$ or Pet CO_2), 48.7% of patients would not have been considered to be hypercapnic by only $PetCO_2$ monitoring, while they had hypercapnia using $TcCO_2$.

Noninvasive transcutaneous measure of CO_2 ($TcCO_2$) has increased diagnostic opportunities, and this measure is considered as a diagnostic tool to detect hypoventilation in the recently published guidelines of the American Academy of Sleep Medicine (AASM) [22].

Georges et al. [20] showed that more than 30% of patients with nocturnal hypoventilation remained undetected using thresholds of the 1999 Chest Consensus Conference (SpO_2) of <88% for at least 5 consecutives minutes of nocturnal recording. Moreover, this study showed that the absence of daytime hypoventilation ($PaCO_2$ > 45 mmHg and raised bicarbonate on a standard HCO_3 > 27 mmol/l measured by arte-

rial blood gas analysis at rest) did not exclude nocturnal hypoventilation defined as mean Tc $PCO_2 > 50$ mmHg during sleep.

Similar results were found by Trucco et al. [23] These authors, using as hypoventilation threshold Tc $PCO_2 > 50\%$ for 25% of time, showed that transcutaneous monitoring of pCO_2 levels could potentially detect nocturnal hypoventilation, even in asymptomatic patients and those without significant nocturnal hypoxemia. Twenty-three of 29 patients with NH did not have nocturnal hypoxemia, and 18 were clinically asymptomatic; therefore, 13 of 29 patients had isolated nocturnal hypercapnia that was not associated with significant nocturnal hypoxia, daytime hypercapnia, or clinical NH symptoms.

In neuromuscular patients Ogna et al. [24] demonstrated that nocturnal capno-oximetry should be included among the diagnostic tools used to detect hypoventilation. They observed that the use of $TcCO_2$ can identify nocturnal hypoventilation in 28% of patients with daytime normocapnia. In patients with daytime normocapnia, nocturnal hypoventilation was present in 28.6% of myotonic dystrophy, 25.0% of spinal muscular atrophy, and 36.8% of Duchenne or Becker muscular dystrophy patients, when the most sensitive criterion (peak $TcCO_2 > 49$ mmHg) was used.

In a retrospective study, Nakamura et al. [25] identified isolated sleep hypercapnia in patients with early-stage BMD with preserved waking lung function. The authors reached nocturnal hypercapnia (defined as average PCO_2 was elevated to >45 mmHg during sleep) in six young Becker muscular dystrophy (BMD) at 12–31 years of age and found it in five BMD patients, including three who were still ambulant. Furthermore, these five patients exhibited sleep hypercapnia, while their FVC% was still greater than 70% of the predicted values.

The characteristics of nocturnal hypercapnia in BMD; sleep hypercapnia without a decline in SpO_2, often asymptomatic; preserved FVC%; and other respiratory parameters are also observed in the early stage of DMD [26].

Till date, several definitions of nocturnal hypoventilation have been used in literature to define nocturnal hypoventilation, but the best strategy to detect nocturnal hypoventilation in daytime normocapnic NMD remains to be defined (there is no agreement on nocturnal hypoventilation definition). Hypoventilation is defined by eight criteria, and just only four consider use of transcutaneous; as summarized by Ogna et al. [24] hypoventilation criteria are daytime partial arterial pressure of $CO_2 > 45$ mmHg, daytime base excess ≥4 mmol/l, nocturnal $SpO_2 \leq 88\%$ for 5 consecutive minutes, mean nocturnal $SpO_2 < 90\%$ or $SpO_2 < 90\%$ during ≥10% of the recording time, $TcCO_2 > 55$ mmHg for ≥10 min, increase in $TcCO_2 \geq 10$ mmHg (in comparison to an awake supine value) to a value exceeding 50 mmHg for ≥10 min, peak $TcCO_2 \geq 49$ mmHg, and mean $TcCO_2 > 50$ mmHg.

A recent study on patients with DM1 [27] showed that NIV initiation was associated not only with hypercapnia, which is itself clinical criteria to start NIV, but also with worse PEF cough test (PCF) values. PCF was an independent predictor to NIV indication after adjustment for age and $PaCO_2$. Moreover risk of NIV initiation was higher in patients with PCF below 180 l/min than patient with PCF from 180 to 270 l/min.

Different results were found in DMD patients: starting NIV was not associated with changes in VC, MIP, and MEP [28].

The choice of both diagnostic tools and thresholds of lung function adequately used to identify correct timing for NIV initiation has relevant clinical consequences, as shown by several studies suggesting that starting NIV both too early (risk to induce atrophy in the diaphragm) [29] and too late may be detrimental (respiratory failure can occur earlier leading to premature death risk). Boussaïd et al. [27] showed that DM1 patients who started NIV over 1 year after meeting criteria for NIV initiation or did not start NIV at all had a higher risk of a severe event (switch to invasive mechanical ventilation or death than in the group who begin NIV within 1 year after meeting criteria for NIV initiation ($P = 0.03$)).

Another new strategy to establish correct time to start NIV is the ultrasound diaphragm patterns, because it has been reported to be correlated with lung function and inspiratory muscle strength [30].

8.2.2 Sleep-Disordered Breathing

The presence of sleep-disordered breathing events is another important indication to NIV initiation in NMD.

Sleep disturbances create fragmented sleep because of frequent arousals and decreased sleep efficiency, leading to sleep deprivation and to a strong contributor to the morbidity of neuromuscular diseases. All sleep-disordered breathing events in NMD may be compensated or resolved by NIV with improvement on survival and quality of life [31].

Sleep-disordered breathing events are frequently in patients with NMD. These patients may have weakness of accessory respiratory muscles and especially of diaphragm that induces hypoventilation, upper airway obstruction due to anatomical anomalies and upper airway muscle dysfunction with propensity to have obstructive respiratory events, and potential cardiomyopathy leading to central respiratory events.

The most common sleep-disorders breathing in neuromuscular diseases are diaphragmatic events due to diaphragmatic weakness. This hypopnea/hypoventilation, with a sawtooth pattern of desaturation dips, is strongly suggestive of early warning of respiratory muscle involvement. Diaphragm dysfunction worsens respiratory muscular atony during REM sleep causing a complete loss of excursion of both chest and abdominal signals on polysomnography, looking as pseudo-central events [32], but diaphragmatic events are hypopneas neither obstructive nor central and they occur generally during phasic REM sleep-disordered (i.e., during bursts of eye movements) breathing events are diaphragm electromyography, esophageal monitoring, supraglottic pressure monitoring, or pulse transit time [32]. It is notable that, if these events are observed in ventilated patients, the correct ventilator strategy contemplates an increase of pressure support without EPAP changes and an adequate backup frequency respiratory rate setting.

Sleep obstructive apnea (OSA) is observed in many NMD: dystrophies or acid maltase deficiency, Charcot-Marie-Tooth disease both cervical and thoracic cord injury, and DMD [33].

Patients with Duchenne muscular dystrophy or acid maltase deficiency [34] have a bimodal pattern: they early develop OSAs, due to the hypotonia of upper airway muscle and macroglossia, and later hypoventilation with or without OSAs. This latter sleep disorder is caused by the inability of weak respiratory muscles to generate the negative pressures necessary for airway collapse, promoting instead REM-related pseudo-central events [35].

In patients with DMD, OSA is also related to the progressive weight gain due to both the use of systemic steroid treatment used in the management of this condition and progressive physical limitations and loss of effective ability to burn calories, as demonstrated by Sawnani et al. [36].

Other mechanism involved in sleep obstructive disorders is pharyngeal neuropathy in patients with Charcot-Marie-Tooth disease, and an increase in passive airway collapsibility in subjects with spinal cord injury has predisposed to OSA. Finally, low lung volumes contribute to the development of OSA in NMD by reducing residual functional capacity (FRC) with resultant traction on the airway [31].

Central sleep disturbances in neuromuscular disorders are characteristics of either Cheyne-Stokes breathing or central apnea. Cheyne-Stokes respiration in cardiomyopathy is associated with increased mortality [32].

Cheyne-Stokes breathing is due dilated cardiomyopathy, as can be seen in both muscular dystrophies (Duchenne muscular dystrophy, Becker muscular dystrophy, limb girdle, and myotonic dystrophies) and glycogen storage diseases (acid maltase deficiency). The key pathophysiologic mechanisms are an instability in the control of breathing for high loop gain with enhanced ventilatory response to CO_2 and the prolonged circulatory time in heart failure [32].

Central apneas and periodic breathing have high prevalence in spinal cord injuries: more in cervical cord injuries than thoracic spinal cord injuries.

8.2.2.1 Treatment of Sleep Respiratory Disorder

If NMD patients have just only signs of OSAs, according to DMD Care Considerations

Working Group steering committee [37], NIV has traditionally been started with a bi-level mode and backup rate (to avoid apnea) rather than CPAP use. Indeed, at the state of the art, we found only one study about CPAP use in DM1 with OSAs alone without nocturnal hypoventilation [38]. In this study, West et al. used CPAP treatment for OSA patients with DM1 and found that 33% of OSAs in CPAP group continued this treatment with beneficial effects.

Most of the authors, in NMD patients with progressive disease, choose bi-level setting with fixed inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) to correct upper airway obstruction with a backup rate (BUR) for the almost always associated diaphragmatic weakness. This NIV mode needs an adequate titration both pressure (IPAP and EPAP) and respiratory backup rate. It must take particular care at the possible presence of diaphragmatic events that cannot be confused with obstructive hypopnea; in these cases it is very important to select a correct IPAP level and a proper BUR.

In the case of central sleep disorders, there isn't a solid consensus for treatment choice, because up-to-date servo ventilation, usually used to stabilize Cheyne-Stokes respiration, seems to be inappropriate in NMD patients [39] (Fig. 8.1).

8.3 NIV Outcome in NMD

Long-term home NIV use in NMD plays an important role in terms of increase on survival.

An important prognostic factor for life expectancy is the age at NIV initiation [40]. Chatwin et al. demonstrated that patients requiring NIV before the age of 17 years have a worse prognosis than those starting NIV at an older age.

Over that, studies more than the past 30 years have demonstrated considerable improvements in survival and a reduction on pulmonary morbidity with NIV and use of cough assistance. Together with this treatment, cardiologic management, scoliosis surgery, prednisolone therapy, and improvements in nutrition [41] have added better outcomes in DMD patients.

HMD in NMD improves daytime hypercapnia [42], morning headaches, respiratory muscle fatigue, and hypersomnolence [43, 44]. It may also ameliorate daytime alertness, promoting growth and development [45] and health-related quality of life [46].

The survival improvement in NMD due to HMV use is recently demonstrated by Mi Ri Suh et al. [47], which followed 180 subjects with diverse NMD: DMD, ASL, SMA, and other congenital myopathy (Guillain-Barre syndrome, Becker muscular dystrophy, facioscapulohumeral dystrophy, limb girdle muscular dystrophy, mitochondria myopathy, myotonic muscular dystrophy, Pompe disease, undetermined myopathy, inclusion body myositis, and Nonaka-type myopathy), individually for 5 years, analyzing survival rates and tracheostomy-free survival 5 years after NIV initiation. The authors observed that daily NIV duration increased in the DMD group (8.0–12.0 h), while there was only a trend toward increased duration in the SMA-congenital myopathy group (8.0–9.0 h); 18 of 85 DMD patients were dependent on NIV for 23 h; however, tracheostomy was rare in this group: only 1 subject underwent tracheostomy, while the other 17 were maintained on continuous NIV. Neither SMA nor other congenital myopathy patients underwent tracheostomy. In subjects with advancing DMD, continuous NIV was found to prolong life and obviate tracheostomy.

The role of NIV on lung function is still debated. In the previous study [47], authors evaluated the variance of forced vital capacity (FVC) at NIV initiation, and after 5 years median FVC in the supine position increased in the SMA-congenital myopathy group, while it decreased significantly in the DMD group; however, they could not explain this solely by NIV use.

Conversely, evidence of NIV benefits on lung function in DMD was demonstrated by Santos et al. [48]: in 71 DMD patients, the decline of lung volumes and maximum airway pressures was more slowly after NIV initiation. Although a causal relationship between NIV initiation and slowing of lung function decline cannot be surely

Sleep events	Reason	Resolution
Obstructive events **Obstructive apnea** **Obstructive hypopnea**	• DMD (60%): ➢ passive airway collapsibility ➢ macroglossia ➢ low lung volumes (by reducing the traction on the airway, which in turn reduces the stability of the upper airway) ➢ use of the systemic steroids • Charcot-Marie-Tooth disease (40%): ➢ hypotonia or neuropathy pharyngeal • spinal cord injury: 33% if cervical and 25% if thoracic ones ➢ increase in passive airway collapsibility • dystrophies or acid maltase deficiency (20%): ➢ upper airway muscle hypotonia ➢ macroglossia	If It possible change with a nasal mask Increase EPAP for obstructive apneas Increase IPAP for obstructive hypopneas
Central events **Central Sleep Apnea and Cheyne-Stokes** **Periodic Breathing and central apnea**	• DMD • Becker dystrophies • Limb girdle dystrophies • Myotonic dystrophies • Acid maltase deficiency • Spinal cord injury: - cervical (between 63% and 88%,) - thoracic (between 13% and 38%)	Treat heart failure. Set BUR Set BUR
Nocturnal hypoventilation	NMD with respiratory muscle weakness	Increase difference between IPAP and EPAP
Diaphragmatic events	• DMD • Myotonic dystrophy • Metabolic: acid maltase deficiency Due to diaphragm weakness; generally happen in phasic REM sleep: during bursts of eye movement • Diaphragm paralysis ➢ asymmetric diaphragm injury, the events are positional • Charcot-Marie-Tooth disease ➢ neuropathy	Set BUR Increase difference between IPAP and EPAP.
Bimodal pattern	• Acid maltase deficiency: (early OSAs, later diaphragmatic events) ➢ Macroglossia ➢ respiratory muscle weakness • DMD (early OSAs, later diaphragmatic and/or central events) ➢ macroglossia ➢ respiratory muscle weakness ➢ cardiomyopathy ➢ use of systemic steroids	If obstructive events: Increase the EPAP for obstructive apneas Increase IPAP for obstructive hypopneas If diaphragmatic events: Set BUR Increase difference between IPAP and EPAP If central events: Treat heart failure. Set BUR
Residual events during NIV	• Air leaks: ➢ mask ➢ elevated pressure • Ineffective efforts: ➢ dynamic hyperinflation, due to higher pressure support and respiratory rate. ➢ muscular weakness • Autotriggering: ➢ high trigger sensitivity ➢ air leaks ➢ water condensation inside circuite • Delayed cycling: ➢ Air leaks (hung up) • Central apnea during NIV (CO2 level below a hypocapnic apneic threshold): ➢ aggressive ventilation strategies aimed at normalizing nocturnal or daytime CO2 levels ➢ Overventilation after obstructive apnea or after auto triggering • Obstructive events with manteinded respiratory drive: ➢ Set too low EPAP to correct OSAs • Obstructive events with abolished respiratory drive (glottic closure): ➢ Overventilation during BUR with a low CO2 level	Change or reposition mask reduce pressure support Reduce pressure support Increase trigger sensitivity if muscular weakness Increase EPAP if dynamic hyper inflation Adjust mask (leaks control) Decrease trigger sensitivity Correct leaks Setting of maximal inspiratory time (Ti control) Titration of exipratory trigger Shift from PSV to PCV Reduce pressure support Avoid asynchronies Compromise on normalizing the CO2 level Increase EPAP Decrease back-up rate or pressure support Try a nasal mask Adopt a spontaneous mode of ventilation, but pay attention to hypoventilation

Fig. 8.1 Sleep disorder and strategy of correction in NMD

established, one author hypothesis to explain the lung volume improvements is that NIV may contribute to preserve lung and chest wall compliance, thereby slowing the lung volume decreases associated with progressive respiratory muscle weakness. NIV use could slow the development of the restrictive respiratory pattern due to rib cage deformities and respiratory muscle weakness.

Furthermore, a slower FVC decline can be obtained by complex management of these patients with scoliosis surgery, use of assisted coughing, recruitment techniques, and other respiratory physiotherapy techniques [49].

Another possible benefit of NIV may be an improvement on breathing-swallowing interaction in ventilator-dependent NMD patients as founded by Garguilo et al. [50] They used life support ventilator able to provide volumetric and assisted modes of ventilation (Elysée 150, ResMed SAS, ResMed Corp, San Diego, USA), altered with the help of its manufacturer, to allow interruption of ventilator support during swallowing. A key-pinch off switch was added to allow ventilation deactivation for as long as pressure was applied to the switch. The switch was easily accessible by the patient and chosen for its ability to be used by patients with severely impaired motor function. Thus, the patient was able to stop insufflations at will, for as long as he maintained pressure with his finger on the switch. Releasing the switch resulted in the immediate start of a new controlled cycle. In this study 13 patients with congenital myasthenia, Duchenne muscular dystrophy, or limb girdle muscular dystrophy were enrolled. The use of a patient-controlled NIV during swallowing significantly improved breathing-swallowing coordination in ventilated neuromuscular patients with severe respiratory failure by increasing the pattern of expiration-followed swallowing and reducing dyspnea during swallowing.

Similar benefits have been obtained through noninvasive intermittent positive pressure ventilator support via 15 mm angled mouthpieces during meals [51]. In a case series on DMD patients [52], NIV is able to relieve tachypnea, increase lung volumes to provide more time to swallow food safely, and allow weight loss reversal.1200–1500 ml volumes are administered to facilitate 6000 ml/min ventilation with 12–15 s between assisted breaths to facilitate safe swallowing. This can provide adequate minute ventilation with only three or four assisted breaths; then MPV ventilation, used during eating, presents an alternative to tracheotomy and premature resort to gastrotomy to reverse weight loss for patients.

During eating, an alternative for NMD patients that can't close lips to activate MPV is the use of NIV with nasal interfaces (mask or nasal pillow) with backup ventilator rates as low as 0; this allows patients to trigger deep insufflations to facilitate eating without an interfering back-up rate. Furthermore this NIV setting may facilitates speech and coughing and decrease aspiration risk.

DMD patients use MPV during meals show relief in dyspnea and fatigue that can accompany eating and drinking, compared to DMD patients that not use ventlation, as obeserved by Britton et al. [51]. In addition these authors found that MPV may improving cough effectiveness, an important pulmonary defense to reduce risk of pneumonia.

A key role in NMD is played by cardiac impairment which influences mortality and morbidity; its management relies mainly on cardiac protective drugs, but recently it has demonstrated that mechanical ventilation may reduce myocardial dysfunction [53]. Fayssoil et al. [54], in DMD and Becker muscular dystrophy patients [30], found that mechanical ventilation may decrease systolic pulmonary pressure and left atrial size as well as left ventricular afterload and myocardial function decline.

An adequate tidal volume during NIV seems to reduce rate of left ventricular (LV) function decline in dystrophinopathies, if it is used in addition with cardioprotective drugs (ACE inhibitors and beta-blockers).

Mechanical ventilation reduces LV afterload by increasing intrathoracic pressure and decreasing transmural pressure of LV and then may ameliorate LV systolic function. On the other hand, high levels of PEEP may reduce cardiac output in NMD with cardiomyopathies [55].

Not only heart impairment but also bulbar symptoms are frequent in dystrophinopathies; together they affect morbidity and mortality. In a retrospective cohort study, Boussaïd et al. [56] analyzed 150 DMD patients of whom 128 had cardiac disorders (half of them had left ventricular dysfunction and 16 had swallowing disorders); they found that the most frequent cause of death was heart failure: 20 patients died from cardiac causes, while 11 died from respiratory causes, and only 1 following a bowel obstruction. Overall risk of death was associated with cardiac failure and swallowing disorders.

This study also underline that HMV is the first type of mechanical ventilation chosen in NMD than IMV. At the beginning of ventilation, 79% of patients used noninvasive ventilation. NIV was the first-line treatment since it is considered to be safer and to cause fewer complications than tracheostomy. In addition, an improvement in interfaces and machines has led to an increase in the effectiveness of NIV, which can now be used to highly ventilator-dependent patients. Moreover, as mentioned above, improvements in nocturnal respiratory monitoring, like transcutaneous $PaCO_2$, have improved the detection of sleep-related disordered breathing and hypoventilation, allowing a close monitoring of the effectiveness of NIV.

In this study, conversely from other study results, the cause of death isn't related to NIV inefficacy because patients could switch to invasive ventilation.

Tracheostomy and invasive mechanical ventilation (IMV) are important solutions for NMD patients which should be considered when desaturation occurs or noninvasive ventilation became ineffective or poorly tolerated due to severe bulbar dysfunction or despite cough assistance is used the patient is unable to prevent aspiration or secretion into the lung (due to too advanced bulbar muscular impairment).

Finally in this study, another interesting result of this study was the absence of relationship between the type of ventilation (IMV or NIV) and the risk of death. These results are similar to those of other studies of life expectancy in patients with DMD [57, 58] and suggest that the respiratory care provided for tracheotomized patients with DMD was effective, despite their more severe clinical condition at the beginning of MV.

In spite of what has been said about NIV outcome in NMD, the NIV benefits in myotonic dystrophy type 1 (DM1) are unclear.

O'Donoghue et al. [59] showed that DM1 patients, with chronic hypercapnic respiratory failure, had little benefit in symptoms or quality of life from NIV. They analyzed DM1 patients 1 month after elective cessation of NIV and again 1 month after NIV reintroduction, and they found no change in sleep architecture or fragmentation during NIV withdrawal or after its reintroduction, despite nocturnal oxygen saturations worsened without NIV. There was a small increase in diurnal $PaCO_2$ but did not reach statistical significance, no change in lung function or muscle strength, and no change in hypercapnic ventilatory response across visits. Quality of life (QLQ), daytime sleepiness, blood pressure, and other indices of cardiovascular risk were also unchanged. On the other hand, there was a significant decrease in diurnal $PaCO_2$ on recommencing NIV, with accompanying small but significant changes in both HCO_3^- and base excess.

This author concluded that delaying initiation of NIV should be considered in DM1 patients with milder respiratory failure with low arrhythmia risk, because they didn't demonstrate a benefit from NIV in terms of QLQ in these patients; it should be considered that this study analyzed merely 12 patients.

The unchanged quality of life and daytime sleepiness may be behind of poor NIV compliance in patients with DM1.

Other factors associated with poor compliance and cessation of NIV use in DM1 patients are patient character or environment, greater body mass index, no professional occupation, persisted excessive daytime sleepiness despite success-

ful treatment of sleep-disordered breathing, discomfort of ventilator or interface with excessive leaks, and timing to start NIV, as demonstrated by Boussaïd et al. [60]

Excessive leaks can due to facial muscle weakness and may cause an ineffective inspiratory trigger, upper airway dryness, and nasal obstruction. Leaks may induce nasal irritations or even epistaxis; furthermore, if leaks occur in the upper part of the mask (nasal or face), they can cause conjunctivitis.

Moreover, timing to start NIV played an important role in NIV adherence: patients with acute respiratory failure did not choose to begin mechanical ventilation, had a worse compliance to NIV than patients with chronic respiratory failure, and consulted department voluntarily. By contrast, the presence of symptoms of chronic respiratory failure before NIV initiation was associated with an improving NIV compliance. Also, symptoms of respiratory failure and nocturnal arterial oxygen desaturation were associated with increases in relative compliance.

The poor NIV compliance of DM1 patients is however associated with increased mortality and has been shown by Boussaïd et al. [61] In this study the worse NIV adherence from the prescription was independently and significantly associated with death. In DM1 patients who started NIV later (1 year after meeting criteria for NIV initiation) on or not at all using NIV, there were two factors independently and significantly associated with death: PCF and older age at NIV prescription. In DM1 patients who met the criteria for starting NIV, two-thirds failed to start NIV within 1 year of prescription, and they had a higher risk for death or tracheostomy than patients starting NIV within 1 year of NIV prescription. The authors mentioned as possible reason for poor NIV adherence, over the abovementioned causes, that the DM1 patients who were recruited to start NIV had more advanced disease associated with marked cognitive dysfunction, which may influence not only adherence to NIV treatment but also the risk of NIV-related complications and symptom control [62] (Fig. 8.2).

- Prevent atelectasis and pulmonary morbidity
- Improve quality of life
- Improve gas exchange
- Improve airway clearance
- Reduce decline in lung function
- Slow down chest wall deformity
- Correct sleep-disorders
- Reduce daytime somnolence
- Reset the sensitivity of central chemoreceptors
- Reduce symptoms due to chronic hypoventilation
- Reduce frequency of hospitalization
- Reduce morbidity
- Improve survival

Fig. 8.2 NIV effects in NMD

8.4 NIV Setting in NMD

Currently, the mechanical ventilation in NMD is initiated with NIV; NIV is usually started during sleep to correct nocturnal hypoventilation and/or other sleep disorders. NIV can now be extended to daytime, due to improvement of muscle weakness, with new approaches (alternation of new and different interfaces, new ventilation modalities, gastrostomy feeding, cough assistance), and the switch to invasive mechanical ventilation (MV) can be ever more delayed.

Actually, there aren't clear recommendations on the correct NIV setting, but the more frequent setting use is pressure-mode ventilation than volume-mode even if isn't demonstrated more efficacy, as you can see in the (Table 8.1).

In NMD patients "bi-level device" in spontaneous/timed mode (ST) has traditionally been used with use of a single limb circuit with passive exhalation port; the correct setting needs a fixed inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) with a backup rate (BUR); EPAP is often set as low as possible.

The minimum EPAP pressure setting of many ventilations with the passive leaks is 4 cmH_2O which provides sufficient flow for CO_2 clearance. If patients don't tolerate minimum EPAP, like 4 cmH_2O, with passive exhalation port, the use of a single limb circuit with exhalation active valve could be useful for a noninvasive ventilation with ZEEP (PEEP = 0 cmH_2O) with nonvented masks.

Table 8.1 NIV setting in current studies

Authors	Study type, type and number of patients	Enrolled period	Inclusion criteria	Aim	Setting NIV	Conclusion
Fayssoil et al. (2018)	Retrospective cohort study DMD and Becker dystrophies 111 (101 DMD-10 BMD)	2006–2016	Age >18 years The date of inclusion was the date of the mechanical ventilation introduction, whatever the procedure was invasive or noninvasive	Analyze the natural history of cardiac function in patients with DMD and BMD (dystrophinopathies) on NIV	46% pts are in IMV when the study start Biphasic ventilator mode 28% Assisted-control volume mode 71%	HMV is not harmful and may protect heart in dystrophinopathies, in addition with cardioprotective drugs
Boussaid et al. (2016)	Observational prospective cohort study 128 DM1	1997–2010, then pts were followed until 2015	Patients with DM1 whose NIV was initiated between 1997 and 2010	Determine compliance with NIV in patients with DM1, and second analyze the predictors of noncompliance and cessation of NIV in initially compliant patients, over 5 years	99 pts: pressometric spontaneous/time (ST) mode with a leakage circuit 29 pts: volume mode	NIV compliance depends by several factors It may not be appropriate to initiate NIV in asymptomatic patients, because they have low compliance
Ciorba et al. (2018)	Prospective cohort study NMD 10 pts (8 with DM1, 1 DMD, 2 ALS)	18 month	Consecutive NMD patients with respiratory failure who need NIV initiation	Validate ineffective effort (IE) detection during expiration using pressure and flow signals, with respiratory effort detection by esophageal pressure (Pes) measurement as the reference	PS mode with a nasal mask and expiratory valve circuit	Flow and pressure signals, which can be provided by the ventilator, can be used to efficiently detect IEs as noninvasive method is easy to use and fast and requires no additional parameters than those routinely recorded. Adding electrocardiographic recordings and/or pulse oximeter plethysmography would be helpful to differentiate IEs from cardiac artifacts. IEs may correlate with the number of controlled cycles, which is rarely provided by ventilator software

Boentert et al. (2016)	Prospective study 22 late onset Pompe disease	Baseline evaluation and the first night on NIV were defined as T0 and T1, respectively. Follow-up at 3–4 months after NIV initiation (T2) and, thereafter, every 6–9 months (T3–T6)	Pts with late-childhood, juvenile, or adult-onset Pompe disease were admitted	Investigate immediate and long-term effects of NIV on sleep and nocturnal ventilation in patients with late-onset Pompe disease (LOPD)	Bi-level S/T mode with a RR backup rate (2 breaths per minute less then RR the night before) and averaged tidal volume support EPAP was 4 or 6 and successfully titrated if necessary IPAP min 2, IPAP max 15–22 Vt titrated from 6 to 10 ml/kg oronasal or nasal mask	In LOPD, SDB is common and comprises both hypoventilation and OSA. NIV significantly improves respiration already in the first night of treatment. NIV warrants nocturnal long-term normoventilation without deterioration of sleep quality
West et al. (2016)	Prospective cohort study 350 DM1 pts with daytime sleepiness	From May 2011 to May 2015	Only 140 met criteria and were referred for sleep and ventilation assessment	Provide targeted therapies and assessed response	CPAP for OSAs NIV for respiratory failure. Modafinil for excessive daytime sleepiness	Causes of sleepiness are variable in DM1: OSAs and respiratory failure and sleepiness with a normal sleep study; 29% of this studied cohort benefited from targeted sleep therapies
Spiesshoefer et al. (2017)	Retrospective study 36 DM1	1 January 2009–1 April 2017	Patients with genetically proven DM1	Investigate the diagnostic utility of transcutaneous capnometry for identification of NH in patients with DM1, and evaluate short-term and long-term effects of NIV on nocturnal ventilation and objective sleep outcomes in this condition	NIV was initiated in 32 out of 33 patients with SDB (1 patient declined NIV after the first night) using a spontaneous/timed (S/T) bi-level mode 30 pts with NH NIV included average volume-assured pressure support (minimum IPAP 8.5, maximum IPAP 18.7, backup respiratory rate 13.6) 2 pts S/T mode was used in 2 patients with isolated CSA	Sleep-disordered breathing is highly prevalent in adult DM1 patients complaining of daytime sleepiness, and noninvasive ventilation significantly, rapidly, and persistently improves nocturnal gas exchange. Capnometry is superior to oximetry for detection of nocturnal hypoventilation Adherence to noninvasive ventilation remains a major issue in DM1, and long-term treatment benefits should be individually assessed

(continued)

Table 8.1 (continued)

Authors	Study type, type and number of patients	Enrolled period	Inclusion criteria	Aim	Setting NIV	Conclusion
Boussaid et al. (2016)	Prospective observational cohort study 150 DMD	January 1997–September 2015	DMD in which NIV had been initiated for at least 6 h per day Data were collected at initiation of MV and during annual follow-up visits, until the 12 year after initiation, death, or loss to follow-up	In DMD who switched to IV because NIV was ineffective or not tolerated, assess the relationship between the method of MV and survival at 12 years	Start time: 4 pts (3%) in pressometric mode 115 (96%) of pts used volumetric mode during NIV, IV pts 31 (100%): volumetric mode	Switching to invasive ventilation is appropriate when noninvasive ventilation is ineffective
Fiorentino et al. (2016)	Prospective cohort study 4 young pts with DMD	January 2015–April 2015	Pts refused NIV	Evaluate mouthpiece ventilation (MPV) in patients with DMD who are noncompliant with NIV	1 pt PC with PS 8–10 cmH_2O which was gradually increased until a suitable tidal volume, an optimal SpO_2, a stable HR, and EPAP 0, rise time 3 or 4, t insp 1.2 or 1.3 Fr backup = 0 Time of connection alarm was set at 15 min	MPV is useful to promote a positive approach and a rapid acceptance of the new condition
Castrillo et al. (2018)	Randomized, open, single-center, crossover design 20 NMD	Between March 2016 and June 2017	Inclusion criteria were documented neuromuscular disease, home NIV with a volumetric mode, no previous experience with cough-assistance techniques, age > 18 years, hemodynamic stability, absence of acute bronchial congestion in the past month, and CPF < 270 l/min or maximum expiratory pressure < 45 cmH_2O Exclusion criteria were concomitant lung disease, respiratory infection on the day of the assessment, and a tracheostomy	Compare two inspiratory cough-assistance techniques, volumetric cough mode (VCM) and breath stacking	VCM intermittently inflated the lungs with a volume greater than the baseline tidal volume (VT). This hyperinsufflation cycle was automatically repeated after 30 s of usual cycles. An audio signal sounded just before the deeper breath to alert the subject	Breath stacking and VCM are useful cough-augmentation techniques. Displaying insufflated volumes on the ventilator screen is a simple and accessible method for selecting the most efficient cough-augmentation technique delivered by a home ventilator

Toussaint et al. (2016)	Prospective randomized study 55 DMD	January 2012–December 2013	Age ≥ 18 years and requiring NIV followed up. They all received volume cycle ventilation. Exclusion criteria included inability to perform lung function tests, tracheostomy in situ, prior formal training in air stacking, and respiratory instability defined as acute respiratory failure	Investigate the effect of air stacking via a volume-cycled home ventilator versus via a resuscitator bag in participants with DMD	Via volume-cycled ventilators and nasal mask nocturnally, with mean tidal volume 720 ± 90 mL and respiratory rate set at 22.2 ± 4.2 cycles/min In addition, 35 subjects received diurnal mouthpiece intermittent positive pressure ventilation for a mean of 4.5 years	No difference in cough effectiveness as measured by air stacking-assisted cough peak flow was found in air stacking via a ventilator compared with via a resuscitator bag. Provision of an inexpensive resuscitator bag can effectively improve cough capacity, and it is simple to use, which may improve access to respiratory care in people with DMD

NMD neuromuscular diseases, *LOPD* late-onset Pompe disease, *DMD* Duchenne muscular dystrophy, *BMD* Becker muscular dystrophy, *DM1* myotonic dystrophy type 1, *ALS* amyotrophic lateral sclerosis, *MPV* mouthpiece ventilation, *VCM* volumetric cough mode, *SDB* sleep-disordered breathing

The difference between EPAP and IPAP or also called pressure support (PS) is central to maintaining acceptable tidal volume (8–10 ml/kg of ideal BMI) [63]. The patients are commonly able to trigger the ventilator, while awake or when they are in no-REM sleep, but they will begin to reveal great difficulty to reliably trigger a breath in REM sleep and/or as a disease progress; for this reason it is important to add an FR backup rate to the ventilator set closely to anticipated physiologic rate for the patient.

A higher EPAP level is useful to correct upper airway resistances, but, till date, there is no clear recommendation about making the titration.

When hypoventilation is associated with obstructive sleep apnea, as often observed in NMD patients, the resolution may require at the beginning to increase positive respiratory airway pressure and only after to increase the PS level with careful monitoring to avoid central events with or without glottic closure from overventilation and to eliminate increased leak and ineffective inspiratory efforts.

In NMD patients a slower rise time (time required to reach the inspiratory pressure) may be better tolerated and should be adjusted to maximize patients comfort.

The use of pressure-controlled mode time-cycled (PCV) is possible when the NMD patients have a very low time constant with inspiratory time very low during pressure-controlled mode flow-cycled (PSV); this is a frequent condition in NMD patients with kyphoscoliosis. As alternative, it is possible to use a pressure mode flow-cycled with Ti control, using a correct setting of Ti min to reach an adequate tidal volume.

Pressure-controlled ventilation mode with fixed inspiratory time (PCV) could be useful also when there are relevant leaks, because too high leaks in pressure-controlled ventilation flow-cycled (PSV) may lead to inability of the patients to trigger (missed trigger or auto-trigger). These conditions are very common in NMD patients during nocturnal NIV with nasal pillow or nasal mask due to mouth leaks.

Volume target assured in pressure mode using bi-level device (VAP), timed or flow-cycled, which target the tidal volume or alveolar ventilation (AVAPS, iVAPS) in the self-adjusting pressure mode (minimum and maximum IPAP or PS), is an option for patients with progressive impairment of their respiratory efforts or variability of their weakness condition for position changes or sleep stages. Minimum IPAP must be set to ensure an adequate tidal volume in awake condition, and maximum IPAP is set to guarantee safety about tidal volume; the VAP device should not be set with a low starting PS to exclude undershooting risk. The VAP limitations are unintentional leaks, obstructive upper airway events, and overshooting.

Actually it is possible to resolve the VAP limitations due to obstructive upper airway events by automatic adjusted EPAP level with minimum and maximum pressure EPAP set (AVAPS-AE Philips; iVAPS-autoEPAP ResMed; Prisma 30; Lowenstein) to maintain airway patency with distinction between obstructive and central events. Although this technology may be a good approach against upper airway obstruction in hypoventilation patients, it is necessary caution because these are new technologies without relevant studies [64]. Although VAP may be a hopeful mode for the group of neuromuscular diseases, its application in daily practice still appears to be limited [65]. Up-to-dately, there is only one study that started NIV using averaged tidal volume support with positive outcome [66].

When the disease progresses, patients need noninvasive ventilation for a large part of the day (daytime ventilation). The mouthpiece ventilation (MPV) effectiveness has widely been demonstrated. The use of nasal or oronasal interface 24 h/day can decrease social interaction, impairing eating, drinking, and speech. The use of MPV is an ideal solution for daytime ventilation in patients with functioning mouth muscle and some preserved neck movements. It can be used as a rescue strategy [67] or as continuous treatment [68]. The new generation of ventilators allows to set a MPV mode with the resolution of alarm problems, with different types of inspiratory trigger (kiss trigger or flow trigger); MPV mode can be set in volume or pressure mode using a single limb circuit without expiratory valve; furthermore the new ventilators allow to set more profiles of ventilation modes to ensure, for instance, a nocturnal ventilation with oronasal or nasal mask, to correct hypoventilation and/or OSAs, and a diurnal ventilation with mouthpiece device.

As alternative, it can be considered as nasal pillow for daytime ventilation, above all in very compromised patients.

NIV can be used in NMD as a technique for lung volume recruitment (LVR) or for inspiratory cough augmentation and as effective alternative to the traditional use of resuscitator bag or other [69]. Breath stacking can be performed using a home ventilator; the glottis must be competent, and a ventilation must be delivered by volumetric mode.

LVR and respiratory cough augmentation technique slow the rate of FVC decline and maintain PCF over time; to do this it is necessary to set a dedicated profile in volumetric mode.

There are valid alternative ventilation mode types like negative pressure ventilation (chest cuirass, poncho) or intermittent abdominal pressure ventilation (pneumobelt) which are chosen in selected NMD patients as a rescue ventilation or when patients don't tolerate positive noninvasive ventilation. These are valid alternative to avoid tracheostomy.

Negative pressure for noninvasive ventilation used ventilator function by applying alternatively subatmospheric (negative) and atmospheric (zero) pressures around the thorax and the abdomen. The result is negative intrathoracic pressure that simulates spontaneous inspirations with airflow into the airways and lungs. Two more common categories of negative pressure are available: the chest cuirass (a rigid shell) and wrap-type system (nylon poncho surrounding a semicylindrical tentlike support).

Negative pressure ventilation was successfully and predominantly used for long-term mechanical ventilation until the mid-1980s,but then interest waned, partly because it is more efficacious in patients with altered pulmonary or chest wall mechanics and in those who have comorbid obstructive sleep apnea-hypopnea. Furthermore, negative pressure ventilation may precipitate upper airway obstruction (i.e., obstructive sleep apnea-hypopnea).

Pneumobelt, also known as exsufflation belt, consists of an air bag or rubber bladder inside a cloth corset that is worn around the abdomen just under the diaphragm. It is connected by tubing to a ventilator that alternately inflates and deflates the bladder, providing a smooth, natural inhalation and exhalation, as well as a natural breathing rate for speaking. It is only effective on the sitting and standing positions and cannot be used at night in the supine position (Table 8.2).

Table 8.2 Setting NIV in neuromuscular diseases

CPAP	Uncommon; used only in OSAs without nocturnal hypoventilation
PSV with BUR/ST	More frequent used as a first choice
PCV	Used if pts open the mouth or pts have inspiratory time too short
VAP	Used when hypoventilation persists during usual setting (ST or PC) due to REM sleep or positional changes It is not recommended in case of residual obstruction events or leaks during NIV
VAP+autoEPAP	Used to correct hypoventilation and obstructive events
Multiple ventilation profile	Different NIV setting between nocturnal ventilation and daytime ventilation Daytime ventilation: • MPV: NIV sets in volumetric or pressure mode to improve social interaction and to allow eating, drinking, and speech • Nasal pillow ventilation (usually sets in PCV with ZEEP): to improve social interaction and to allow eating, drinking, and speech LVR: NIV sets in volumetric mode (technique for lung volume recruitment as valid alternative to the traditional use of resuscitator bag or other) Cough assistant by ventilator: NIV sets usually in volumetric mode (valid alternative to traditional air stacking)
Negative ventilation	Chest cuirass, poncho Used as a rescue ventilation or when patients don't tolerate positive NIV
Pneumobelt (exsufflation belt)	Intermittent abdominal pressure ventilation through air bag or rubber bladder Used as a rescue ventilation or daytime ventilation in multiple ventilation profile when patients don't tolerate positive NIV

CPAP continuous positive airway pressure, *PSV with BUR/ST* pressure-controlled mode flow-cycled with backup respiratory rate, *PCV* pressure-controlled mode time-cycled, *VAP* pressure mode timed or flow-cycled with volume target, *VAP+autoEPAP* pressure mode timed or flow-cycled with volume target assured and automatic adjusted EPAP level (between minimum and maximum pressure EPAP), *MPV* mouthpiece ventilation, *ZEEP* zero EPAP, *LVR* lung volume recruitment

NIV titration is essential to monitor the NIV efficacy over time; for this purpose Somno-NIV proposed an algorithm that include built-in software use, oximetry, and $TcCO_2$ [70]; integrating this data it is possible to identify and correct residual events (leaks, obstructive events, residual nocturnal hypoventilation, asynchronism, and undershooting). Recently, these parameters may be observed not only during outpatient visit but also by telemonitoring: home-based monitoring that, through a cloud-based system, send data to the clinicians.

8.5 Conclusions

The respiratory failure management in NMD is complex. A correct choice of NIV initiation is very important with a correct evaluation of lung function, sleep disorders, and symptoms, besides a selection of appropriate interfaces and ventilator settings. With the progression of NMD, there is an increase of NIV dependence with the evaluation of multiple interface exchanges and different ventilation profiles for daytime and nocturnal ventilation, and for this reason a key role is played by a proper follow-up. Adequate NIV management and mucus clearance therapy reduce morbidity and mortality.

References

1. Hull J, Aniapravan R, Chan E, et al. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. Thorax. 2012;67(Suppl. 1):i1–i40.
2. Bush A. Spinal muscular atrophy with respiratory disease (SMARD): an ethical dilemma. Intensive Care Med. 2006;32:1691–3.
3. Thil C, Agrinier N, Chenuel B, et al. Longitudinal course of lung function in myotonic dystrophy type 1. Muscle Nerve. 2017;56(4):816–8.
4. Bonne G, Leturcq F, Ben Yaou R. Emery-Dreifuss Muscular Dystrophy GeneReviews® [Internet]. Seattle: University of Washington, Seattle; 1993-2019. Initial Posting: 29 Sept 2004; Last Update: 25 Nov 2015.
5. Shneerson JM, Simonds AK. Noninvasive ventilation for chest wall and neuromuscular disorders. Eur Respir J. 2002;20:480–7.
6. Gregoretti C, Pisani L, Cortegiani A, Ranieri VM. Noninvasive ventilation in critically ill patients. Crit Care Clin. 2015;31(3):435–57.
7. Cortegiani A, Russotto V, Antonelli M, Azoulay E, Carlucci A, Conti G, et al. Ten important articles on noninvasive ventilation in critically ill patients and insights for the future: a report of expert opinions. BMC Anesthesiol. 2017;17(1):122.
8. Mehta S, Hill NS. Noninvasive ventilation. Am J Respir Crit Care Med. 2001;163(2):540–77.
9. Windisch W. Quality of life in home mechanical ventilation study group. Impact of home mechanical ventilation on health-related quality of life. Eur Respir J. 2008;32(5):1328–36.
10. Veale D, Gonzalez-Bermejo J, Borel JC, et al., Groupe CasaVNI. [Initiation of long-term non-invasive ventilation at home: current practices and expected issues. Surveys from the CasaVNI working party]. Rev Mal Respir. 2010;27(9):1022–9.
11. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J. 2005;25(6):1025–31.
12. Ishikawa Y, Miura T, Ishikawa Y, et al. Duchenne muscular dystrophy: survival by cardio-respiratory interventions. Neuromuscul Disord. 2012;21(1):47–51.
13. Oskoui M, Levy G, Garland CJ, et al. The changing natural history of spinal muscular atrophy type 1. Neurology. 2007;69:1931–6.
14. Chatwin M, Bush A, Simonds AK. Outcome of goal-directed non-invasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. Arch Dis Child. 2011;96:426–32.
15. Yang ML, Finkel RS. Overview of paediatric neuromuscular disorders and related pulmonary issues: diagnostic and therapeutic considerations. Paediatr Respir Rev. 2010;11:9e17.
16. Bach JR, Rajaraman R, Ballanger F, et al. Neuromuscular ventilatory insufficiency: effect of home mechanical ventilator use vs oxygen therapy on pneumonia and hospitalization rates. Am J Phys Med Rehabil. 1998;77:8e19.
17. Duboc D, Meune C, Lerebours G, et al. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. J Am Coll Cardiol. 2005;45:855–7.
18. Bushby K, Bourke J, Bullock R, Eagle M, Gibson M, Quinby J. The multidisciplinary management of Duchenne muscular dystrophy. Curr Paediatr. 2005;15:292–300.
19. Consesus conference-clinical indications for noninvasive positive pressure ventilation in chronic respiratory failuredue to restrictive lung disease, COPD, and nocturnal hypoventilation--a consensus conference report. Chest 1999;116(2):521–34.
20. Georges M, Nguyen-Baranoff D, Griffon L, et al. Usefulness of transcutaneous PCO_2 to assess nocturnal hypoventilation in restrictive lungdisorders. Respirology. 2016;21(7):1300–6.

21. Won YH, Choi WA, Lee JW, et al. Sleep transcutaneous vs. end-tidal CO2 monitoring for patients with neuromuscular disease. Am J Phys Med Rehabil. 2016;95:91Y95.
22. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597–619.
23. Trucco F, Pedemonte M, Fiorillo C, et al. Detection of early nocturnal hypoventilation in neuromuscular disorders. J Int Med Res. 2018;46(3):1153–61.
24. Ogna A, Quera Salva MA, Prigent H, et al. Nocturnal hypoventilation in neuromuscular disease: prevalence according to different definitions issued from the literature. Sleep Breath. 2016;20(2):575–81.
25. Nakamura Y, Saito Y, Kubota N, et al. Identification of sleep hypoventilation in young individuals with Becker muscular dystrophy: a pilot study. Brain Dev. 2018;40(7):537–43.
26. Sawnani H, Thampratankul L, Szczesniak RD, et al. Sleep disordered breathing in young boys with Duchenne muscular dystrophy. J Pediatr. 2015;166(3):640–5.e1.
27. Boussaïd G, Wahbi K, Laforet P, et al. Genotype and other determinants of respiratory function in myotonic dystrophy type 1. Neuromuscul Disord. 2018;28(3):222–8.
28. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bonehealth, and orthopaedic management. Lancet Neurol. 2018;17(4):347–61.
29. Hussain SNA, Cornachione AS, Guichon C, et al. Prolonged controlled mechanical ventilation in humans triggers myofibrillar contractile dysfunction and myofilament protein loss in the diaphragm. Thorax. 2016;71(5):436–45.
30. Fayssoil A, Chaffaut C, Ogna A, Stojkovic T, et al. Echographic assessment of diaphragmatic function in duchenne muscular dystrophy from childhood to adulthood. J Neuromuscul Dis. 2019;6(1):55–64.
31. Aboussouan LS. Sleep-disordered breathing in neuromuscular disease. Am J Respir Crit Care Med. 2015;191(9):979–89.
32. Aboussouan LS, Mireles-Cabodevila E. Sleep-disordered breathing in neuromuscular disease: diagnostic and therapeutic challenges. Chest. 2017;152(4):880–92.
33. Sawnani H, Thampratankul L, Szczesniak RD, et al. Sleep disordered breathing in young boys with Duchenne muscular dystrophy. J Pediatr. 2015;166(3):640–5.e1.
34. Boentert M, Dräger B, Glatz C, et al. Sleep-disordered breathing and effects of noninvasive ventilation in patients with late-onset Pompe disease. J Clin Sleep Med. 2016;12(12):1623–32.
35. LoMauro A, D'Angelo MG, Aliverti A. Sleep disordered breathing in Duchenne muscular dystrophy. Curr Neurol Neurosci Rep. 2017;17(5):44.
36. Albdewi MA, Liistro G, El Tahry R. Sleep-disordered breathing in patients with neuromuscular disease. Sleep Breath. 2018;22(2):277–86.
37. Birnkrant DJ, Bushby K, Bann CM. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bonehealth, and orthopaedic management. Lancet Neurol. 2018;17(4):347–61.
38. West SD, Lochmüller H, Hughes J. Sleepiness and sleep-related breathing disorders in myotonic dystrophy and responses to treatment: a prospective cohort study. J Neuromuscul Dis. 2016;3(4):529–37.
39. Sahni AS, Wolfe L. Respiratory care in neuromuscular diseases. Respir Care. 2018;63(5):601–8.
40. Chatwin M, Tan HL, Bush A, et al. Long term noninvasive ventilation in children: impact on survival and transition to adult care. PLoS One. 2015;10: e0125839.
41. Bushby K, Bourke J, Bullock R, et al. The multidisciplinary management of Duchenne muscular dystrophy. Curr Paediatr. 2005;15:292–300.
42. Boentert M, Dräger B, Glatz C, et al. Sleep-disordered breathing and effects of noninvasive ventilation in patients with late-onset Pompe disease. J Clin Sleep Med. 2016;12(12):1623–32.
43. Allen J. Pulmonary complications of neuromuscular disease: a respiratory mechanics perspective. Paediatr Respir Rev. 2010;11:18e23.
44. Young HK, Lowe A, Fitzgerald DA, et al. Outcome of noninvasive ventilation in children with neuromuscular disease. Neurology. 2007;68:198e201.
45. Panitch HB. Diurnal hypercapnia in patients with neuromuscular disease. Paediatr Respir Rev. 2010;11:3e8.
46. MacIntyre EJ, Asadi L, Mckim DA, et al. Clinical outcomes associated with home mechanical ventilation: a systematic review. Can Respir J. 2016;2016:6547180.
47. Suh MR, Choi WA, Kim DH, et al. Five-year follow-up and outcomes of noninvasive ventilation in subjects with neuromuscular diseases. Respir Care. 2018;63(3):274–81.
48. Brasil Santos D, Vaugier I, Boussaïd G, et al. Impact of noninvasive ventilation on lung volumes and maximum respiratory pressures in Duchenne muscular dystrophy. Respir Care. 2016;61(11):1530–5.
49. Birnkrant DJ, Bushby K, Bann CM. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bonehealth, and orthopaedic management. Lancet Neurol. 2018;17(4):347–61.
50. Garguilo M, Lejaille M, Vaugier I, et al. Noninvasive mechanical ventilation improves breathing-swallowing interaction of ventilator dependent neuromuscular patients: a prospective crossover study. PLoS One. 2016;11(3):e0148673.
51. Britton D, Hoit JD, Benditt JO, et al. Swallowing with noninvasive positive-pressure ventilation (NPPV) in individuals with muscular dystrophy: a qualitative analysis. Dysphagia. 2020;35(1):32–41.
52. Deoa JR, Bachb P. Noninvasive ventilatory support to reverse weight loss in Duchenne muscular dystrophy: a case series. Pulmonology. 2019;25(2):79–82.
53. Lee S, Lee H, Eun LY, et al. Cardiac function associated with home ventilator care in Duchenne muscular

dystrophy. Korean J Pediatr. 2018;61(2):59–63. https://doi.org/10.3345/kjp.2018.61.2.59. Epub 2018 Feb 28.
54. Ashwath ML, Jacobs IB, Crowe CA, et al. Left ventricular dysfunction in muscular dystrophy and genotype. Am J Cardiol. 2014;114:284–9.
55. Baydur A. Mechanical ventilation in neuromuscular disease. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. 3rd ed. New York: McGraw-Hill Education; 2013. p. 761–75.
56. Boussaïd G, Lofaso F, Santos DB. Impact of invasive ventilation on survival when non-invasive ventilation is ineffective in patients with Duchenne muscular dystrophy: a prospective cohort. Respir Med. 2016;115:26–32.
57. Villanova M, Brancalion B, Mehta AD. Duchenne muscular dystrophy: life prolongation by noninvasive ventilatory support. Am J Phys Med Rehabil. 2014;93(7):595–9.
58. McKim DA, Griller N, LeBlanc C, et al. Twenty-four hour noninvasive ventilation in Duchenne muscular dystrophy: a safe alternative to tracheostomy. Can Respir J. 2013;20(1):e5e9.
59. O'Donoghue FJ, Borel JC, Dauvilliers Y, et al. Effects of 1-month withdrawal of ventilatory support in hypercapnic myotonic dystrophy type 1. Respirology. 2017;22(7):1416–22.
60. Boussaïd G, Lofaso F, Santos DB, et al. Factors influencing compliance with non-invasive ventilation at long-term in patients with myotonic dystrophy type 1: a prospective cohort. Neuromuscul Disord. 2016;26(10):666–74.
61. Boussaïd G, Prigent H, Laforet P, et al. Effect and impact of mechanical ventilation in myotonic dystrophy type 1: a prospective cohort study. Thorax. 2018;73(11):1075–8. https://doi.org/10.1136/thoraxjnl-2017-210610. Epub 2018 Mar 23.
62. Poussel M, Thil C, Kaminsky P, et al. Lack of correlation between the ventilatory response to CO2 and lung function impairment in myotonic dystrophy patients: evidence for a dysregulation at central level. Neuromuscul Disord. 2015;25:403–8.
63. Alexiou S, Piccione J. Neuromuscular disorders and chronic ventilation. Semin Fetal Neonatal Med. 2017;22:256–9.
64. Couillard A, Pepin JL, Rabec C, et al. Noninvasive ventilation: efficacy of a new ventilatory mode in patients with obesity-hypoventilation syndrome. Rev Mal Respir. 2015;32:283–90.
65. Lofaso F, Prigent H, Tiffreau V, et al. Long-term mechanical ventilation equipment for neuromuscular patients: meeting the expectations of patients and prescribers. Respir Care. 2014;59:97–106.
66. Boentert M, Dräger B, Glatz C, et al. Sleep-disordered breathing and effects of noninvasive ventilation in patients with late-onset Pompe disease. J Clin Sleep Med. 2016;12(12):1623–32.
67. Fiorentino G, Annunziata A, Cauteruccio R. Mouthpiece ventilation in Duchenne muscular dystrophy: a rescue strategy for non compliantpatients. J Bras Pneumol. 2016;42(6):453–6.
68. Pinto T, Chatwin M, Banfi P, et al. Mouthpiece ventilation and complementary techniques in patients with neuromuscular disease: a brief clinical review and update. Chron Respir Dis. 2017;14(2):187–93.
69. Del Amo Castrillo L, Lacombe M, Boré A, et al. Comparison of two cough-augmentation techniques delivered by a home ventilator in subjects with neuromuscular disease. Respir Care. 2019;64(3):255–61.
70. Janssens JP, Borel JC, Pépin JL et al; on behalf of the SomnoNIV Group. Nocturnal monitoring of home non-invasive ventilation: the contribution of simple tools such as pulse oximetry, capnography, built-in ventilator software and autonomic markers of sleep fragmentation. Thorax. 2011;66:438–45.

Airway Clearance Techniques in Neuromuscular Disorders

9

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Abbreviations

ACTs	Airway clearance techniques
ALS	Amyotrophic lateral sclerosis
AS	Air stacking
CWS	Chest wall strapping
FVC	Forced vital capacity
GPB	Glossopharyngeal breathing
HFCWC	High-frequency chest wall compression
HFCWO	High-frequency chest wall oscillations
IPPB	Intermittent positive pressure breathing
IPV	Intrapulmonary percussive ventilation
LIC	Lung insufflation capacity
MAC	Manually assisted cough
MEP	Maximal expiratory pressure
MIC	Maximum insufflation capacity
MI-E	Mechanical insufflation-exsufflation
MIP	Maximal inspiratory pressure
NMD	Neuromuscular diseases
NIV	Noninvasive ventilation
PCF	Peak cough flow
PEP	Positive expiratory pressure
RV	Residual volume
SMA	Spinal muscle atrophy
VC	Vital capacity

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9.1 Introduction

Mucus clearance is used as a primary defence mechanism, making an excellent tool against microorganisms that can cause infection, atelectasis and even respiratory failure. This preservation can improve pulmonary function. [1, 2] Usually there are three phases to mucus excretion, an inspiratory phase, contraction and expiratory phase. During the first phase, occurs an inhalation of 60–90% of the total lung capacity, then the contraction phase consists in the glottis and supraglottic ventricular folds close for 0.2 seconds, and then, expiratory muscles, such as rib cage, diaphragm and abdomen begin to contract significantly increasing the intrathoracic pressure until 300 cmH_2O. Finally, the expiratory phase occurs with the rapid opening of the glottis during 20–40 ms creating a strong airflow and making secretions and other foreign material to move out of the airway. The maximum airflow of 360–1000 L/min can make the velocity go until 12 m/s. Velocity and efficacy of the final phase depend on viscosity and composition of the mucus [1].

An effective cough is fundamental to mucus clearance of the proximal airways, and for that, it is essential to have an entire work in all the phases of the cough. When some of the cough phases are compromised, such as in case of weakness in respiratory muscles or in case of scoliosis, they are unable to generate their maximal strength. In addition, by decreasing the inspiratory capacity, these patients can increase the mechanical disadvantage of the rib cage expiratory muscles and worsen the chest wall compliance [3].

Neuromuscular diseases (NMD) associated or not with cough impairment involve many morbidity and mortality in the early stages of life, as it can be an important economic burden [4]. In these patients, the composition and volume of secretion are generally normal. However, the effectiveness of cough is affected in the inspiratory and expiratory phases due to muscular weakness. Among NMD, those with severe bulbar dysfunction and glottic dysfunction, such as amyotrophic lateral sclerosis (ALS), spinal muscle atrophy (SMA) type 1 and others, glottic closure impairment can result in the inability to cough or even to swallow, which can bring more saliva and mucus to the superior airway [5].

The beginning of noninvasive ventilation (NIV) becomes an essential tool among the quality and prolonged survival in these patients [6]. Unfortunately, with NIV comes an adverse effect, that is, the secretion impaction and consequently the lung atelectasis on patients under NIV [7]. It is essential to have airway clearance techniques to help prevent some adverse effects and to improve the quality of life in NMD patients.

There is a growing development of new techniques in airway clearance, so it is essential for the physicians to know the most recent updates on this topic.

9.2 Methodology

We performed a systematic search on the literature in PubMed database from January 2017 up to March 2019 including clinical trials, meta-analysis and review articles. We searched for a combination of "NIV", "neuromuscular diseases" and "airway clearance techniques" words.

9.3 Management to Assess Cough Impairment

The most used measurements to assess cough are the vital capacity (VC), peak cough flow (PCF), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). Some recent consensus talk also about the importance of lung insufflation capacity (LIC) and maximum insufflation capacity (MIC) [8]. In Table 9.1 the indications to start airway clearance techniques are summarised.

The VC is measured in standard pulmonary function tests. The American Thoracic Society and European Respiratory Consensus suggest its assessment in every visit. However, the value of VC or its percentage predicted does not correlate with cough impairment, but with the severity of the restrictive disease. When the strength is above 50%, usually it is not related with VC impairment

Table 9.1 Indications to start treatment with cough augmentation techniques

PCF < 160 L/min to start cough augmentation therapy
PCF in NMD patients <270 L/min could benefit from assisted cough techniques to prevent worsening during respiratory infections; it is suggested to start cough augmentation therapy when PCF falls below 270 L/min
MEP < 60 cmH_2O associated with diminished cough effectiveness and warrants the use of cough-assisting techniques
History of repeated hospitalisation by respiratory infections
Low pulse oximetry, during the acute infective episodes, used to screen for the lower airway complications and poor airway clearance to intensify airway clearance therapy

PCF peak cough flow, *DNM* neuromuscular disease, *MEP* maximal expiratory pressure

or minimally impaired, but when it is below 50%, it is usually a predictor of severity decreased in VC, secondary to decreasing of lung and chest compliance. Also, when diaphragm weakness is present, there is a difference in VC from sitting to supine positions >25%.

PCF is measured by simple measurement tools, when, during the test, patients breathe, through a mouthpiece while wearing nose clips linked to a peak flow meter or a pneumotachograph. This test evaluates cough impairment and cannot differentiate the separate components of cough decrease. In patients with muscular weakness in whom effort-related test reproducibility is difficult, the better and more reliable measurement of expiratory muscle strength is considered. A standard test should have a PCF ≥ 360 L/min. In neuromuscular disease patients, a PCF > 270 L/min is considered normal. PCF values of 160 L/min and below are considered as ineffective airway clearance and demand to prompt cough augmentation therapy in these patients.

MIP and MEP are measured by asking the patient to perform a maximal inspiration from residual volume and to perform a maximal exhalation from total lung capacity against a closed shutter, respectively. They are also recommended for follow-up of respiratory strength. A MIP > 35% of the baseline or a MIP < −80 cmH_2O and a MEP > 60–90 cmH_2O indicate an effective cough and excludes significant muscle weakness [9].

Both LIC and MIC are measured on exhalation, on the maximum, tolerable, externally assisted insufflation capacity. LIC does not involve the patient holding their breath, in opposite to MIC that is dependent on the patient being able to hold their breath. The "lower value" of the LIC or MIC is residual volume (RV) as per VC. The "upper value" of LIC is assisted inspiration, which may be provided using a bag valve mask, NIV in volume preset ventilator mode, the inflation component of mechanical insufflation-exsufflation (MI-E), an MI-E device or intermittent positive pressure breathing (IPPB). The "upper value" of a MIC is assisted inspiration, which may be provided using glossopharyngeal breathing (GPB), a bag valve mask with or without a one-way valve or a NIV device in a volume mode. The technique of MIC generation is also delivered by volume device and is usually not pressure limited or limited to a pressure of 40 cmH_2O.

9.4 Management of Airway Clearance

A recent consensus has divided airway clearance techniques (ACTs) in proximal and peripheral [8], so that is the terminology that we will use from now on.

Management of airway clearance begins, by far, with respiratory physiotherapy, and it can be applied in all the phases of cough. There is controversial data about if chest physiotherapy can strengthen and improve the endurance of respiratory muscles with specific training programs, but some authors rely upon the usage of the sitting position, in both resistive breathing manoeuvres and maximal static inspiratory efforts against an almost occluded resistance to improve strength and endurance [6, 10]. A recent study shows that even exercise among mucus producer patients could improve cough [11]. Among neuromuscular patients, there is some benefit in cough by promoting yoga exercises. However, MIP and MEP do not improve.

Proximal ACTs aim to augment the cough, assisting expiration, inspiration or both. They could support and imitate the cough, by clearing mucus from the larger airways.

On the assisted expiration, these techniques aim to help the expiratory muscles that are incapable of generating enough increases in intra-abdominal and intrathoracic pressure and increasing the expiratory flow generated during the expiratory phase of cough. This way, there is the manually assisted cough (MAC), using either or a combination of a manual Heimlich/abdominal thrust manoeuvre and manual costo-phrenic compression to increase expiratory airflow. Also, the expiratory assistance could be attained by a self-induced lunge to the abdomen or chest from a standing object such as a table [12]. Exsufflation alone could be performed using an MI-E device by delivering negative pressure (on exsufflation) alone by a full-face mask or catheter mount attached to an artificial airway. This method also aims to increase expiratory airflow during the expiratory phase of cough [13].

The assisted inspiration is usually used before coughing and is usually used in weak patients with NMD. The assisted inspiration, by augmentation of inspiratory lung volumes, is associated with increased PCF. These techniques are relatively cheap methods of cough increasing. Assisted inspiration may be either a single or stacked breath inspirations. A single breath-assisted inspiration is where a bag valve mask increases the patient's inspiratory VC, NIV (in a preset of pressure or volume mode) or IPPB device with a single breath by an oronasal mask or mouthpiece. This technique aims to reach LIC. The patient gives a long deep breath in by the chosen device and then instructed to cough autonomously or with MAC. On the other hand, in stacked breath-assisted inspiration, the patient performs repeated inspirations without breathing out until they reach their MIC. There are various techniques used, including GPB, air stacking (AS) by a bag valve mask or a lung volume recruitment circuit (which has a one-way valve to restrict exhalation) or a preset volume-cycled ventilator. GPB is also known as self-air stacking or frog breathing, in which the patient increases inspiratory capacity by consecutive inhalations using the mouth, tongue, pharynx and larynx in order to offset the weakness of the inspiratory muscles. AS augmented inspiratory capacity by providing a set of breaths in, without the patient breathing out. Either the patient is instructed to take a deep breath in first, and then the inspiratory capacity is increased by a sequence of breaths in without the patient breathing out, or the patient is passively provided with a series of breaths without breathing out. After the patient reaches close to their total lung capacity, the patient is instructed to cough unassisted or with a MAC [14]. However, lung volume recruitment acutely increases respiratory system compliance in patients with severe respiratory muscle weakness; the high airway pressures during inflations cause reductions in the mean arterial pressure that should be considered when used [15].

The assisted inspiration (one or multiple breaths) combined with MAC is an advantageous way to assist both inspiration and expiration. There is a very cheap and common combination in clinical practice.

Mechanical insufflation-exsufflation (MI-E) devices work by providing a profound inspiration to the lungs (insufflation) and, after 10 ms, a deep expiration (exsufflation), using sequentially positive and negative pressure by a full-face mask or catheter mount attached to an artificial airway. These techniques simulate the usual cough, by rapidly switching from positive to negative pressures, potentially assisting secretion clearance. For instance, MI-E works both for weak inspiratory and expiratory capacities [16, 17]. The usual set-up pressures are titrating up from ±15 to ±40 cmH_2O, but it should be personalised to each patient, as should be the inspiratory, expiratory and pause times (s) and the inspiratory flow rate (L/min) [3, 7, 16]. In the paediatric settings, the clinical use varied greatly and is altered with age, highlighting the need for more studies to improve our knowledge of optimal settings of MI-E in children with NMD [10, 18]. In Table 9.2 the recommendations to use MI-E are summarised.

Table 9.2 Recommendations to use mechanical insufflation-exsufflation device

Adult recommendations	Paediatric recommendations
SCI, if more straightforward techniques fail to produce an adequate result	Fragile children
Bulbar patients who are unable to do AS	Bulbar insufficiency
Patients who remain unable to increase PCF to an adequate level with other ACT or where cough remains ineffective with MI-E alone, it should be combined with a MAC	Uncooperative with MAC or AS or in whom these methods are not effective
Available in the acute setting in all hospitals as an alternative method of ACT, preventing deterioration and the need for intubation and mechanical ventilation	

SCI spinal cord injury, *AS* air stacking, *PCF* peak cough flow, *MI-E* mechanical insufflation-exsufflation, *MAC* manual air clearance, *ACT* airway clearance techniques

A recent study using direct visualisation of the upper airway during MI-E by flexible laryngoscopy showed that all patients, despite the type of disease onset, developed laryngeal collapse during assisted inhalation. They are occurring even before the onset of other bulbar symptoms in many patients. Importantly, the research also demonstrated that individually adjusted pressure settings seemed to minimise these futile efforts during mechanically assisted cough and may extend successful use of this technique [5]. Also, flexible laryngoscopy can be an efficient tool in selected patients who do not respond as expected [19].

Peripheral airway clearance techniques' main objective is to improve ventilation, by clearing secretions and enhancing mucus transport from the peripheral airways to the central airways and creating higher expiratory than inspiratory airflows. As we know, patients with NMD do not have excessive lung secretion production (sputum) because the lung parenchyma, respiratory mucosa, mucociliary function and mucus rheology are not commonly affected. However, because of bulbar muscle dysfunction, the patients could have difficulty swallowing, hypersecretion and pooling of oral secretions. In these cases, the techniques mostly used are manual techniques, high-frequency chest wall oscillations (HFCWO) or compression (HFCWC), intrapulmonary percussive ventilation (IPV) and chest wall strapping (CWS). These peripheral ACTs do not require patient cooperation, and its use is possible in any age from infants to elderly, even in the presence of a tracheostomy or bulbar failure or intellectual impairment.

The use of manual techniques consists of chest percussion, vibrations or shaking; can be performed using a hand, fingers or facemask; and is generally well tolerated and widely used in uncooperative patients, such as babies or small children. This technique consists of applying rapid extra-thoracic force at the beginning of expiration, followed by compressions until the end of expiration [12].

Peripheral airway clearance can also be done through instrumental techniques, like high-frequency chest wall oscillations (HFCWO) or high-frequency chest wall compression (HFCWC). The first one provides compression of the chest wall at frequencies that are close to the resonant frequency of the lungs, between 5 and 20 Hz, by a negative pressure ventilator attached to a jacket. The negative pressure causes the air to get into the lungs, followed, when the pressure ceases, by a breath out. The usual set-up starts with a frequency of 5 Hz titrating up to 10–15 Hz. Treatments are individualised or based on manufactures preset programs, but often the patients need a 5-min staged treatment or until the patient needed to cough. The second one, HFCWC, also gives compression of the chest wall at frequencies that are close to the resonant frequency of the lung but with intermittent positive airflow by an air pulse generator through a jacket. The jacket expands compressing the chest wall and produces a transient/oscillatory increase in airflow mobilising secretions from the peripheral airways toward the mouth. These devices could work concomitantly with NIV-supported breathing.

High-frequency oscillatory ventilation in ALS patients has been shown to reduce breathlessness and stabilise forced vital capacity (FVC) in patients who had FVC of 40–70% predicted. In patients with NMD, the total medical costs, hospitalisation and pneumonia after high-frequency oscillatory ventilation were reduced [20].

An IPPB pneumatic device delivers intrapulmonary percussive ventilation (IPV). IPV gives air into the lungs at frequencies of 100–300 cycles per minute at peak pressures from 10 to 40 cmH_2O, giving a high-frequency burst of gas on top of the patient's respiration, creating a global effect of internal percussion of the lungs, which promotes clearance from the peripheral airways. Some studies report that IPV improves airway clearance and lung function in patients with NMD. Among paediatric patients, there is a study suggesting that airway clearance by IPV therapy could be more effective and beneficial in specific subsets of the paediatric population. Suggesting its use over a 1-year period was superior to high-frequency chest wall oscillation therapy in providing airway clearance in patients with NMD and chronic respiratory disease [21].

CWS is used through the application of elastic material around the thorax reducing the restriction of the chest wall, without using expiratory muscles, lowering the functional residual capacity and benefitting lung secretion clearance.

Recently a robot, using a belt-driven that surveys muscle tension and mimics the contraction of the abdominal muscles, has been proposed in patients with NMD, with a 1.59 times improvement in exhalation and inhalation and 1.52 times better coughing ability [22].

Some other devices can be used to mobilise secretions; however, positive expiratory pressure (PEP) and oscillatory PEP devices in patients with NMD generally cannot generate enough expiratory flow for the technique to be effective, and therefore, these devices for patients with NMD are not currently recommended [8].

A flowchart depicting the ACT management is presented in figure 9.1.

9.5 Newer Airway Clearance Techniques

Small studies talk about newer airway clearance techniques, one through vigorous capsaicin-induced reflex coughs that can achieve movement of secretions from the lungs into the oropharynx, allowing the patient to spit out or have secretions cleared by suctioning from the oropharynx, thus avoiding the need for suction catheter penetration to the trachea. It is hypothesised that capsaicin-induced reflex cough could be used as a treatment for acute secretion retention in self-ventilating, non-intubated and non-tracheotomised patients [23].

Another case report talks about Free Aspire, which is an electromedical machine for removing bronchoalveolar secretions. The case shows that Free Aspire in patients with ineffective cough and impaired removal of secretions is a safe and effective device for the removal of bronchial secretions and could be another help in the management of airway clearance [24].

9.6 Key Major Practical and Clinical Recommendations

- Airway clearance techniques should be initiated with PCF < 270.
- Mechanical I-E should be initiated with PCF < 160**,**
- MI-E is the choice of treatment for the weaker group of patients with NMD.
- In MI-E, the settings like inspiratory and expiratory timing/pressures should be individualised with progressive titrating up of pressure until efficacy is achieved, with higher expiratory than inspiratory pressures being advisable.
- Manual techniques can be considered as a treatment option.
- Peripheral ACT should be initiated before and after clearing any secretions from the upper airway with proximal ACT.
- Almost all peripheral ACTs do not require physical or intellectual patient cooperation.
- Infants, children, adults and even in the presence of a tracheostomy and/or bulbar failure are candidates to peripheral ACT.
- In the ventilatory-dependent patient, peripheral ACT should be used in combination with ventilator support.
- Some newer techniques such as capsaicin, CWS and belt-driven are promising and worth evaluating under clinical trial.

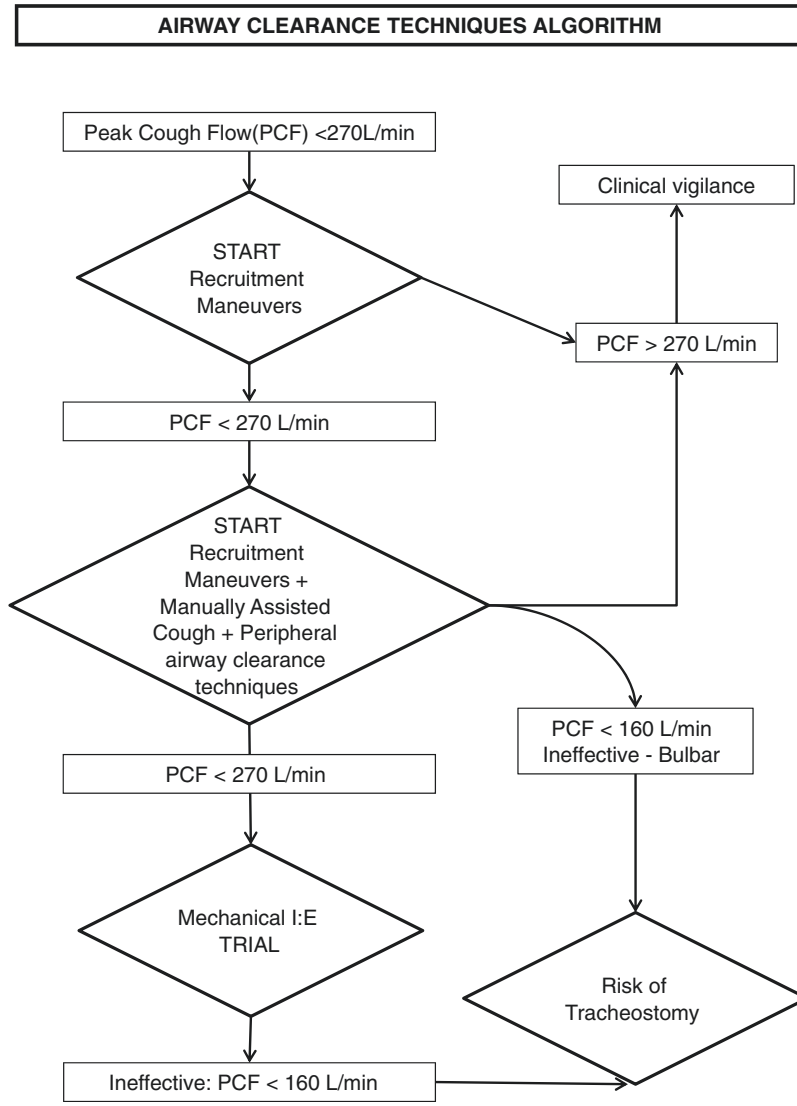

Fig. 9.1 Airway Clearance Techniques Algorithm

References

1. Rajendran RR, Banerjee A. Mucus transport and distribution by steady expiration in an idealized airway geometry. Med Eng Phys. 2019;66:26–39. https://doi.org/10.1016/j.medengphy.2019.02.006.
2. Bustamante-Marin XM, Ostrowski LE. Cilia and mucociliary clearance. Cold Spring Harb Perspect Biol. 2017;9(4):a028241. https://doi.org/10.1101/cshperspect.a028241.
3. Sahni AS, Wolfe L. Respiratory care in neuromuscular diseases. Respir Care. 2018;63(5):601–8. https://doi.org/10.4187/respcare.06210.
4. Rose L, McKim D, Leasa D, et al. Monitoring cough effectiveness and use of airway clearance strategies: a Canadian and UK survey. Respir Care. 2018;63(12):1506–13. https://doi.org/10.4187/respcare.06321.
5. Andersen TM, Sandnes A, Fondenes O, et al. Laryngeal responses to mechanically assisted cough in progressing amyotrophic lateral sclerosis. Respir Care. 2018;63(5):538–49. https://doi.org/10.4187/respcare.05924.
6. Bach JR. Noninvasive respiratory management of patients with neuromuscular disease. Ann Rehabil Med. 2017;41(4):519–38. https://doi.org/10.5535/arm.2017.41.4.519.
7. Sheers N, Howard ME, Berlowitz DJ. Respiratory adjuncts to NIV in neuromuscular disease. Respirology. 2019;24:512–20. https://doi.org/10.1111/resp.13431.
8. Chatwin M, Toussaint M, Gonçalves MR, et al. Airway clearance techniques in neuromuscular disorders: a

state of the art review. Respir Med. 2018;136:98–110. https://doi.org/10.1016/j.rmed.2018.01.012.
9. Camela F, Gallucci M, Ricci G. Cough and airway clearance in Duchenne muscular dystrophy. Paediatric Respiratory Reviews. 2019;31:35–9. http://doi.org/10.1016/j.prrv.2018.11.001.
10. Siriwat R, Deerojanawong J, Sritippayawan S, Hantragool S, Cheanprapai P. Mechanical insufflation-exsufflation versus conventional chest physiotherapy in children with cerebral palsy. Respir Care. 2017;63(2):187–93. https://doi.org/10.4187/respcare.05663.
11. Dwyer TJ, Daviskas E, Zainuldin R, et al. Effects of exercise and airway clearance (PEP) on mucus clearance in cystic fibrosis: a randomised cross-over trial. Eur Respir J. 2019;53:1801793. https://doi.org/10.1183/13993003.01793-2018.
12. Cabillic M, Gouilly P, Reychler G. Techniques manuelles de drainage bronchique des adultes et adolescents : quel niveau de preuve ? Rev Mal Respir. 2018;35(5):495–520. https://doi.org/10.1016/j.rmr.2015.12.004.
13. Gaynor M, Wood J. Mechanical insufflation-exsufflation for airway clearance in adults with cystic fibrosis. Respirol Case Rep. 2018;6(4):1–3. https://doi.org/10.1002/rcr2.307.
14. Sarmento A, Resqueti VR, Dourado-Júnior MET, Aliverti A, Fregonezi G, de Andrade AD. Effects of air stacking maneuver on cough peak flow and chest wall compartmental volumes of amyotrophic lateral sclerosis subjects. Eur Respir J. 2017;50:PA2224. https://doi.org/10.1183/1393003.congress-2017.PA2224.
15. Molgat-Seon Y, Hannan LM, Dominelli PB, et al. Lung volume recruitment acutely increases respiratory system compliance in individuals with severe respiratory muscle weakness. ERJ Open Res. 2017;3(1):00135–2016. https://doi.org/10.1183/23120541.00135-2016.
16. Auger C, Hernando V, Galmiche H. Use of mechanical insufflation-exsufflation devices for airway clearance in subjects with neuromuscular disease. Respir Care. 2017;62(2):236–45. https://doi.org/10.4187/respcare.04877.
17. Cesareo A, LoMauro A, Santi M, Biffi E, D'Angelo MG, Aliverti A. Acute effects of mechanical insufflation-exsufflation on the breathing pattern in stable subjects with Duchenne muscular dystrophy. Respir Care. 2018;63(8):955–65. https://doi.org/10.4187/respcare.05895.
18. Hov B, Andersen T, Hovland V, Toussaint M. The clinical use of mechanical insufflation-exsufflation in children with neuromuscular disorders in Europe. Paediatr Respir Rev. 2018;27:69–73. https://doi.org/10.1016/j.prrv.2017.08.003.
19. Esquinas AM, Fiorentino G. Considerations about the effect of cough assist on laryngeal function in neurologic disease. Respir Care. 2018;63(11):1459.1–1459. https://doi.org/10.4187/respcare.06547.
20. Sahni AS, Wolfe L. Respiratory care in neuromuscular diseases. Respir Care. 2018;63(5):601. https://doi.org/10.4187/respcare.06210.
21. Bidiwala A, Volpe L, Halaby C, Fazzari M, Valsamis C, Pirzada M. A comparison of high frequency chest wall oscillation and intrapulmonary percussive ventilation for airway clearance in pediatric patients with tracheostomy. Postgrad Med. 2017;129(2):276–82. https://doi.org/10.1080/00325481.2017.1264854.
22. Lee S-Y, Cho K-J. A study on the cough augmentation using a belt-driven assistive. In: 2017 International Conference on Rehabilitation Robotics (ICORR), vol. 2017. IEEE 2017. p. 1654–9. https://doi.org/10.1109/ICORR.2017.8009485.
23. Kulnik ST. Could reflex cough induced through nebulized capsaicin achieve airway clearance in patients with acute retention of lung secretions? Med Hypotheses. 2018;119:104–9. https://doi.org/10.1016/j.mehy.2018.08.004.
24. Bertelli L, Di Nardo G, Cazzato S, Ricci G, Pession A. Free-Aspire: a new device for the management of airways clearance in patient with ineffective cough. Pediatr Rep. 2017;9(3):7270. https://doi.org/10.4081/pr.2017.7270.

10 High-Flow Nasal Cannula Oxygen Therapy in Patients with Chronic Respiratory Disease

Miyuki Okuda, Yuto Kido, Yuto Kato, and Nobuya Tanaka

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Abbreviations

AHI	Apnea-hypopnea index
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
FiO_2	Fraction of inspired oxygen
HFNC	High-flow nasal cannula
NPPV	Noninvasive positive pressure ventilation
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PEEP	Positive end-expiratory pressure
PSG	Polysomnography
SpO_2	Peripheral capillary oxygen saturation
QOL	Quality of life

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10.1 Introduction

The high-flow nasal cannula (HFNC) is an oxygen therapy system that delivers suitably heated and humidified oxygen using a special nasal cannula capable of high flow of up to 60 L/min. The interface is even less invasive than noninvasive positive pressure ventilation (NPPV); therefore, it has great potential for use in a variety of conditions, and its efficacy has already been reported for patients with type I acute respiratory failure in a large-scale randomized controlled trial [1]. With regard to

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respiratory physiology, this system also has various advantages in that it is possible to administer a certain oxygen concentration by delivering an oxygen flow volume that is equal to or greater than the patient's tidal volume. This reduces the dead space by expelling expired gas that has accumulated in the anatomical dead space of the nasopharynx and improves the mucociliary movement in the respiratory tract [2, 3]. Delivering high-flow oxygen increases the airway pressure and alveolar pressure, which is reported to create a positive end-expiratory pressure (PEEP)-like effect [4–6]. There are also a large number of reports of the efficacy of HFNC therapy for avoiding intubation and for respiratory management after extubation and after cardiac surgery [6–8].

HFNC therapy with the NPPV/continuous positive airway pressure (CPAP) device creates high oxygen flow using a similar blower to that of a dedicated HFNC device. However, unlike a dedicated HFNC device, this device can also be used for NPPV/CPAP with the same circuit by simply changing the device to a nasal mask. Recent reports have demonstrated that the use of home-based HFNCs improves the quality of life (QOL) and reduces the acute exacerbation rate in chronic obstructive pulmonary disease (COPD) patients with hypercapnia [9, 10], and it is also possible to perform NPPV at home with HFNCs using an NPPV/CPAP machine. Furthermore, a variety of nasal cannulas can be used, as different machines do not require specific nasal cannulas. Thus, there are various advantages to this method.

This chapter will describe the principles and administration of HFNC therapy with pressure control using the NPPV/CPAP device.

10.2 Principles

According to the law of conservation of mass, when fluid is flowing through the tube, the flow rate Q, density ρ, cross-sectional area S, and velocity v are:

$$Q = \rho S_1 v_1 = \rho S_2 v_2 \qquad (10.1)$$

(continuity equation)

Then, according to the law of the conservation of energy, the relation of:

$$P_1 + \rho gh + \frac{1}{2}\rho v_1^2 = P_2 + \rho gh + \frac{1}{2}\rho v_2^2 \quad (10.2)$$

is established for pressure P, height h, and gravitational acceleration g (theorem of Bernoulli).

Substituting Eq. (10.1) into Eq. (10.2) becomes:

$$Q = \sqrt{2\rho\left(P_1 - P_2\right)} \cdot \frac{S_1 \cdot S_2}{\sqrt{S_1^2 - S_2^2}} \qquad (10.3)$$

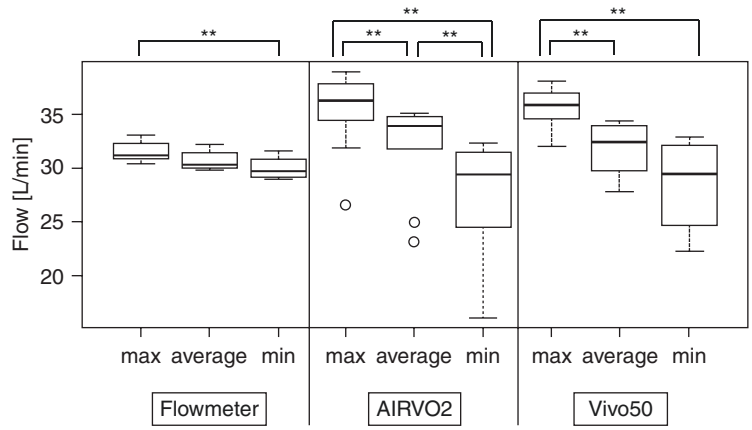
Therefore, the flow rate Q is determined by $P_1 - P_2$ (pressure gradient ΔP) and cross-sectional area S_1, S_2. If S_1 is the circuit diameter and S_2 is the cannula diameter and if the pressure is maintained at a constant rate using the same circuit and cannula, then the flow rate would also be constant [11].

Using these principles, machines that create constant flow using functions to control pressure at a constant level, such as CPAP, are pressure control devices.

10.3 Comparison of Flow Control Between Blower Systems

There is no significant difference in the change in flow rate with pressure control and flow control if the same blower system is used (submitted) (Fig. 10.1).

We previously investigated the insufflation flow rate during quiet breathing with a flowmeter-type device (flowmeter; PMB-7000 (Pacific Medico, Tokyo, Japan)) and two blower systems (flow control type, AIRVO 2 [Fisher & Paykel, New Zealand]; pressure control type, Vivo 50 [NPPV device, Breas AB—Sweden]). The flow rate was significantly more stable when the flowmeter type was used than when the blower system was used. With the blower system, the flow rate increased during inspiration and decreased during expiration with both the flow control type and the pressure control type (Fig. 10.1).



	Max flow (L/min)	Average flow (L/min)	Min flow (L/min)
Flowmeter (constant flow)	31.47±0.91	30.72±0.83	29.92±0.91
AIRVO2 (constant flow)	35.34±3.56	31.92±4.12	27.64±4.88
Vivo50 (constant pressure)	36.54±1.85	31.89±2.31	28.46±3.71

Fig. 10.1 Comparison of the flow rate between constant flow and constant pressure

There was no significant difference in flow fluctuation between the two blower system groups, so it is presumed that HFNC therapy using Vivo 50, which was originally an NPPV device, can deliver the same flow rate as that of HFNC using AIRVO 2, a dedicated blower system HFNC device (paper submitted).

We also investigated the physiological effect (tidal volume, transcutaneous partial pressure of carbon dioxide ($PaCO_2$), respiration rate, and inspiration/expiration esophageal pressure) of the pressure control-type HFNC using Vivo 50 (NPPV device) and the flow control type using AIRVO 2 and steady air (Atom Medical, Tokyo) in healthy individuals. The tidal volume increased, the transcutaneous $PaCO_2$ and respiration rate decreased, and the inspiration esophageal pressure decreased with the use of all devices. There were no significant differences in any investigated items [12].

Thus, it is also considered possible to implement a blower system HFNC using functions to control pressure at a constant level, such as CPAP (Fig. 10.2).

10.4 Usable Flow Generators

In principle, devices equipped with a mode to control pressure at a constant level, such as CPAP/NPPV, could be used as a pressure control-type device.

10.4.1 Ventilation Mode

CPAP mode should be selected. However, the spontaneous-timed (S/T) mode and bi-level nasal positive pressure (BiPAP) mode may be compatible in models in which the low respiration rate alarm cannot be switched off.

When using the S/T mode and BiPAP mode, the pressure should be set to that of the inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). With this setting, the circuit pressure is constant, but forced ventilation is performed by switching between IPAP and EPAP. Forced ventilation is regarded as the respiration rate, so this can prevent sounding of the low respiration rate alarm.

	AIRVO 2 Constant flow	Steady air Constant flow	Vivo 50 Constant pressure	*P*-values
Difference Tidal volume (ml)	221.40 ± 263.92	257.30 ± 315.06	244.24 ± 268.63	P>0.99
Difference $PtcCO_2$(mmHg)	-0.50 ± 2.37	-0.30 ± 1.06	-0.60 ± 2.32	P>0.05
Difference RR (bpm)	-3.26 ± 2.14	-3.17 ± 4.93	-4.18 ± 2.68	P>079
Difference IEP (cmH_2O)	-3.18 ± 4.70	-2.04 ± 1.74	-1.77 ± 2.56	P>0.85
Difference EEP (cmH_2O)	-0.51 ± 2.80	0.71 ± 2.34	1.02 ± 3.99	P>0.92

transcutaneous PCO_2 ; $PtcCO_2$, Respiratory Rate ; RR , End-inspiratory esophageal pressure ; EIEP , End-expiratory esophageal pressure ; EEEP
Okuda M, Tanaka N, Naito K, Kumada T, Fukuda K, Kato Y, Kido Y, Okuda Y, Nohara R.BMJ Open Respir Res. 2017 Jul

Fig. 10.2 Evaluation by various methods of the physiological mechanism of a high-flow nasal cannula (HFNC) in healthy volunteers. *PtcCO*$_2$ transcutaneous PCO_2, *RR* respiratory rate, *EIEP* end-inspiratory esophageal pressure, *EEEP* end-expiratory esophageal pressure [12]

10.4.2 Flow Rate Adjustment

The flow rate taken from Eq. (10.3), described in the Principles section, is proportional to the square root of the pressure gradient ΔP. If the CPAP is increased, the flow rate increases, while if the CPAP is reduced, the flow rate decreases. This principle is used to adjust the CPAP and generate the desired flow rate.

Artificial ventilators are equipped with flow sensors, which measure the flow rate. When using artificial ventilators as HFNCs, leaks may be regarded as the flow rate. Confirm the leak (flow rate) after fitting the cannula and adjust the CPAP as needed.

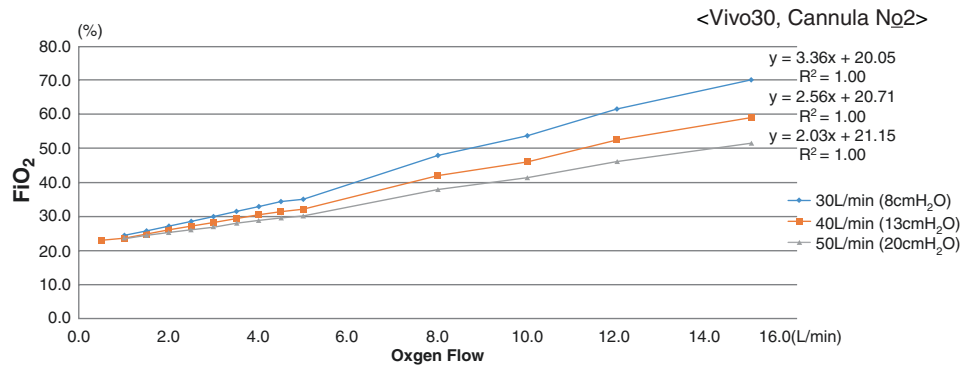
10.4.3 Oxygen Concentration Adjustment

The required oxygen concentration differs among patients. Adjust the fraction of inspired oxygen (FiO_2) after setting the flow rate to accommodate mixed gas leakage during inspiration. Adjust the oxygen saturation to 94–98% for type I respiratory failure and to 88–92% for type II respiratory failure.

With pressure control-type devices (particularly those that do not display the oxygen concentration), it is essential to use a conversion table and calculate the FiO_2, which makes the use of such devices slightly complicated. However, in reality, checking that the patient's oxygen saturation is reaching the indicated amount is more important than the FiO_2 that was set when starting HFNC therapy for the patient.

10.5 Case Report

We previously reported the efficacy of HFNC therapy with an NPPV device for the treatment of a COPD patient with sleep-related hypoventilation [13, 14]. The patient was a 73-year-old woman, who was being treated by her local doctor for dementia and insomnia caused by hypertension, depression, and subarachnoid hemorrhage sequelae. The patient's level of consciousness declined after developing cold-like symptoms, and she was therefore admitted for detailed examination and treatment. She was found to have marked hypoxemia and hypercapnia on blood gas analysis at admission (pH 7.32, $PaCO_2$ 84 mmHg, partial pressure of oxygen



Airflow (CPAP pressure)	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	8.0	10.0	12.0	15.0	O_2 (L/min)
30L/min (8cmH_2O)	23.1	24.4	25.7	27.2	28.5	30.0	31.5	32.9	34.3	35.1	48.0	53.6	61.5	70.0	
40L/min (13cmH_2O)	22.9	23.8	24.9	26.1	27.1	28.2	29.3	30.4	31.5	32.1	42.0	46.2	52.4	59.0	
50L/min (20cmH_2O)	22.8	23.6	24.5	25.4	26.2	27.1	28.0	28.9	29.7	30.2	37.9	41.4	46.2	51.5	

Fig. 10.3 Relationship between FiO_2 and oxygen flow [13]

[PaO_2] 37 mmHg, nasal oxygen 2 L/min); therefore, NPPV was started with reference to the NPPV guideline as respiratory management for type II respiratory failure.

The hypercapnia gradually improved, but the restlessness and delirium associated with dementia worsened as the patient's consciousness level improved, which made mask management impossible. Therefore, HFNC therapy using NPPV (Vivo 50 Breas AB—Sweden) was started (CPAP 8 cmH_2O, oxygen 5 L/min, oxygen flow rate 30 L/min, oxygen concentration 35%). Thereafter, hypoxemia improved with no recurrence of CO_2 narcosis (pH 7.47, PaO_2 57 mmHg, $PaCO_2$ 62 mmHg). Figure 10.3 illustrates the relationship between the additional oxygen flow rate and the FiO_2 in the HFNC we used for this patient. When CPAP was set to 8 cmH_2O using cannula No. 2 (Pacific Medico, Tokyo), the flow rate was 30 L/min. When 1 L/min oxygen is added, the FiO_2 was 24.4%, which achieved an equivalent effect to that of the high flow rate system using a 24% Venturi mask. When 2.5 L/min oxygen is added, the FiO_2 was 28.5%, which is an equivalent effect to that of a 28% Venturi mask. In this manner, the HFNC has the advantage of delivering low-concentration oxygen at a constant rate rather than administering high-concentration oxygen, which makes it a superior oxygen administration system for patients with type II respiratory failure. In addition, changing the CPAP pressure to 8, 13, and 20 cmH_2O can increase the oxygen flow rate to 30, 40, and 50 L/min, respectively. Therefore, unlike the Venturi mask, the HFNC can also be used to treat patients with high respiratory rates, such as patients with interstitial pneumonia. When such patients use this device, it is important to understand that increasing the CPAP pressure will decrease the FiO_2 with the same amount of added oxygen.

Thereafter, we conducted a polysomnography (PSG) test to assess the presence of sleep-related alveolar hypoventilation complications. As a result, the patient was found to experience 12.1 sleep-related hypoventilation events per hour according to the apnea-hypopnea index (AHI). When we conducted the PSG test again when the patient was using an HFNC, there was marked improvement in sleep-related hypoventilation; her AHI score was 3.7 events/h, mean SpO_2 had increased from 89 to 93%, the percentage time at $SpO_2 \leq 90\%$ had decreased dramatically from 30.8 to 2.5%, and the previously completely absent deep sleep (sleep stage 4) was detected for 38.5 min. HFNC therapy enabled appropriate supply of high-flow nasal oxygen, which also improved the sleep-related hypoventilation. It is reported that HFNCs are

also effective for obstructive apnea syndrome [15]. Sleep-related hypoxemia increases pulmonary arterial pressure, which is an aggravating factor for right-sided heart failure, and can also cause arrhythmia and polycythemia, thereby increasing the mortality rate of such patients [16]. Home-based NPPV would normally be indicated for cases with a $PaCO_2$ of ≥55 mmHg, persistent nighttime hypoventilation, and cor pulmonale, as observed in this patient, but there was no exacerbation of pulmonary hypertension even with continued HFNC therapy. If oxygen is simply administered to a patient with sleep-related hypoxemia without considering the complication of sleep-related hypoventilation, marked hypercapnia can occur. Therefore, HFNC therapy, which can deliver constant oxygen, is extremely effective. HFNC therapy during sleep also reduces respiratory effort, thereby improving sleep quality and respiratory muscle fatigue, and can also reduce daytime $PaCO_2$ by resetting the CO_2 adjustment. That is, continuously using HFNCs at home during nighttime sleeping in the same manner as NPPV can be expected to improve chronic type II respiratory failure. HFNC therapy using the NPPV device does not adopt the Venturi system, which makes it a quiet system that can be easily used at home. Even in cases such as the current patient, who had severe dementia, HFNC therapy has been used continuously and safely in the home for a long period of time (3 years and 8 months), with the cooperation of visiting nurses and doctors.

10.6 Conclusion

It is highly likely that HFNC therapy using NPPV/CPAP devices can deliver high-flow oxygen therapy similar to that of dedicated HFNC devices. This method would enable HFNC therapy to be implemented using the same circuit as the intubation respirator/NPPV used during the acute phase of treatment, which could contribute to reducing the cost of medical treatment. Furthermore, as these devices are blower systems, they can be used at home.

Key Major Practical and Clinical Recommendations

- HFNC therapy is useful for patients with chronic respiratory disease.
- HFNC therapy using NPPV/CPAP devices can deliver high-flow oxygen therapy similar to that of dedicated HFNC devices.
- HFNC therapy using NPPV/CPAP devices reduce the cost.

References

1. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372:2185–96.
2. Hasani A, Chapman TH, McCool D, et al. Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis. Chron Respir Dis. 2008;5:81–6.
3. Kernick J, Magarey J. What is the evidence for the use of high flow nasal cannula oxygen in adult patients admitted to critical care units? A systematic review. Aust Crit Care. 2010;23:53–70.
4. Ritchie JE, Williams AB, Gerard C, et al. Evaluation of a humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures. Anaesth Intensive Care. 2011;39:1103–10.
5. Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. Br J Anaesth. 2009;103:886–90.
6. Corley A, Caruana LR, Barnett AG, et al. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth. 2011;107:998–1004.
7. Roca O, Riera J, Torres F, et al. High-flow oxygen therapy in acute respiratory failure. Respir Care. 2010;55:408–13.
8. Parke RL, McGuinness SP, Eccleston ML. A preliminary randomized controlled trial to assess effectiveness of nasal high-flow oxygen in intensive care patients. Respir Care. 2011;56:265–70.
9. Nagata K, Kikuchi T, Horie T, et al. Domiciliary high-flow nasal cannula oxygen therapy for patients with stable hypercapnic chronic obstructive pulmonary disease. A multicenter randomized crossover trial. Ann Am Thorac Soc. 2018;15:432–9.
10. Storgaard LH, Hockey HU, Laursen BS, et al. Long-term effects of oxygen-enriched high-flow nasal cannula treatment in COPD patients with chronic hypoxemic respiratory failure. Int J Chron Obstruct Pulmon Dis. 2018;13:1195–205.

11. Shah VK, Enderle JD. Computer modeling and functional evaluation of Venturi flow generators for use in ventilators. Biomed Sci Instrum. 1991;27:313–20.
12. Okuda M, Tanaka N, Naito K, et al. Evaluation by various methods of the physiological mechanism of a high-flow nasal cannula (HFNC) in healthy volunteers. BMJ Open Respir Res. 2017;4:e000200.
13. Okuda M, Kashio M, Tanaka N, et al. Nasal high-flow oxygen therapy system for improving sleep-related hypoventilation in chronic obstructive pulmonary disease: a case report. J Med Case Reports. 2014; 8:341.
14. Okuda M, Tanaka N, Fukuda K, et al. The high-flow system manual made by multidisciplinary team. J Jpn Soc Respir Care Rehabil. 2018;27: 146–52.
15. McGinley BM, Patil SP, Kirkness JP, et al. A nasal cannula can be used to treat obstructive sleep apnea. Am J Respir Crit Care Med. 2007;176: 194–200.
16. Austin MA, Wills KE, Blizzard L, et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. BMJ. 2010;341:c5462.

What About Patient-Ventilator Interactions During Noninvasive Mechanical Ventilation?

11

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Abbreviations

AHI	Apnoea-hypopnoea index
ALS	Amyotrophic lateral sclerosis
ARF	Acute respiratory failure
BIS	Built-in software
COPD	Chronic obstructive pulmonary disease
CRF	Chronic hypercapnic respiratory failure
EMG	Electromyography
EPAP	Expiratory positive airway pressure
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
NIV	Noninvasive ventilation
NMD	Neuromuscular disease
OHS	Obesity hypoventilation syndrome
OSA	Obstruction sleep apnoea
PG	Respiratory polygraphy
PSG	Polysomnography
PVA	Patient-ventilatory asynchrony
UA	Upper airway

11.1 Introduction

Noninvasive ventilation (NIV) is frequently utilised in the treatment of patients with acute respiratory failure (ARF) and chronic hypercapnic respiratory failure (CRF); NIV utility is well stabilised, so the number of patients provided with NIV devices has been steadily increasing all over the world [1]. Patient-ventilator synchrony during partial ventilatory support has constantly grown attention in the last time.

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Poor patient-ventilator synchrony increases the work of breathing and worsens patient comfort, which leaks also during NIV [2, 3]. Poor comfort causes NIV intolerance and describes one of the important determinants of NIV failure and endotracheal intubation, both in hypercapnic and hypoxaemic ARF [3].

Longhini et al., in a study performed in eight ICU in China, Italy and the Netherlands, showed that asynchrony detection is inversely associated to their prevalence, meaning that the chance for waveform view to correctly quantify asynchrony gets lower when their appearance grows. Reasonably, it might be that detection of asynchronies during NIV is extremely problematic irrespective of the level of expertise [3].

With the new built-in software (BIS), the performance of NIV can be monitored simpler at home, which can guarantee compliance and appropriate use. The progressive development of the technologies allowed to study patient ventilation interaction with the help of software and handy and portable instruments. The patient is more often monitored in addition to the hospital at home. This permits to detect anomalies and to modify and correct ventilator settings to optimise ventilation therapy. The technology holding the advancement of novel ventilatory modes for NIV of patients with chronic hypercapnia is continuously evolving. For example, in recent years, hybrid ventilation modes are born, as volume-targeted pressure-controlled ventilation, produced to mix the advantages of conventional ventilation modes, while bypassing their drawbacks [3]. The NIV has two particular aspects: the non-hermetic composition of the circuit and the evidence that the assembly of the respirator lung cannot be considered a single compartment model due to the presence of variable resistance characterised by the upper airways (UA) and all factors that come into action during a breath. When NIV is started, the ventilator settings are defined empirically based on clinical evaluation, daily blood gas variations and polysomnographic data [4]. Notwithstanding the knowledge of these data, however, the parameters for each subject may be different, also in similar clinical conditions and similar functional values. Recent researches have proved that variations in the values of parameters recorded by NIV devices may be associated with modifications in clinical status and severity of CRF [4, 5]. However, no direct evidence-based data are determining the best way of monitoring patient-ventilator interaction during NIV. Similarly, no trials are comparing various levels of monitoring, which could give us evidence-based arguments to apply in clinical practice. The monitoring of NIV is not an argument that could be simply systematised under the rigid evaluation of random control trials. Few studies are available concerning the monitoring of patient-ventilator interaction during NIV. Furthermore, the number of patients included in the studies is small and is affected by different illnesses [5–8].

11.2 Patient-Ventilator Interaction

Patient-ventilator asynchrony (PVA) can influence the efficacy and success of NIV. Tangible levels of asynchrony, defined as >10% of all patient's respiratory works, occur in >40% of patients [6]. PVA is a mismatch among the patient's respiratory neural pattern (respiratory frequency, initiation and termination of inspiration) and pressurisation delivered by the ventilator. Phase asynchronies, described by a mismatch between the start and the conclusion of the subject's and the ventilator's inspiratory time, are the prevalent type of asynchronies. They may happen at two periods: during inspiratory triggering, in conditions in which there is a mismatch between subject's inspiratory effort and ventilator triggering (ineffective inspiratory effort, double triggering or autotriggering), or while cycling from inspiration to expiration; when machine cycling does not accord with the conclusion of patient effort, this is premature cycling [7, 8].

The most common phenomenon is ineffective triggering (the ventilator does not recognise patient effort; may be secondary to high positive end-expiratory pressure intrinsic or inappropriate inspiratory trigger sensitivity). These are, after, autotriggering (delivery of preset pressure

in the absence of patient effort, described as the appearance of at least three rapid pressurisations at a respiratory rate of 40 breaths/min and higher than that of the patient's respiratory rate) and double triggering (two cycles divided by a short expiratory time, defined as less than one-half of the mean inspiratory time with the first cycle triggered by the patient) [7, 8]. Other types of asynchrony consist of late cycling (mechanical inspiratory time major than neural inspiratory time), premature cycling (mechanical inspiratory time minor than neural inspiratory time) and flow asynchrony (improper rate of pressurisation to inspiratory positive airway pressure (IPAP)) [8, 9].

A high quantity of PVA is correlated with decreased patient comfort and possibly tolerance to NIV. The number of asynchronies is often correlated with the significance of the leak and higher pressure support [10]. These situations may be due to leaks, upper airway instability, intrinsic positive end-expiratory pressure, devices or inappropriate ventilator settings. NIV proposes to improve quality of life and to reduce morbidity and mortality; however, residual respiratory events under NIV may negatively affect survival, sleep quality, gas exchange, tolerance and adherence to treatment and patients' symptoms. Consequently, in the follow-up of NIV patients, it appears appropriate to recognise these events to optimise ventilator perspectives. Many studies have explained that PVA frequently occurs during NIV in chronic and acute settings. Studies of PVA in CRF patients during sleep, however, are limited and report contrasting results [5, 6, 9, 11, 12].

Polysomnography remains the gold standard for monitoring NIV according to the AASM, but its availability is low in many European countries, and thus its systematic use is unrealistic in daily clinical practice. Aarrestad et al. quantified PVA and AHI by performing sleep polygraphy in 67 patients with different diseases [4]. They, also, examined data memorised by ventilator software, including both the prior 3 months and the night-time study; sleep polygraphy during NIV was performed using the following signals as recommended by the SomnoNIV group [10]: mask pressure, flow rate in the circuit measured by a pneumotachograph close to the mask, thoracic and abdominal movements with respiratory inductive plethysmography effort belts, body position, pulse oximetry and photoplethysmographic pulse wave amplitude. SpO_2 and $PtcCO_2$ monitored nocturnal blood gases. The study relates the reading of the polysomnographic recording with the analysis of waveforms derived from software. Two trained physicians scored traces. The study described that 21% of the subjects had PVA > 10% of complete registration time.

Borsini examined 50 patients with obesity hypoventilation syndrome (OHS), neuromuscular disease (NMD), overlapping syndrome of obstructive sleep apnoea and chronic obstructive pulmonary disease (OSA-COPD) monitored during NIV. They reported the analysis of respiratory polygraphy residual AHI 15.1 ± 10.6, which is conventionally interpreted as non-optimal titration. PVA > 20% of record time was observed in 12% of patients. The average leak (L/min) was 35.1 ± 13.7. There was no capnography in this investigation, a clear limitation at the time of determining effective ventilation. During NIV with leaks, transcutaneous capnography could be necessary, though it is costly and the signal drift frequently makes analysis difficult. The shortened number of patients and the heterogeneity of the population and NIV indications, however, do not allow comparisons [15].

Duiverman et al. found that in COPD, high-intensity NIV might provide optimal unloading of respiratory muscles, without undue increases in PVA; they showed that with high backup breathing frequencies fewer breaths were pressure supported (25% vs. 97%). PVA occurred more frequently with low-frequency settings [13]. This study considers that respiratory EMG (electromyography) being a direct parameter of the respiratory drive is better to represent patients' requests, instead of an indirect parameter such as respiratory movements by body plethysmography or flow estimations. They affirm that COPD patients on long-term NIV can adjust quickly to several settings of NIV, resulting in infrequent PVA. Importantly, this research

found that a high backup frequency does not promote the occurrence of PVA nor does it diminish patient satisfaction with the setting. The clinical significance of PVA in stable COPD patients on NIV, however, is dubious, as they occur in very low frequencies, and in this investigation, also in other reviews [14], gas exchange, patient comfort or overall respiratory drive was not affected. Therefore, there is no evidence that the occurrence of infrequent PVA is a reason to change settings. In individual cases, however, it is worthy of studying PVA, as this might influence ventilatory efficiency. The gold standard for measuring PVA is EMG, a record of the electrical activity of the diaphragm and pressure variations in the oesophagus, which requires complex devices and is invasive. EMG is however an invasive technology not available in all settings, which cannot be considered routinely a practical monitoring of patient-ventilator interaction.

The most reasonable method should be an analysis of the pressure and flow waveforms, with polysomnography and pulse oximetry. These techniques are minimally invasive and can be used routinely for PVA monitoring. Modern portable ventilators allow for online monitoring of pressure and flow waveforms, which make them an appropriate device of ventilation in a hospital setting. However, clinicians must be aware that observation of respiratory waveforms is not the ideal method of detecting asynchrony: the patient's effort may not change the flow-time or pressure-time curves, and other factors may influence them, e.g. airway secretions or cardiac oscillations [15]. In a study by Younes et al., 20% of ineffective efforts were not detected by waveform analysis [16]. We can, therefore, obtain data from the reading of the waveforms of the traces of the NIV and the data of the machine software. With current technology, patient's respiratory efforts are derived from thoracoabdominal tracings and changes in the flow and pressure curves [9, 10]. There are now portable machines with thoracoabdominal and pulse oximetry sensors.

Also using oxygen can contribute to the appearance of PVA; Puyol et al. demonstrated gas-induced asynchronies during NIV in a bench model. They examined trigger, effort and source of introduced gas (continuous versus pulsating flow compressor) through a breathing simulator connected to an external pneumotachograph. Ventilation periods were 1 min (gas-free, gas, gas-free). Asynchronies were induced by gas in 49% (81/165) of simulations. The autotrigger was the most prevalent (59/81), followed by ineffective effort (22/81). Pulsating flow induced more asynchronies than continuous gas [17].

Clinical conditions may additionally cause PVA: UA obstruction and respiratory diseases. Intermittent obstruction of UA during the night is frequent with NIV and may be associated to obstructive events, because of deficient expiratory positive airway pressure (EPAP) during sleep, in patients with increased UA collapsibility. Often, obstructive sleep apnoea-hypopnoea may be seen in any patients undergoing NIV, especially those with OHS. Therefore, the EPAP should be increased before any modifications in inspiratory trigger sensitivity while obstructive respiratory events happen, mainly for low breathing efforts such as the case of neuromuscular diseases. Ultimately, an adaptable inspiratory trigger is an option presently available in most home ventilators, and manual correction of the inspiratory trigger sensitivity allows a decrease of PVA. In this type of patient, it is important to monitor the diurnal parameters, but it may not be sufficient as the alterations are only nocturnal.

The occurrence of PVA is complex and affected by both patient-related factors, such as respiratory drive, respiratory muscle strength and increased inspiratory load due to augmented airway resistance, and ventilator-related factors, such as oxygen supplement, mask leaks and ventilatory settings. An important mechanism implicated in the genesis of PVA is dynamic hyperinflation. Dynamic hyperinflation might be a consequence of a too short expiratory time, which can be the case with high breath frequency, or high IPAP, levels. Dynamic hyperinflation raises the work of breathing and might induce ineffective effort, as inspiratory resistance has to be overcome before the patient can generate a negative inspiratory flow to trigger the ventilator.

11.3 Leaks

Leaks are common in patients in NIV and comprise one of the main problems because they can reduce the effectiveness of ventilation and treatment compliance. Polygraphy signals were interpreted as periods with high unintentional leaks when there was a fall in pressure signal and, in pressure-controlled ventilators, a simultaneous increase in flow signal. Pulse oximetry, which we use systematically to monitor patients with NIV, forms a fundamental part of screening for leak detection. The clinician detects the need for the greater requirement of oxygen in the circuit. Leakage may be missing or minimal when the subject is awake but frequently worsen during sleep as a result of the lack of intentional control and reduced muscle tone. First, because NIV is given via a nasal or full-face mask, the unintentional leak is a generally observed drawback as a result of the non-hermetic nature of the system [9, 10].

A leak during NIV can be the intentional leak through the passive exhalation port or unintentional leaks in the circuit, at the interface or from the mouth with a nasal interface or the nose with an oral interface or happen as an effect of an increase in airway resistance, for example, recognised as "secondary leaks" or "reflex obstruction during ventilation". In the past, pressure ventilation was preferred over volume ventilation because of better leak compensation. But some current-generation ventilators compensate for leaks with either pressure ventilation or volume ventilation when a passive circuit is used. Some current-generation ventilators use redundant leak estimation algorithms. An unintentional leak less than 0.5 L/s is generally well tolerated. Some ventilators track the leak rate and display this on the ventilator screen. Effects of inconsequential leaks (of around 0.5 L/s) are discomfort and treatment intolerance (eye irritation, mouth dryness, rhinorrhoea or nasal obstruction) and decrease in ventilation effectiveness and in case of significant leaks, reduction of pressure in mask, sleep fragmentation, decrease in ventilation effectiveness (if pressure support ventilation), inspiratory trigger failure or prolongation of inspiratory time (end of inspiration of the patient not detected).

For all patients using NIV 24 hours a day, the problem of leaks is difficult to control, due to the imperfect holding of the mask or the voluntary disconnection of the patient to eat, speak or call a family member. Neuromuscular patients might be particularly sensitive to NIV, and usually, there is a progression of the disorder including diaphragmatic weakness and growth in NIV demand to 24 h/day. The reduction in muscular effort makes these patients especially prone to desaturations and hypoventilation in cases of essential pressure variations. This may cause glottis closure in patients with amyotrophic lateral sclerosis (ALS), for example [18].

Surely, an accurate titration process is required to reduce or avoid PVA and correct any leaks. Vrijsen et al. performed accurate titration (using fixed bi-level PSV) during three night-time of polysomnography in subjects with ALS [19]. On the last night of titration and following 1 month of home mechanical ventilation, there was an important change in sleep quality, carbon dioxide and nightly oxygen. In fact, in consideration of the respiratory alterations in the patient with neuromuscular pathology, in a titration performed during the day, guided only by the patient's comfort, the patient does not describe any improvement in sleep efficiency, sleep awakenings or the architecture of the sleep. These dissatisfied goals are not presumably due to the absence of an optimal titration method that addresses insufficient ventilation settings.

Zhu et al. compared in a bench model, the maximal leak level tolerated without significant asynchrony "critical leak" in ventilators subjected to three clinical situations: COPD, OHS and NMD. Any disease was simulated with both open and closed UA, COPD, OHS and NMD. This is as clinically effective as inpatient set-up in the NMD population and obese population [20].

They found that with open UA, all the machines were capable to bypass PVA up to a 31 L/min leak and even up to 55 L/min in any cases. UA closing and respiratory disorders, especially OHS, dramatically influenced PVA. Inspiratory trigger sensitivity change is frequently required to bypass PVA. Since the leak is the first cause of failure of NIV, inspiratory trigger performance

of ventilators needs to be tested in the presence of a leak. On new ventilators inspiratory triggers are improved. The new flow-based triggering algorithms are more sensitive than classical flow triggering and allow adjusting trigger sensitivity in the presence of a leak and, in this way, help to reduce ineffective efforts and autocycling. Applying an "NIV algorithm" in ICU ventilators has been attested to significantly reduce the impact of leaks on the appearance of patient-ventilator trigger asynchrony. The threshold value of clinically tolerable leaks must be defined for each ventilator and that these thresholds differ between different devices and clinical situations. Perhaps, without UA obstruction, all ventilators performed well with leaks lower than 30 L/min which are clinically tolerable.

Furthermore, the methods of calculating leaks applied by ventilators remain to be standardised, particularly those concerning the timing in a breathing cycle at which leaks are estimated. Unfortunately, in case of unusual mechanical properties of the respiratory system or closed UA, this function is strongly compromised with very different results, and manual changes in trigger sensitivity are often necessary to avoid PVA. Besides, in the case of closed UA, the principal setting to modify should be the EPAP rather than the inspiratory trigger.

Automated discovery of leaks and agreement of triggering sensitivity by the machine are pleasing, but further efforts are required to develop leak calculation and ventilator performance during leaks and to define how leaks must be recognised and understood: when are they "tolerable" and at what point do they become an obstacle. Currently, home ventilators provide leaks to be estimated, but the performance of their algorithms is variable. Also, intentional leaks are variable and proportional to the level of pressure. They differ between interfaces and are included in the estimation of leaks in most algorithms. The machine can exclusively read a patient's inspiratory effort when airflow is recognised within the ventilator circuit. Trigger failure will happen if the trigger sensitivity is low, ordinarily because of an improper setting or because the appearance of a leak does it easier for air to be induced in around the interface rather than through the ventilator circuit. Leaks can additionally alter the machine's capacity to cycle into expiration. With a pressure-limited device, the ventilator will improve flow to try to maintain the preset pressure; as a consequence, the flow rate does not reach the start for cycling into expiration.

11.4 Apnoea and Hypopnoea

It is essential to screen for residual apnoea events, and most built-in software provides residual apnoea-hypopnoea indexes (AHI). AHI supplied by the ventilator is sufficiently precise to discern patients who had more than 10 events/h, but the recording of the actual number of events is not accurate enough. Some other study found that the AHI provided by ventilator was not sufficiently sensitive to detect residual sleep-disordered breathing compared to standard polygraphy. Few studies, all with a limited number of patients, have quantified residual obstructive and central events in patients undergoing long-term NIV.

Aarrestad et al. examined their patients with polysomnography and capnometry, examined their patients. They found residual that AHI were frequent: 34% of the patients had an AHI > 5/h, with obstructive hypopnoea being the most frequent event [4]. They described a significant association between AHI and both ODI and SpO_2. Conversely, no correlation was found between AHI or asynchrony and nocturnal $PtcCO_2$ or between leaks and either nocturnal SpO_2 or $PtcCO_2$. Oximetry integrates both short recurrent desaturations and prolonged desaturation during NIV. Brief intermittent desaturations could be caused by AHI, leaks or asynchrony, while continued desaturations reflect ventilation/perfusion mismatch or persistent alveolar hypoventilation. Desynchronisations associated with desaturation were rare, and asynchrony explained only 6% of the variance of SpO_2. Thus, in their study, AHI and PVA do not seem to be significant contributors to oxygen desaturation during overnight treatment with NIV. Other factors, such as ventilation/perfusion mismatch and hypoventilation, are probably of greater importance. Nocturnal hypercapnia, assessed by transcutaneous CO_2,

reflects persisting alveolar hypoventilation during NIV, taking into account the limitations of this technique. The possible explanation is that it may result from insufficient ventilatory support, prolonged leaks or prolonged asynchrony, although the latter has yet to be shown. Also, a high AHI may lead to accumulation of CO_2. They found no correlation between AHI and nocturnal hypercapnia in their study population.

Under NIV, intermittent obstruction of the UA is commonly observed during sleep in subjects with oropharynx collapse as OHS. In chronic NIV, both obstructive breathing episodes and unintentional leaks are identified to induce the occurrence of PVA, which may reduce both ventilator efficacy and sleep quality and are associated with decreased patient survival. UA obstruction during sleep is common in obesity hypoventilation and in many neuromuscular diseases, sometimes described in overlap syndrome (OSAS-COPD), and may persist under NIV due to inappropriate ventilator settings. NIV may also trigger undesired respiratory events, such as recurrent decreases in ventilatory drive leading to central apnoea-hypopnoea with or without glottic closure.

Nilius et al., in a recent study, compared the effects of NIV with pressure-controlled and NIV with intelligent volume-assured pressure support in 14 chronic hypercapnic COPD. They found obstructive hypopnoeas were the most frequent type of event detected during both ventilation modes [21]. The overall number of ventilation-related respiratory events was very low in both NIV modes, and there were no statistically important differences between the two modes of ventilation.

Borsini described in ICU ventilated patients a mean respiratory disturbance index of 15.1 ± 10.6 events/h, which is conventionally defined as non-optimal titration [15]. Asynchronies during NIV have been described for up to 50% of the patients and can cause O_2 desaturation and sleep fragmentation, thus reducing sensitivity to hypoxia and hypercapnia. A European study used EMG to describe severe asynchronies in 25% of their patients (50% of these cases were due to leaks). Even though the tolerance threshold has not been defined yet, we found asynchronies that were classified as severe or long in 12% of the patients. They were frequently related to non-intentional leaks although patients were monitored [22].

The optimal monitoring of patient-ventilator interaction is still a matter of debate. Hence, the methods used to assess patient-ventilator interaction and the effects of NIV may vary greatly, from a single blood gas measurement to full polysomnography. Recent "best clinical practice" recommendations regarding NIV in chronic respiratory failure state that PSG or respiratory polygraphy (PG) should be performed for each patient to verify its efficiency (American Task Force) [23].

11.5 Built-in Software

At this time, there is minimum evidence for using data downloads in the monitoring, treatment and management of people receiving domiciliary NIV. Mansell et al. monitored ventilator data remotely via a modem by a consultant physiotherapist between the first review and second appointment; they evaluated leak; VT and compliance data were collected for comparison at the first review and 3–7 weeks later, after any changes were required. Analysis of data from 52 patients showed increased patient compliance (% days used >4 h) from 90% to 96% ($p = 0.007$); 12% ($n = 6$) of participants had a measured leak >60 L/min; post-review only 4% ($n = 2$) continued to have a measured leak >60 L/min. The study design, as in most of the other studies, did not include a control group, and thus the effect of the intervention is uncertain. Second, it was not feasible to blind the investigators collecting data, which may have resulted in observer bias; however, the real nature of the data helps mitigate this risk [24]. The use of ventilator data downloads may, therefore, help promote the wider use of outpatient set-up for home NIV; indeed ventilator download data, transmitted via a modem, can be described as a form of telemedicine. Data are available by both secure data (SD) card download and via modem technology, which means this data can be viewed remotely daily. Bench studies have demonstrated ventilator data param-

eters provided in manufacturer software are reliable, and clinical studies have demonstrated the apnoea-hypopnoea index recorded by built-in software is also reliable. Borel et al. demonstrated that ventilator download data, particularly respiratory rate, trigger % and usage, can predict an exacerbation of COPD [22].

It was demonstrated that analysis of data provided by home NIV devices might allow simplifying the monitoring of ventilation quality and limiting the indication for PG/PSG to complex cases [24]. Alvarez et al. studied the reliability of BIS compared with PG in a cohort of OHS patients on NIV [25]. Thirty stable OHS patients on NIV were evaluated in an outpatient setting with simultaneous PG and BIS recordings. The automated apnoea-hypopnoea event index provided by software and manual scoring based on possible traces obtained from the software was compared with manual PG scoring. The median unintentional leak obtained from the built-in monitoring devices was 1.2 L/min (range, 0–3.1). The mean respiratory rate delivered by the ventilator was 15 ± 3, and the estimated expiratory minute volume was 8.8 ± 2. Event index, AHI by two observers, was 4.9–6.1/h from BIS.

In unstable OHS patients on NIV, unattended home-based monitoring using machine software is reproducible and reliable to assess the quality of ventilation when compared with PG. Besides, manual scoring of events using data obtained with this device is more consistent than software-based automated analysis. Alvarez data support the proposal by the SomnoNIV group to assess the quality of ventilation by combining medical history, arterial blood gas, nocturnal pulse oximetry with or without transcutaneous capnography and BIS data. A limitation of BIS devices is the lack of thoracoabdominal belts. Combined with flow and pressure recording, thoracoabdominal belt signals are crucial to understanding patient-ventilator synchrony. New machine for NIV is developing, provided by thoracoabdominal belts.

BIS may reveal intermittent obstruction of the UA with thoracoabdominal belt signals; it is due to one of two problems. The first corresponds to obstructive events at the oropharyngeal level and, as a result, insufficient expiratory positive airway pressure. This mechanism may occur in patients with OSA or OHS. The other mechanism corresponds to episodes of intermittent obstruction at the glottal level reflecting cyclic glottal closure induced by hyperventilation. While a sudden reduction in flow amplitude characterises both situations during insufflation, obstruction occurring at the oropharyngeal level is accompanied by progressively increased inspiratory activity, indicating a struggle against UA collapse.

The other problem is glottal closure; the essential feature is a decrease in flow with a simultaneous reduction in or disappearance of the thoracoabdominal signal. A limitation of home NIV devices is that both mechanisms are indiscriminately expressed as a sudden reduction in flow amplitude. Nevertheless, in Alvarez study, as well as in others, most respiratory events were related to UA collapse. This is particularly evident in patients with OHS, where OSA is present in 90% of patients.

Zhou investigated effects of home use of NIV in hypercapnia in COPD patients, using the ventilator with built-in software for monitoring. It is the first randomised controlled trial report [26] to date of using NIV ventilator equipped with integrated software to monitor patient-ventilator interaction in a home setting in stable hypercapnic COPD. To determine the precision of built-in software in respirators, data downloaded from software showed that mean estimation of the leak was 37.99 L/min and 87% of the leaks were 40 L/min, which was significantly lower than the threshold leak influencing the effects of NIV.

By using BIS and ventilators, respiratory events were occurring in 12 patients (21%) during NIV. Also, this trial provided evidence that 3-month use of NIV at home could improve PaCO2 and 6-min walking test in chronic stable COPD with hypercapnia as compared with long-term oxygen therapy alone. Quality of life evaluated by questionnaire was shown to tend to improve, but the development did not achieve the level of statistical significance ($p = 0.06$) probably due to the small sample size.

NIV has been demonstrated as an effective treatment, and current guidelines recommend polysomnography (PSG) accompanied by wave-

form analysis and retrospective NIV modification on the following day to direct NIV titration [27]. Patout tried to determine the efficacy of limited respiratory monitoring using transcutaneous oxi-capnometry and nurse-led titration, compared with PSG and retrospective NIV modification, for the set-up of NIV in patients with chronic respiratory failure secondary to COPD-OSA overlap [28]. This pilot randomised physiological effectiveness trial demonstrated that using transcutaneous oxi-capnometry and nurse-led NIV titration, in patients with COPD-OSA with chronic respiratory failure, resulted in a more significant fall in daytime $PaCO_2$ at 3 months compared with gold standard PSG monitoring and retrospective NIV modification. The improvements in health-related quality of life and daytime sleepiness were confirmed. The small sample size of the study prevents the completion of an adjusted analysis from trying and accounting for the differences in NIV adherence or any other baseline differences between the two groups. The results from this pilot proof-of-concept clinical trial need to be interpreted with caution and are hypothesis making rather than hypothesis testing, which is the role of a multicentre clinical trial. Despite these limitations, the data support the use of transcutaneous combined oxi-capnometry monitoring, in combination with a nurse-led titration protocol to safely establish NIV in patients with chronic respiratory failure secondary to COPD-OSA overlap syndrome. These data confirm the security and effectiveness of limited respiratory monitoring and nurse-led titration as an alternative method to PSG for home NIV set-up.

11.6 Summary of the Evidence (Table 11.1)

Significant levels of different asynchrony have also been reported with patients receiving NIV [3, 4, 6, 7]. Identifying PVA during NIV by visual examination of the ventilator-displayed waveforms is difficult. Because the use of inva-

Table 11.1 Summary of evidence

Author	Aims	Methods	Patients (pt)	Results
Aarrestad 2017	To quantify and describe AH/PVA in pt. with CRF in NIV; to analyse the influence of PVA on overnight pulse oximetry and transcutaneous CO_2	Polygraphy, oximetry, capnography, BIS	67 pt. OHS, NMD, restrictive thoracic disorders	Residual AH and PVA were frequent. No correlation between respiratory events and overnight hypercapnia
Borsini 2017	To evaluate utility of polygraphy for monitoring NIV and impact on patients in NIV of intensive care unit	Polygraphy	50 pt. OHS, NMD, COPD, restrictive thoracic disorders Setting ICU	Bedside polygraphy in the ICU may be useful to change NIV program for patients with indication for chronic NIV
Duiverman 2017	To assess the degree of respiratory muscle unloading and PVA by EMG during different settings of NIV in stable hypercapnic COPD	Electromyography	10 COPD pt	With high backup breathing frequencies, less breaths were pressure supported. PVA occurred more frequently with the low-frequency settings
Nilius 2017	To compare the effects of pressure-controlled NIV and NIV with intelligent volume-assured pressure support in chronic hypercapnic COPD	PSG and transcutaneous carbon dioxide pressure ($PtcCO_2$)	14 COPD pt	The total number of respiratory events was low. There were also no clinically relevant differences in $PtcCO_2$ between two modes

(continued)

Table 11.1 (continued)

Author	Aims	Methods	Patients (pt)	Results
Vrijsen 2017	To provide more insight into NIV titration by comparing the effects of different NIV modes on gas exchange and PVA	Polysomnography, oximetry and transcutaneous carbon dioxide ($PtcCO_2$)	13 ALS pt	ST mode shows better results in gas exchange, respiratory events and PVA. Accurate NIV titration remains necessary
Longhini 2017	To assess ability to identify asynchronies during NIV through ventilator waveforms	35 expert and 35 non-expert physicians evaluated 40 5-min NIV reports displaying flow-time and airway pressure-time tracings	40 5-min traces	Sensitivities to detect asynchronies were low. PVA during NIV is difficult to recognise solely by visual inspection of ventilator waveforms
Patout 2017	To compare set-up guided by PSG to limited respiratory monitoring and nurse-led titration	Polysomnography transcutaneous oxi-capnometry	14 COPD-OSA pt	Transcutaneous oxi-capnometry and nurse-led NIV titration, resulted in a greater fall in daytime $PaCO_2$ at 3 months compared with PSG
Mansell 2018	To assess the potential impact of ventilator data downloads on management of patients in home NIV	Ventilator data downloads	52 pt	Using ventilator data downloads in this outpatient setting facilitated objective assessment of leak and ventilator prescriptions
Alvarez 2017	To assess the reliability of BIS compared with PG.	Simultaneous PG and BIS recordings	30 stable OHS	Unattended home-based monitoring using BIS is reproducible and reliable to assess quality of ventilation when compared with PG
Zhou 2017	To investigate effects of home use of NIV using the NIV ventilator with built-in software for monitoring	BIS	115 COPD	BIS provided methodology for monitoring NIV use at home, which could facilitate the improvement of compliance and quality control of NIV use
Zhu 2017	To comparatively assess, on a bench model, the highest leak level tolerated without inducing significant asynchrony in three home ventilators (Astral 150, Trilogy 100 and Vivo 60)	Bench model	Not applicable	Home ventilators were able to avoid PVA in high-level leak conditions. Asynchrony appeared in cases of abnormal mechanical properties of respiratory system or closed UA

sive means to accurately recognising patients respiratory movement is unreliable for most subjects undergoing NIV, the future advancement of dedicated tools for these purposes is advisable. Today, in different disease, NIV is predominantly applied during sleep, when profound ventilatory changes may occur, particularly in patients with respiratory failure [7]. Such changes comprise adjustments of ventilatory control, upper airway patency and respiratory muscle recruitment. Consequently, changing NIV settings into the day and minimising these physiological differences may lead to a suboptimal patient-ventilator interaction that reduces NIV effectiveness. It may be necessary to use a ventilation mode during the hours of the day and a different one during the night, due to the different physiopathological mechanisms during sleep in various diseases.

As result, to assess overnight patient-machine interaction and efficacy of ventilation, nocturnal monitoring is needed [29].

The effectiveness of NIV might, therefore, be more correctly estimated by sleep investigations than by daytime evaluation. The most accessible and simple monitoring can be done from flow and pressure curves from the mask or the ventilator circuit. Pulse oximetry and, if possible, polygraphy provide additional information for the decision of the clinician. Analysis of these tracings can provide useful information to evaluate if the settings chosen by the operator were the right ones for that patient. However, as NIV allows an extensive range of ventilatory parameters and settings, it is mandatory to have information about this to understand patient-ventilator interaction better.

Observation of pressure-time and flow-time waveforms during NIV can be useful not only for detection of patient-ventilator asynchrony but also other additional information about the quality of the ventilation, magnitude of leaks, obstruction of airways and inspiratory/expiratory ratio. The visualisation of these phenomena makes them more comfortable to spot and to react adequately in terms of titration of the settings of the ventilator. In a multicentre random control trial on a cohort of patients with COPD, Di Marco et al. [29] showed that titration of ventilator settings based on analysis of respiratory waveforms in real time resulted in more rapid improvement in pH and $PaCO_2$ and better tolerance of ventilation by patients. However, identifying PVA during NIV by visual examination of the ventilator-displayed waveforms is difficult. Because the use of invasive means to accurately recognise patients' respiratory movement is unreliable for most subjects undergoing NIV, the future advancement of dedicated tools for these purposes is advisable.

Future standardisation of PVA scoring and reporting is desirable to help to assess the clinical relevance of these events and for comparing studies. Employing ventilator download functions can inform clinicians' decision-making to facilitate the optimal delivery of NIV. Utilising ventilator data downloads in this outpatient setting facilitated an objective assessment of leak and ventilator prescriptions. In conclusion, ventilator data downloads can give clinicians with essential information and therefore can be a useful interventional adjunct in the clinicians' toolbox receiving into account the presence of leaks but also of PVA that could be useful in the future. Current knowledge, in continuous evolution, has allowed the progressive improvement of home ventilator technology. The monitoring techniques are not yet standardised, due to the clinical heterogeneity of patients subjected to NIV, even if suffering from the same pathology.

The studies carried out to date provide information about the population of patients examined, but these are small samples, with different aims and different methods. Probably the difference in method depends on the availability of the technologies of the centre where each study is carried out but also on the level of experience of the work group. A standardisation of the monitoring techniques of the patient undergoing NIV is necessary, considering the different pathologies (COPD, NMD, OHS) and different care settings (hospital, ICU, home).

References

1. Skoczyński S, Scala R, Navalesi P. Survey on accessibility and real-life application of noninvasive ventilation. ERJ Open Res. 2018;4(4):00062–2018. https://doi.org/10.1183/23120541.00062-2018.
2. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR, et al. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med. 2010;182:325–31.
3. Longhini F, Colombo D, Pisani L, Idone F, Chun P, Doorduin J, Ling L, Alemani M, Bruni A, Zhaochen J, Tao Y, Lu W, Garofalo E, Carenzo L, Maggiore SM, Qiu H, Heunks L, Antonelli M, Nava S, Navalesi P. Efficacy of ventilator waveform observation for detection of patient-ventilator asynchrony during NIV: a multicentre study. ERJ Open Res. 2017;3(4):pii: 00075-2017. https://doi.org/10.1183/23120541.00075-2017.
4. Aarrestad S, Qvarfort M, Kleiven AL, Tollefsen E, Skjønsberg OH, Janssens J-P, Sleep-related respiratory events during non-invasive ventilation of patients

with chronic hypoventilation, Respir Med 2017. https://doi.org/10.1016/j.rmed.2017.10.025.
5. Ergan B, Nasiłowski J, Winck JC. How should we monitor patients with acute respiratory failure treated with noninvasive ventilation? Eur Respir Rev. 2018;27:170101.
6. Vignaux L, Vargas F, Roeseler J, Tassaux D, Thille AW, Kossowsky MP, Brochard L, Jolliet P. Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive Care Med. 2009;35:840.
7. Antonogiannaki E-M, Georgopoulos D, Akoumianaki E. Patient-ventilator dyssynchrony. Korean J Crit Care Med. 2017;32(4):307–22.
8. Colombo D, Cammarota G, Alemani M, et al. Efficacy of ventilator waveforms observation in detecting patient-ventilator asynchrony. Crit Care Med. 2011;39:2452–7.
9. Rabec C, Rodenstein D, Leger P, Rouault S, Perrin C, Gonzalez-Bermejo J, Somno NIV group. Ventilator modes and settings during non-invasive ventilation: effects on respiratory events and implications for their identification. Thorax. 2011;66(2):170–8.
10. Gonzalez-Bermejo J, Perrin C, Janssens JP, Pepin JL, Mroue G, Leger P, Langevin B, Rouault S, Rabec C, Rodenstein D, Somno NIVG. Proposal for a systematic analysis of polygraphy or polysomnography for identifying and scoring abnormal events occurring during non-invasive ventilation. Thorax. 2012;67:546–52.
11. Arellano-Maric MP, Gregoretti C, Duiverman M, et al. Long-term volume-targeted pressure-controlled ventilation: sense or nonsense? Eur Respir J. 2017;49:1602193.
12. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ, Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;7:CD004104.
13. Duiverman ML, Maagh P, Magnet FS, et al. Impact of high-intensity-NIV on the heart in stable COPD: a randomised cross-over pilot study. Respir Res. 2017;18:76.
14. Duiverman ML. Noninvasive ventilation in stable hypercapnic COPD: what is the evidence? ERJ Open Res. 2018;4(2):00012-2018.
15. Borsini E, Ernst G, Blanco M, et al. Respiratory polygraphy monitoring of intensive care patients receiving non-invasive ventilation. Sleep Sci. 2017;10(1):35–40.
16. Younes M, Brochard L, Grasso S, et al. A method for monitoring and improving patient:ventilator interaction. Intensive Care Med. 2007;33:1337–46.
17. LalmoldaPuyol C, Larrosa R, Luján M, Sayas J. Trigger asynchronies induced by the introduction of external gas into the circuit in non-invasive ventilation: a bench study. Eur Respir J. 2018;52:PA2402.
18. Hess DR. Noninvasive ventilation for neuromuscular disease. Clin Chest Med. 2018;39:437–47.
19. Vrijsen B, Buyse B, Belge C, Vanpee G, Van Damme P, Testelmans D. Randomized cross-over trial of ventilator modes during non-invasive ventilation titration in amyotrophic lateral sclerosis. Respirology. 2017;22(6):1212–8.
20. Zhu K, Rabec C, Gonzalez-Bermejo J, et al. Combined effects of leaks, respiratory system properties and upper airway patency on the performance of home ventilators: a bench study. BMC Pulm Med. 2017;17:145.
21. Nilius G, Katamadze N, Domanski U, Schroeder M, Franke KJ. Non-invasive ventilation with intelligent volume-assured pressure support versus pressure-controlled ventilation: effects on the respiratory event rate and sleep quality in COPD with chronic hypercapnia. Int J Chron Obstruct Pulmon Dis. 2017;12:1039–45.
22. Borel J-C, Pelletier J, Taleux N, et al. Parameters recorded by software of non-invasive ventilators predict COPD exacerbation: a proof-of-concept study. Thorax. 2015;70(3):284–5.
23. AMERICAN TASK FORCE, Berry RB, Chediak A, Brown LK, et al. NPPV titration task force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2010;6:491–509.
24. Mansell SK, Cutts S, Hackney I, et al. Using domiciliary non-invasive ventilator data downloads to inform clinical decision-making to optimise ventilation delivery and patient compliance. BMJ Open Respir Res. 2018;5(1):e000238. https://doi.org/10.1136/bmjresp-2017-000238.
25. Fernandez Alvarez R, Rabec C, RubinosCuadrado G, et al. Monitoringnoninvasive ventilation in patients with obesity hypoventilation syndrome: comparison between ventilator built-in software and respiratory polygraphy. Respiration. 2017;93:162–9.
26. Zhou L, Li X, Guan L, et al. Home noninvasive positive pressure ventilation with built-in software in stable hypercapnic COPD: a short-term perspective, multicenter, randomized, controlled trial. Int J Chron Obstruct Pulmon Dis. 2017;12:1279–86.
27. Murphy PB, Rehal S, Arbane G, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomised clinical trial. JAMA. 2017;317:2177–86.
28. Patout M, Arbane G, Cuvelier A, Muir JF, Hart N, Murphy PB. Polysomnography versus limited respiratory monitoring and nurse-led titration to optimise non-invasive ventilation set-up: a pilot randomised clinical trial. Thorax. 2019;74(1):83–6. https://doi.org/10.1136/thoraxjnl-2017-211067.
29. Di Marco F, Centanni S, Bellone A, et al. Optimization of ventilator setting by flow and pressure waveforms analysis during noninvasive ventilation for acute exacerbations of COPD: a multicentric randomised controlled trial. Crit Care. 2011;15:R283.

12 Using Domiciliary Noninvasive Ventilator Data Downloads to Inform Clinical Decision-Making to Optimize Ventilation Delivery and Patient Compliance

Fabrizio Rao

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12.1 Introduction

Long-term noninvasive ventilation (LTNIV) has become a therapeutical option in chronic hypercapnic respiratory failure (CHRF) from the mid-1980s, following the first case reports of the use of nasal ventilation in patients affected by Duchenne muscular dystrophy. At first, volume-limited modalities were preferred, but, from the 1990s, pressure-limited modalities established themselves as the most used in the noninvasively ventilated patients, particularly by means of the flow-cycling bi-level ventilators [1] that became the gold standard in the large part of the diseases ultimately leading to CHRF [2]. In the last 20 years, huge technological progresses have been achieved, obtaining optimal air leak compensation, quietness, pressurization and patient-ventilator synchronization. LTNIV, when appropriately prescribed, can correct nocturnal hypoventilation and improve quality of sleep and life and has a proven role in the prolongation of survival [3].

12.2 Discussion

12.2.1 How to Evaluate Long-Term Noninvasive Ventilation (LTNIV) Efficacy

The most important issues affecting NIV adaptation process can be briefly summarized as leak management, patient-ventilator interaction, obstructive/central apnoeic or hypopnoeic events and a periodical check-up of the patient's compliance to ventilation.

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In the last few years, noninvasive ventilatory approach has grown exponentially both in adults and in children, as demonstrated by a recent Canadian study [4]. Consequently, an exceptional pressure of work, represented by complex and medicalized patients, started to overburden intensive and sub-intensive care units, with as a consequence the associated and unavoidable increase of economic costs.

The possibility of a home-care management of these patients, with different programs that range from the domiciliary monitoring to telemedicine, has become of more interest over time.

Nocturnal oxyhaemoglobin desaturations are considered the principal responsible for the cardiovascular and neurocognitive adverse consequences in CHRF and obstructive sleep apnoea syndrome (OSAS)-affected patients [5]. Nocturnal pulse oximetry is an important test that allows the monitoring of LTNIV patients and is also known as a useful tool to detect breathing disorders during spontaneous breathing. Nevertheless, the desaturation pattern is not precise enough to differentiate central from obstructive events: that is the reason why the variations in oxyhaemoglobin saturation must be carefully interpreted by the clinician. The most limiting factor in this test is the scarce sensitivity in defining the aetiology of the detected drop in SpO_2: they can be determined by recurring episodes of upper airway obstruction, from a reduced activity of respiratory central drive with or without associated glottis involvement or from continuous leaks, when in NIV, causing frequent microarousals. During spontaneous breathing, prolonged desaturations can reflect some ventilation/perfusion alterations in patients with a severe restrictive or obstructive ventilatory defect that can depend from body position as in obesity-hypoventilation syndrome (OHS) or can be caused by alveolar hypoventilation. Moreover, prolonged desaturations of 10–30 min associated with a tachycardic rhythm can often be related to REM sleep-associated hypoventilations; in patients already treated with NIV, however, the same pattern can be related to continuous mask leaks or to an insufficient pressure support. In particular, in case of oxygen supplementations, nocturnal pulse oximetry is not reliable at all in detecting hypoventilation [6]. During pulse oximetry an important data that we can analyse is the pulsed wave amplitude (PWA), measured from pulse oximeter by means of a photoplethysmographic method: every microarousal causes a peripheral reflexed vasoconstriction that can be detected by a marked reduction in the amplitude of PWA (Fig. 12.1). If this kind of pattern is seen at nocturnal pulse oximetry test, we can obtain important information not only on desaturations but also on sleep structure and fragmentation. Nowadays, guidelines that address the issue of a well-performed nocturnal pulse oximetry are not available; a reasonable approach is to adjust NIV settings to obtain a median oxyhaemoglobin saturation (SpO_2) higher than 90% and to correct the mask leaks to obtain less than the 10% of the total registration time characterized by an SpO_2 below 90% [7].

More information on the kind of respiratory event responsible for a reduced compliance to NIV in our patients can be obtained from nocturnal cardiorespiratory monitoring (nocturnal polygraphy—PG) or from polysomnography (PSG) that allows, in almost all cases, to understand the underlying mechanism at the basis of the nocturnal respiratory event: if we have important leaks during NIV, for instance, we could see a drop in the positive pressure wave associated with an increasing ventilatory flow and a simultaneous reduction in abdominal and thoracic excursions. Upper airway obstruction can be seen as a fall in the amplitude of inspiratory flow with a stable positive airway pressure or, more frequently, as a phasic opposition between thoracic and abdominal signals, suggesting a continuous inspiratory effort caused by the obstructive event. On the other hand, a linear and progressive drop in respiratory flow, with a steady pressure and a concomitant reduction or disappearance of thoraco-abdominal signals, is highly suggestive of a central event.

Due to the possibility to precisely identify the mechanism at the basis of incoordination between NIV and patient, PG/PSG are considered comprehensive tests that allow NIV titration and optimization; they are still expensive and second-level exams. The optimal monitoring of CHRF patients

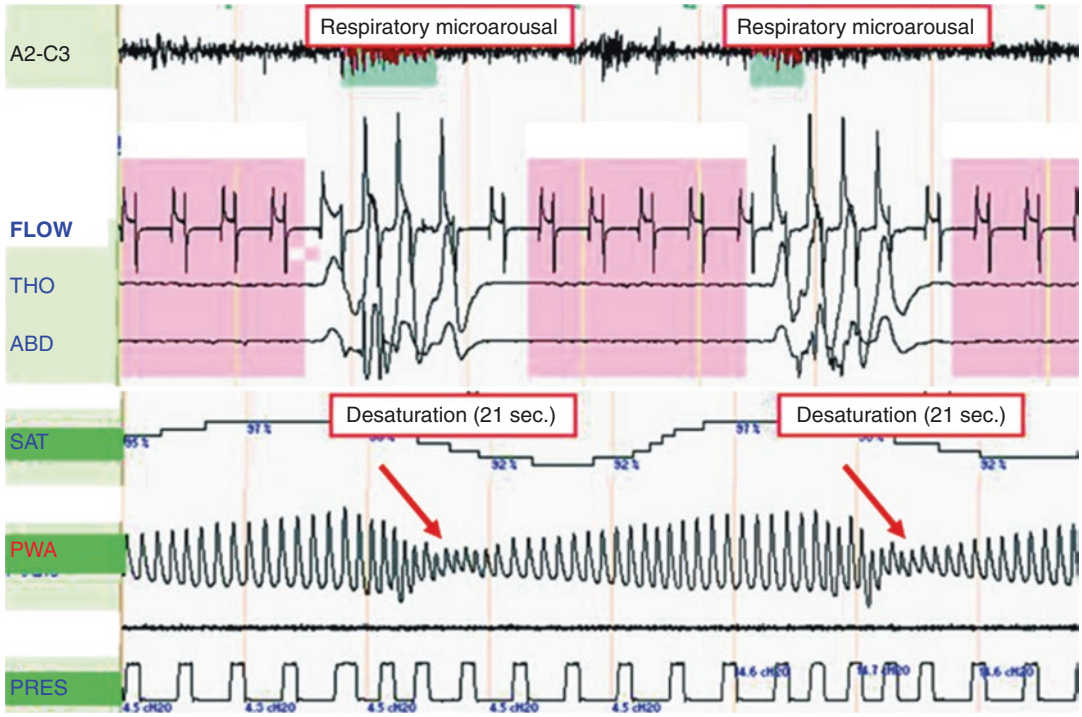

Fig. 12.1 Indirect assessment of sleep fragmentation under NIV using variations in pulse wave amplitude (PWA): tracing shows respiratory microarousals ending recurrent glottic closure episodes, causing transient desaturations in a patient treated by NIV with simultaneous marked reduction in PWA (red arrows). *Adapted from Janssens JP, Thorax 2011;66:438–445*

is still under discussion: to evaluate NIV effects, we are nowadays using a range of tests that go from arterial blood gas analysis (ABG) to a complete PSG. Recent recommendations of good clinical practice on NIV optimization in chronic respiratory failure suggest performing PG/PSG in every ventilated patient in order to evaluate NIV efficacy [8].

12.2.2 Built-in Software (BIS)

In the last 15 years, together with the important technological achievements in ventilator-building techniques, it has been possible to better understand the nature of patient-machine interaction and the different effects of various ventilator modalities and their role in modifying the respiratory mechanic. Consequently, many manufacturers incorporated in their ventilators several softwares, allowing the monitoring of respiratory parameters and the data gathering in their internal memory program. The emerging problem was then to validate the data extracted from these softwares, and this problem remains present nowadays. At the moment, a limited amount of literature dealing with the reliability of these data is available, so the clinician has to interpret these results with caution.

The most important information that can be obtained by downloading the stored data is related to the patient's ventilatory compliance, to NIV utilization pattern, to the leaks' quantification, to the tidal volume quantification and to the percentage of breaths triggered by the patient and provided by the machine compared to the total number of respiratory acts granted from the ventilator.

Before starting to analyse item by item the points that we cited, it seems necessary to understand the way in which the ventilator records all

the data and the differences between the various available machines.

Despite the important technological progresses achieved in the last decades, the clinician must bear in mind the limitations of these softwares. The first important issue is to determine how reliable the recorded data and signals are: a study by Rabec et al. [9] suggests that, in at least one of the ventilators available with this technology, the calculation of leaks and of volume/minute (VE) can be considered reliable, whereas another recent study proves that the reliability of the signals recorded by ventilators are highly variable between different devices [10]. The second issue is that the clinician must analyse a cohort of stable patients, in terms of ventilation modality, trigger and leaks, even when considering different groups of diseases leading to CRF.

The data downloaded from ventilator's memory can be divided in three categories (Fig. 12.2):

(a) Synthesis report: defined as the trend of all the analysed parameters recorded in a precise period of time from the ventilator. It depends from the manufacturer and can comprise parameters such as utilization compliance, settings, leak evaluation, tidal volume, respiratory rate, minute/ventilation and patient-triggered breaths.
(b) Precise analysis of the above-mentioned respiratory parameters evaluated cycle by cycle.
(c) A polygraphic analysis obtained by connecting an external device to the ventilator that allows the measurement and the recording of parameters such as peripherical oxyhaemoglobin saturation, cardiac rate and respiratory effort.

Wide inconsistencies are detectable in the data recorded by different devices; this can depend on the inaccurate clinicians' definition.

Device	Software	Synthesis data	Detailed data	Polygraphic data
VPAPIII-ST (A) VPAPIV-ST ResMed	ReScan 3.10	Compliance, ventilator settings, V_E, V_T, RR, leaks, residual AHI	V_E, RR, leaks, residual AHI and flow cycle by cycle for VPAP IV	Simultaneous recording of Spo_2 and heart rate (avaiable with additional module: RESLINK)
HARMONY SYNCHRONY Philips Respironics	Encore Pro 2	Compliance, ventilator settings, V_E, V_T, RR, leaks, flow, total number of apnoeas, alarms	V_E, V_T, RR, leaks, flow (cycle by cycle display possible with additional Alice PDX module)	Simultaneous recording of Spo_2, heart rate and respiratory effort (available with additional Alice PDX module)
Triogy Philips Respirorics	Direct view	Compliance, ventilator settings, V_E, V_T, RR, leaks, flow, total number of apnoeas, alarms	V_E, V_T, RR, leaks, pressure, flow (display cycle by cycle) and alarms	
VENTIMOTION Weinman (Hamburg, Germany)	Ventisupport	Compliance, ventilator settings, V_E, V_T, RR, leaks, flow, inspiratory time/total time, alarms	Pressure, flow, level of leaks	Pressure, flow and leaks can be transferred to any polygraph with the 'Analog box-Weinmann'
GK 425 Tycohealthcare (Pleasanton, CA, USA)	Silverlining 3	Compliance, ventilator settings, RR, pressure	NA	
SMARTAIR, SMARTAIR+ LEGENDAIR, SUPPORTAIR Airox-Covidien (Pau, France)	Airox Com 3.5.1	Compliance, ventilator settings, technical alarms and ventilation alarms	V_T, RR, inspiratory time/total time, leaks, pressure/time and flow/time curves (online or differed cycle by cycle display require connection to a PC while patient is under NIV)	Simultaneous recording of Spo_2 available with SUPPORTAIR monitoring of Spo_2
Monnal T30 AirLiquide (Antony, France)	Bora Soft V.6	Compliance, ventilator settings, V_E, V_T, RR, leaks,	NA	
VS III, VS INTEGRA ResMed	Easydiag 2	Compliance, ventilator settings, V_E, V_T, RR, leaks,	V_E, V_T, RR, leaks (online or differed cycle by cycle display are possible)	
ELYSEE 150 ResMed	Easyview 150 (2.11)	Compliance, ventilator settings, V_E, V_T, RR, leaks,	V_E, V_T, RR, leaks (online cycle by cycle display is possible while patient is under NIV)	
VIVO 30–40 Breas (Mölnlycke, Sweden)	Vivo PS software 3	Compliance, ventilator settings, V_E, V_T, RR, leaks, flow, alarms	Pressure, flow, V_T, leaks (online or differed cycle by cycle display are possible)	
VIVO 50 Breas (Mölnlycke, Sweden)	VIVO 50 PC software	Compliance, ventilator settings, V_E, V_T, RR, leaks, flow, alarms	Pressure, flow, V_T, leaks (online or differed cycle by cycle display are possible)	

AHI, estimation of apnoea-hypopnoea index under NIV (residual AHI); NA, not available; NIV, noninvasive ventilation; PC, portable computer; RR, respiratory rate measured by ventilator; V_E, estimation of minute ventilation; V_T, estimation of tidal volume.

Fig. 12.2 Summary of data available from built-in software in home ventilators. From *Janssens JP, Thorax 2011;66:438–445*

Moreover, the recommendations to interpret them should be drafted by scientific societies; in addition, these data should be further validated from clinical independent studies. Without this kind of validations, all the information that can be drawn from ventilators should be interpreted very cautiously from the clinician with the aim of titrating and optimizing NIV. They cannot, in any case, be taken as the only tools to rely on for a complete evaluation of the appropriateness of the patient's nocturnal ventilator profile.

12.2.2.1 Compliance

Very often, the patient's compliance is not reliable. Therefore, the data we can obtain from the ventilators are a great help for the clinician, who is able to evaluate the actual use of the machine. Moreover, from these data, more important information can be drawn: for example, frequent interruptions in the use of the ventilator during the night can enlighten a scarce adaptation to NIV (Fig. 12.3). In an observational study from Pasquina et al., which analysed 150 patients in LTNIV [11], we can see that a neuromuscular diagnosis leads to a higher compliance when compared to central sleep apnoea syndrome (CSAS) patients; this is probably due to the higher level of dependence from ventilation. The compliance report is further important in the decision of continuing NIV treatment or not. Moreover, an increasing use of NIV during the daily hours can suggest an impending re-exacerbation of a respiratory disease.

12.2.2.2 Air Leaks

Air leak control represents one of the most important elements in determining NIV efficacy. Non-intentional air leaks can lead to NIV intolerance, to NIV-patient asynchrony and to the scarce clinical control of hypoventilation and alveolar gas exchanges. Consequently, having a reliable estimate of this parameter can be extremely valuable. A particular care must be taken in analysing the way in which the ventilator detects the air leaks, since different softwares are used to measure different parameters: for instance, in some cases, the intentional leaks through the vented masks are already included in the ventilatory report downloaded from the machine (e.g. DirectView, Philips Respironics, Murrysville, PA, USA), but in some other ventilators, this is not the case (e.g. ResScan, ResMed, North Ryde, NSW, Australia). Indeed, in this particular software, the machine subtracts from the total leaks the intentional ones, and the provided air leak value is the effective one. Moreover, the air leaks must be related to pressure support levels: an increase in pressure support of 10 cmH_2O can double the air leak detected value. Due to all these variables, the

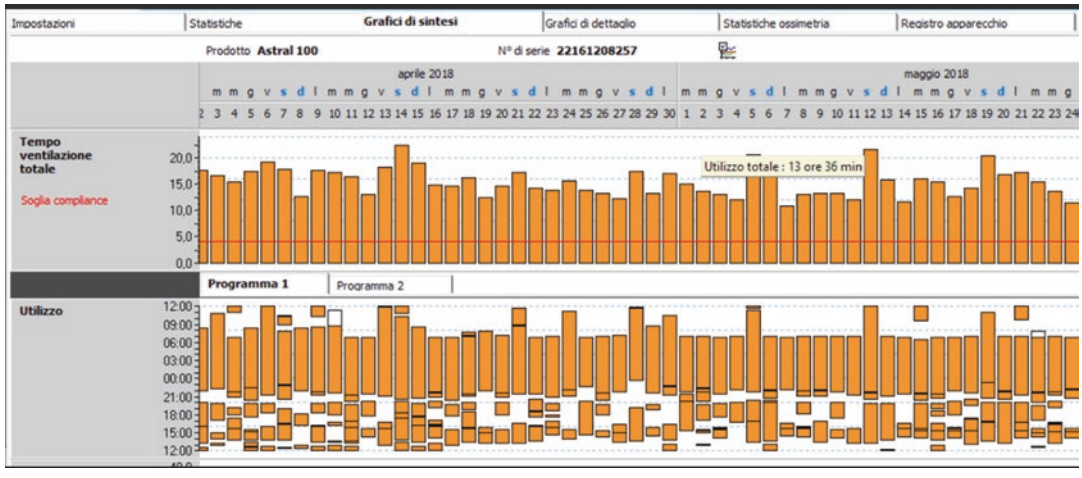

Fig. 12.3 Compliance data from built-in software

maximum values of air leaks set out from the manufacturers are arbitrary and always depend from the characteristics of the different masks and from the pressures applied for NIV [12]. The presence of relevant air leaks during NIV can have immediate clinical consequences: it can lead to a change in the mask, to the caregiver's better training in mask positioning or to the adjustment of some NIV settings.

12.2.2.3 Tidal Volume (TV) and Volume/Minute (VE)

The tidal volume (TV) recorded from the machine can state NIV efficacy, even though it is always dependent from a minimum variability derived from air leaks. In this respect, it is really important to consider the kind of ventilator we are dealing with: if we are working with a single limb circuit with expiratory valve and the pneumotachograph is placed between the ventilator and the expiratory valve itself, it will give information only on the inspiratory phase of the respiratory cycle, while, if it is positioned between the expiratory valve and the patient, it will record data on both the inspiratory and expiratory phases. On average, an acceptable TV should be around 10 ml/kg during NIV, having as a reference the patient's ideal body weight. A high variability in TV may suggest important air leaks or the presence of a spontaneous or ventilator-induced periodic breathing pattern. It should be noticed that, in many domiciliary ventilators, the TV tends to be underestimated and this variability increases with a higher-pressure support: this fact must be considered by the clinician when he/she needs to optimize NIV settings, when high insufflation pressures are required.

12.2.2.4 Respiratory Rate and Patient's Triggering Percentage

The patient's spontaneous respiratory rate and the percentage of respiratory acts triggered by the patient and recorded by the ventilator are data that must be cautiously interpreted by the clinician. A low percentage of triggered acts can be indicative of a backup respiratory rate settled in the ventilator at a higher level than the patient's spontaneous breathing rate. Moreover, if there are significant air leaks or other conditions that can make it difficult for the ventilator to perceive the patient's respiratory effort, as the presence of intrinsic positive end-expiratory pressure in a COPD (chronic obstructive pulmonary disease) patient or a severe neuromuscular weakness, a low percentage of spontaneous breaths can reliably reflect the inability to perceive the patient's effort from the ventilator. All these items can lead to a patient-ventilator asynchrony sometimes resolvable by increasing the inspiratory trigger sensitivity or the expiratory positive pressure (EPAP). The ideal backup rate to set is still a matter of debate; the neuromuscular patient, most of all in the advanced phases of the primary disease, tends to "lean" on the settled rate with a ventilator pattern similar to a controlled modality.

12.2.2.5 Apnoea-Hypopnoea Index (AHI)

Some softwares report AHI between the measured data during NIV; the reliability of this parameter has never been completely validated since different devices use the same event-detecting algorithms already developed for auto-CPAP machines, and these can be inappropriate during NIV. One of the problems is the lack of a standardized definition of hypopnoea during ventilation even if different and recent suggestions have been presented in literature [13]. Another point is due to the not clear definition of the way in which the software recognizes the events during NIV and is able to differentiate between obstructive and central events.

12.3 Conclusions

Many tools are available to monitor LTNIV. In a phase of stability, nocturnal pulse oximetry represents the easiest way to identify a nocturnal desaturation. It does not allow, however, the highlighting of hypoventilation signs in case of oxygen supplementation.

Moreover, most of the alterations identified through nocturnal pulse oximetry are non-specific and cannot reliably distinguish a venti-

lation/perfusion ratio alteration from a hypoventilation. The analysis of the pulse oximetric wave width (PAW) is a method that can indirectly give information on sleep fragmentation during NIV. The transcutaneous capnography is the only noninvasive method that can identify hypoventilation. However, it is expensive and not widespread or immediately available in most of the centres. The built-in softwares installed in the next-generation ventilators can give much information to the clinician on air leaks, percentage of patient's spontaneously triggered breaths, residual apnoeic or hypopnoeic events, usage patterns and compliance, but they represent rough estimates of the real data and must be cautiously interpreted since they have not yet been validated from independent clinical trials. The air leak estimate is a parameter that can be affected by the mechanism of detection typical of every different software (total leaks or only unintentional leaks). Other parameters, like tidal volume and volume/minute, should be related to the pressure and support set from the clinician since they have an extreme variability; in literature, usually, tidal volume is reported as underestimated by the ventilators. Considering this, the clinician should not rely exclusively on the data recorded and downloaded from the ventilator to optimize NIV but should use the information obtained by all the different available and validated tools as arterial blood gas analysis (ABG), nocturnal pulse oximetry, nocturnal polygraphy and capnography; the integration of all this information can avoid gross mistakes in LTNIV settings.

12.4 Key Major Recommendations

1. Nocturnal pulse oximetry in a stable patient in LTNIV is a simple tool to identify sleep pattern alterations, but it is not completely reliable to detect hypoventilation.
2. Nocturnal polygraphy and polysomnography during NIV can precisely define the specific kind of breathing disorder.
3. The most useful and reliable parameters recorded and downloaded from the built-in software are data on compliance and on the air leak estimates; it is necessary to understand the identification mechanism of air leaks set on the specific ventilator (whether it is total or only unintentional).
4. Tidal volume (TV) and volume/minute (VE), when downloaded from the ventilator, should always be compared to the provided pressure support.
5. To evaluate NIV efficacy, the clinician must not rely only on the data that can be downloaded from the ventilator but should also integrate the whole set of information obtained from the different available tools.

   (ABG, oximetry, polygraphy/polysomnography, transcutaneous capnography and clinical data).

References

1. Sanders MH, Kenn N. Obstructive sleep apnea treated by independently adjusted inspiratory and expiratory positive airway pressures via nasal mask. Physiologic and clinical implications. Chest. 1990;98:317–24..
2. Janssens JP, Derivaz S, Breitenstein E, et al. Changing patterns in long-term non-invasive ventilation: a 7 years prospective study in the Geneve lake area. Chest. 2003;123:67–79.
3. Tsolaki V, Pastaka C, Kostinas K, et al. Non-invasive ventilation in chronic respiratory failure: effects on quality of life. Respiration. 2011;81:402–10.
4. Amin R, Sayal P, Syed F, et al. Pediatric long-term home mechanical ventilation: twenty years of follow-up from one Canadian center. Pediatr Pulmonol. 2014;49(8):816–24.
5. Punjabi NM, Newman AB, Young TB, et al. Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. Am J Respir Crit Care Med. 2008;177(10):1150–5.
6. Fu ES, Downs JB, Schweiger JW, et al. Supplemental oxygen impairs detection of hypoventilation by pulse oximetry. Chest. 2004;126(5):1552–8.
7. Gonzalez C, Ferris G, Diaz J, et al. Kyphoscoliotic ventilatory insufficiency: effect of long-term intermittent positive-pressure ventilation. Chest. 2003;124(3):857–62.
8. Berry RB, Chediak A, Brown LK, et al. NPPV titration task force of the american academy of sleep medicine. Best clinical practices for the sleep center adjustement of non-invasive positive pressure ventilation (NPPV) in stable chronic alveolar hypoventilation syndromes. J Clin Sleep Med. 2010;6(5):491–509.
9. Rabec C, Georges M, Kabeya NK, et al. Evaluating non-invasive ventilation using a monitoring system

coupled to a ventilation: a bench-to-bedside study. Eur Respir J. 2009;34(4):902–13.
10. Contal O, Vignaux L, Combescure C, et al. Monitoring of a non-invasive ventilation by built-in software of home bilevel ventilators: a bench study. Chest 2012;141(2):469–76.
11. Pasquina P, Adlen D, Farr P, et al. What does built-in software of home ventilators tell us? An observational study of 150 patients on home ventilation. Respiration. 2012;83(4):293–9.
12. Borel JC, Sabil A, Janssens JP, et al. Intentional leaks in industrial masks have a significant impact on efficacy of bilevel non-invasive ventilation: a bench test study. Chest. 2009;135(3):669–77.
13. Gonzales-Bermejo J, Janssens JP, Pepin JL, et al. Proposal for a systematic analysis of polygraphy or polysomnography for identifying and scoring abnormal events occurring during non-invasive ventilation. Thorax. 2012;67(6):546–52.
14. Sanders MH, Kern N. Obstructive sleep apnea treated by independently adjusted inspiratory and expiratory positive airway pressures via nasal mask. Chest 1990;98(2):317–24.

Noninvasive Ventilation in End-of-Life Care and Palliative Care

13

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Abbreviations

ALS	Amyotrophic lateral sclerosis
COPD	Chronic obstructive pulmonary disease
DNI	Do not intubate
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
IPF	Idiopathic pulmonary fibrosis
MND	Motor neuron disease
NIPPV	Noninvasive positive pressure ventilation
NIV	Noninvasive ventilation
PC	Palliative care

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13.1 Introduction

The term "end-of-life care" is different, and it usually refers to care concerning the final stage of life and focuses on the care of the dying person and their family. The period for end-of-life care is arbitrary and should be considered variable depending on the patient's trajectory of illness.

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Using these descriptions, the palliative care includes end-of-life care, but is broader and also includes attention centered on promoting quality of life and reducing symptoms before the end-of-life period. Some symptoms accompany the end of life especially in respiratory diseases: dyspnea, weakness, physical fatigue, decreased activity, mental fatigue, and lack of motivation. According to one study, patients may experience distress and pain during the last month of life and often receive suboptimal treatment. Symptomatic treatments for dyspnea such as opioids should be readily available, even relatively early in the course of the disease, if dyspnea is not adequately relieved by NIV.

13.2 NIV In-Home Support for End of Life: Is It for the Patient or Family/Caregiver?

Patients' preferred place of death is usually at home, but distressing symptoms, unanticipated crisis, or increasing carer burden can make end-of-life care at home challenging. The experience at the end of life can have a significant impact on patients and their families. Advanced planning, excellent communication, and access to expertise in palliative and social care, mainly out of office hours, can avert crises and promote a peaceful death. Palliative care aims to check and reduce affliction and to promote the high-grade quality of life for patients and their parents, despite the stage of disease or the need for other therapies. Palliative care improves quality of life, supports medical decision in performing and recognizing the goals of care, marks the essentials of family and other informal caregivers, and implements opportunities for personal growth [1]. A strong correlation between dyspnea and pain has been described in patients who are effectively reduced by NIV [2]. Although ventilatory support can expressively extend life, the patient sometimes requests the cessation of NIV when allowed by local legislation. However, discontinuation of NIV will inevitably be accompanied by severe symptoms or even real acute respiratory distress.

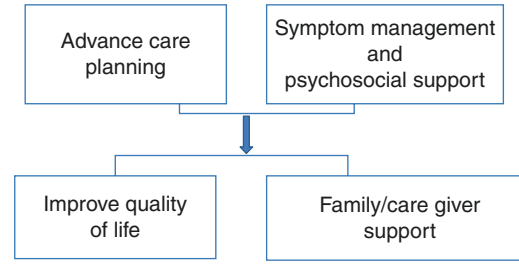

Fig. 13.1 NIV in-home support for end life

This type of situation must be anticipated, which necessitates rigorous and carefully appropriate drug treatment. As in any case of end-of-life dyspnea, opioids and benzodiazepines, possibly associated with the administration of oxygen, effectively relieve the symptoms induced by discontinuation of ventilatory support. It is only common sense to initiate these treatments before discontinuing ventilatory support, which can be legitimately temporarily resumed if the doses administered are insufficient to relieve the patient's symptoms and promote patient comfort [2]. It is crucial to ensure the continuous presence of a doctor or a nurse in the patient's room after stopping ventilatory support, to allow a rapid response when the doses need to be increased to reassure the family about the significance of any respiratory pauses or agonal gasps, which, despite their spectacular nature, must not be interpreted as signs of suffering. If death does not occur rapidly, a doctor or nurse should frequently visit the patient's room or may need to be continuously present in some cases (Fig. 13.1).

13.3 Neuromuscular Patients

Progressive respiratory deterioration is a hallmark of many neuromuscular diseases (NMD). The respiratory decline can be postponed through such interventions; it cannot be avoided. Noninvasive positive pressure ventilation (NIPPV) may "buy time" for loved ones to visit and say goodbye, but in these situations, it will not prevent the patient's death. Whereas in decades past this necessarily led to an end, now there are multiple modalities of support that can

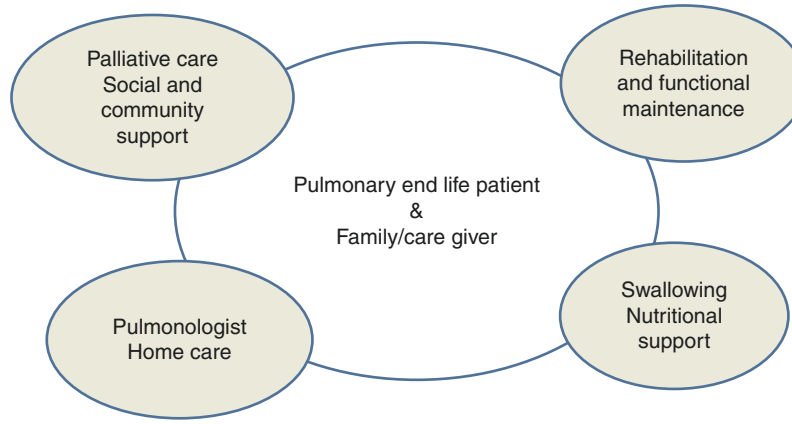

Fig. 13.2 Neuromuscular patient care

sustain life, beginning with suctioning and cough assist, progressing to intermittent and then chronic noninvasive positive pressure ventilation, and ultimately invasive ventilation. Indeed, the burden of NIPPV is not insignificant, however, often requiring restraints and being uncomfortable for the patient. In situations that represent an incremental decline in respiratory function rather than an acute decompensation, NIPPV may herald the need for ever-increasing respiratory support, if life is to be sustained. To be sure, instituting NIPPV does not commit the patient to continue respiratory support, for there is no ethical difference between withdrawing and withholding (Fig. 13.2). From an emotional standpoint, however, withdrawing may be more difficult on a patient and family [3].

Recently, Gleeson examines data from different states through a 25-item questionnaire. A connection to the survey was sent by email to every medical director of inpatient hospices/SPCUs (specialist palliative care units) in the UK and Ireland. The response rate was 42.4%. From the analysis of data, only a few units (7.7%) have expertise with tracheostomy patients. In the UK, patients with motor neuron disease (MND) using NIV greatly outnumber those using the tracheostomy ventilation (TV). Only 14.1% of respondents had been included in the care of patients with MND using TV, in the expert palliative care environment in the last 5 years. During end-of-life assistance, considerable expertise is required to facilitate long-term mechanical ventilation. Respiratory tract obstruction due to bronchial secretions can require urgent action as suctioning, and there is also a potential for accidental ventilator disconnection or failure of the ventilator requiring bag-valve-mask respiratory support by a suitably trained healthcare professional. In literature, there are several case reports which focus on ventilator withdrawal and highlight the associated legal and practical challenges and disparity in current practice. The data revealed considerable differences in the provision of specialist palliative care for patients with MND using NIV, in comparison to those using tracheostomy ventilation (TV). 97.4% of units indicated that they currently admit patients with MND on NIV, but only 28.2% admit MND patients using TV. Palliative care support was more accessible to MND patients using TV in the community; 80.8% of respondents indicated that sufficient expertise in the management of NIV is available at their unit. This study has several limitations (the nature of data collection, less than half responded, etc.). There is no standard for adequate support, and therefore there may be significant inter-respondent variation in what is considered "adequate" for patients and their family [4].

Health-related quality of life (HRQOL) may improve at a different rate in NMD patients on long-term NIV. *Crimi* et al. in their work affirm that NIV plays a crucial role in the projection of progressive NMD improving HRQOL and survival. NIV might be challenging for NMD patients, and early end-of-life discussion is mandatory as to put in place proper advanced

directives. Conversely, initiation of NIV in Duchenne muscular dystrophy (DMD) patients is not perceived as adversely affecting their HRQOL [5].

Anticipatory outlining and palliative care should be carried out to lessen the burden of responsibility, to maintain or withdraw from NIV, and to guarantee the most respectful management in the last days of NMD patients' life. One study reported that the last days of life for amyotrophic lateral sclerosis (ALS) patients who did not choose invasive mechanical ventilation (IVM) are usually characterized by dyspnea, pain, and fatigue and that more than one-third of patients decide to continue NIV to relieve symptoms up until the last 24 h rather than oxygen alone. In the case of patient compliance, there are strong recommendations for continuation of NIV up to 24 h according to patient interface preferences. Facing end-of-life discussion is difficult, especially in young patients [6]. Only recently has the literature been gaining information regarding end-of-life discussion and care for NMD patients, and palliative care is often not mentioned to any family of patients with DMD.

In one study, older interviewed DMD patients emphasized that it is crucial to face end-of-life issues "within a positive frame of reference, focusing first, on living with DMD and having a good life with it and then, as a natural part of it, about death and dying." These patients underlined the importance to die at home, surrounded by family, and not in the hospital and emphasized the need for home-based palliative care training to deal with NIV-dependent patients. They conclude that the use of NIV in the palliative care setting of patients with ALS is controversial and only a few studies have explored this topic [7]. The burden of becoming dependent on NIV is exceptionally distressful, and it sums up to the other discouraging experiences that this fatal disease carries with itself. Withdrawing from long-term NIV has not fully been explored.

Cheng et al. in their study evidence that the real experience at the end of life can have a significant effect on patients and their families. Owing to the complexities of the management of advanced ALS, a coordinated team of medical, nursing, and associated health professionals creates constitutes a multidisciplinary care (MDC) model that results in improved care and quality of life (QOL), reduction in the length and recurrence of hospitalization, and prolongation of survival in MND subjects. The multidisciplinary hospital typically includes a neurologist, MND nurse, physiotherapist, and occupational and speech therapists. Patients' preferred place of death is habitually at home, but distressing symptoms, unanticipated crisis, or developing carer burden can make end-of-life care at home challenging. Advanced planning, excellent communication, and access to expertise in palliative and social care, mainly out of office hours, can avert crises and promote a peaceful death. Anticipatory prescribing of symptomatic therapies in a range of routes is encouraged [8].

Brunaud et al. in his work affirm that the primary goal of treatment in caring for ALS patients is to minimize morbidity and maximize the quality of life (QOL). The most common symptoms at the end of life (pain and dyspnea) need to be stringently verified. Socioeconomic factors and caregiver preferences may also influence patients' choices. Anticipatory palliative treatment, according to the advance care planning already discussed with the patient, may be prescribed. With the use of palliative medication, most patients can die peacefully at home due to carbon dioxide narcosis. A prospective French study of the causes of death showed that most ALS patients die of respiratory failure (77%), which includes terminal respiratory failure (58%), pneumonia (14%), asphyxia due to a foreign body (3%), and pulmonary embolism (2%). Also, 10% of ALS patients die from other causes, such as postsurgical or traumatic conditions (5%), cardiovascular causes (3.4%), suicide (1.3%), and sudden death of unknown origin (0.7%). Most patients (63%) died in a medical facility. At autopsy, bronchopneumonia is the leading cause of death. A study of North American multidisciplinary ALS centers has also confirmed that most ALS patients die peacefully (90.7%). The remaining patients (9.3%) exhibited distress during the dying process, which included breathing difficulties (82.1%), fear or anxiety (55.2%), pain

(23.9%), insomnia (14.9%), and choking (14.93%); 62.4% of patients died in a hospice or supported environment, and 88.9% had completed their ADs. To increase survival time, therapeutic strategies should be rapidly implemented to compensate for malnutrition and respiratory insufficiency and to prevent aspiration, falls, and pneumonia [9].

Time is needed to discuss therapeutic options. When respiratory failure occurs and confusion sets in (due to hypercapnia), it is not possible for patients to provide informed consent for treatment. Nevertheless, the management of ALS patients still reveals situations that serve as ethical paradigms in modern medicine. Despite the lack of a cure for ALS, significant changes in the management of ALS patients have taken place over the last few years: increased survival, better QoL, and greater respect for patients' autonomy. Noninvasive ventilation (NIV) has become an essential part of the treatment of amyotrophic lateral sclerosis (ALS). More advanced use of NIV also requires pulmonologists to master the associated end-of-life palliative care, as well as the modalities of discontinuing ventilation when it becomes unreasonable. The circumstances of death and palliative end-of-life care for patients who choose to remain on NPPV as the ceiling of medical treatment for respiratory failure have received little focus. Furthermore, some patients were found to be close to death despite a high level of independence in activities of daily living.

Ushikubo's work about ALS patients and their caregiver's experiences with NIPPV described the caregiver's experience periods of stress and interrupted sleep. NIPPV does not impart a sense of severity or gravity, which sometimes results in a tendency to treat ALS lightly. Measures must be taken to prevent human error, such as forgetting to flip switches. Also, home visiting nurses should be educated regarding their legal obligation to report their concern over suspicious events so that law enforcement can follow up. Assessment by home visiting nurses of the caregiver's age, sex, relationship to the patient, competence, and fatigue is essential. Home care providers need to collaborate to introduce necessary social resources at appropriate times. For patients receiving treatment who have decided to go as far as using NIPPV as the final symptomatic treatment of respiratory failure, end-of-life care is best provided in the patients' preferred place. If they want to die in their home, the preparedness of the patient and his/her family and how to provide palliative care are important factors. Family physicians and home visiting nurses should make efforts to obtain advance directives to avoid the patient's wishes being overruled later by his/her family; doing so can minimize legal risks as well. Therefore, family education or family care is vital in end-of-life care. Moreover, palliative care urgently needs to be developed to mitigate the final circumstances of patients receiving NIPPV treatment [10].

The circumstances of the death of in-home patients with ALS who used NIPPV indicated a close relationship between death and the nature of caregiving in the handling of NIPPV. Home care nurses should consider caregiving aspects, as well as physical elements when predicting death. Furthermore, patients' statements that they are independent with activities of daily living were mostly unreliable indices for predicting mortality. However, several clinical parameters for predicting death were identified: weight loss, shorter intervals between bouts of pneumonia, the onset of oral problems, and the onset of skin problems. Further research is necessary to develop palliative care for ALS patients on NIPPV approaching the end of their lives.

13.4 COPD Patients

COPD represents the third leading cause of death universal and the seventh in combination of years of life spent or lived with disability. Patients with COPD have been recognized to have high symptom loads as those with lung cancer. Increasing symptom burden, particularly dyspnea, correlates with increased mortality. Compared with those with cancer, patients with COPD are more likely to receive aggressive interventions at the end of life, including ICU admission for invasive or noninvasive ventilation and cardiopulmonary

resuscitation [11]. Identification of the limits of curative treatment and acceptance of palliative care is hard for all (clinicians, patients, and their parents), but is an essential and often neglected part of clinical practice, particularly beyond oncology. Even in late-stage COPD, palliative care remains an underutilized resource. Factors associated with a palliative care referral were age, cancer, invasive and noninvasive ventilation, and do not resuscitate (DNR) status. Breathlessness is a principal symptom of COPD, which progresses with the developing condition and has a profound influence on patients' QOL. There is no widely accepted practice of either predicting diagnosis or defining end-stage COPD [12], which may contribute to the extended variation and lowering quality of end-of-life care for COPD patients compared to lung cancer cases. The American Thoracic Society recommends that palliative care should be possible to all patients regardless of the grade of their disease and that relieving dyspnea should be a key problem. The palliation of dyspnea may have advantages going beyond symptom relief with some evidence of an influence on mortality from dyspnea-specific palliative care plans. NIV is used in nearly one-third of COPD patients recognized to have a poor life expectancy. Its use in this context has a weak database but used judiciously can add to symptom relief without joining to the care responsibility. NIV can relieve breathlessness by relieving the respiratory muscles. One prospective cohort study in a group of patients with solid organ cancers proved that NIV significantly reduced breathlessness and oxygenation. Although often uncomfortable for clinicians, open dialogue regarding death is essential to reduce patients' anxieties and to sustain them to make decisions regarding the management of their care at the end of life. Patients with COPD find it especially motivating to make choices in approach about maximums of care and even when they have had a prior familiarity of interventions such as NIV. They anticipate their decisions for the future medical treatment [13, 14]. Nevertheless, it is critical that they are allowed to discuss such issues. Shah in a review article examines NIV in COPD in a different clinical condition. In palliative care, NIV can relieve breathlessness by discharging the respiratory muscles. Breathlessness is a fundamental indicator of COPD, which progresses with improving disease and has an important influence on patients' QoL. There is no generally accepted method of either predicting prognosis or defining end-stage COPD, which may provide to a wide divergence and lower quality of end-of-life care for COPD patients associated with lung cancer patients. Duek et al. in his survey study, performed by the members of the Netherlands Association of Physicians for Lung Diseases and Tuberculosis, described that most pulmonologists (92.2%) showed to distinguish a palliative stage in the COPD trajectory, but there was no consensus about the various criteria used for its classification. Aspects of palliative care in COPD considered significant were advance care planning conversation (82%), communication linking pulmonologist and general practitioner (77%), and association of the palliative phase (75.8%), while the latter was considered the most crucial aspect for improvement (67.6%). Pulmonologists showed to prefer organizing palliative care for hospitalized patients with COPD themselves (55.5%), while 30.9% showed to favor cooperation with a specific palliative care team (SPCT). In the ambulatory setting, multidisciplinary cooperation between pulmonologist, common practitioner, and a respiratory nurse specialist was preferred (71.1%) [15]. The palliation of dyspnea may have advantages extending beyond symptom support with some data of impact on mortality from dyspnea-specific palliative care plans [15, 16]. NIV is used in nearly one-third of COPD patients recognized to have a decreased life expectancy. Its use in this context has a limited affirmation but administered judiciously can contribute to symptom change without adding to the care burden [17]. However, some barriers preclude its widespread use, including understanding among both patients and clinicians that NIV can prolong suffering during the dying process since the mask can be uncomfortable and claustrophobic and may impede communication with friends and relatives. The real planned goals of NIV should, therefore, be established before its

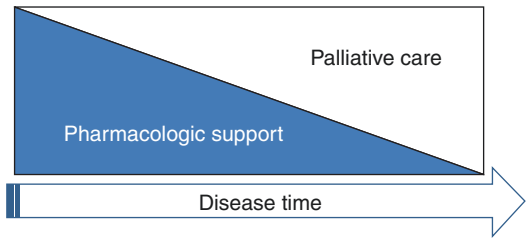

Fig. 13.3 NIV intervention in palliative care

application in patients evaluated to be in the final stage of their life, with a definite discussion between patients, carers, and healthcare teams (Fig. 13.3). Identification of explanation about the presumed therapy response, treatment escalation, and/or withdrawal of treatment should be documented at the initiation of therapy [16].

13.5 IPF Patients

Idiopathic pulmonary fibrosis (IPF) is an advancing illness with a median survival from 2 to 7 years. Although there is a remarkable development in the pharmacological therapy of IPF and some patients support lung transplantation, IPF is also a disease with high mortality and morbidity [18].

The symptom care is crucial, with shortness of breath and cough being the most common symptoms [19]. According to new interview research, the diagnosis of IPF has a significant influence on daily living and family relationships. The preponderance of IPF patients expires in a hospital setting, but the contents of care during the last days of life are frequently unknown. Death appears to be unpredictable in many cases. Despite the evidence of integrated palliative care, there are only a few studies on current end-of-life (EOL) care applications in patients with advanced IPF [20].

Rush analyzes an IPF group in the USA undergoing mechanical ventilation and their use of palliative care (PC). In this national examination of mechanically ventilated patients with IPF, only a minority of patients were referred to PC. In their work is evident a racial disparity of treatment that influenced access to PC services, with Hispanic patients less likely to be involved. Hospital characteristics, including a region of the country and teaching status, were significant predictors of PC referral. The findings of this study demonstrate that there is differential access to care for patients with IPF who are in the end stages of their disease. The significant increase in access to PC for ventilated patients with IPF is encouraging and a testament to the general increased awareness of the benefits of PC. It is impossible to determine whether the increased use of PC in patients with IPF is unique to this population or instead reflects a general trend in increased availability and understanding of the benefit of PC. As would be expected, patients treated in large academic hospitals were more likely to receive PC referral. These hospitals may be more likely to have developed PC services with more significant resources available for end-of-life planning. It is also possible that these types of institutions may have specialized clinics for patients with IPF, which may integrate PC and be available for liaison when their patients are treated in the intensive care unit. The indications of future policy developments in the USA on the access to PC for patients are unknown. In the setting of significant funding cuts across all areas of healthcare, it is possible that "nonessential" services such as PC may be at higher risk for being reduced [21].

Further research should be done on this subject to inform representatives and improve the care of patients with significant symptom burdens at the end of life. In a national representation of IPF patients, mechanical ventilation (MV) was used in 11–12% of those hospitalized due to a respiratory diagnosis with no important variation in its use over time. MV use was more frequent in younger male IPF patients, those admitted at university hospitals, and those with any chronic medical conditions or a no-IPF respiratory diagnosis. Its use was correlated with a fourfold improvement in admission cost ($49,924 compared to $11,742) and a sevenfold increase in mortality (56% compared to 7.5%). NIV was associated with increased LOS and cost, although to a lesser extent than MV. Further research in IPF treatment and development of IPF-specific decision support is needed to enhance the resource burden, consequences,

and use of MV in IPF. The unchanging nationwide use of MV over time, notwithstanding IPF treatment guidelines hypothetically recommending against MV use, reflects the limited possibility accessible to clinicians approaching acute worsening of IPF and the difficulty of advance care planning in IPF [22].

Spagnuolo analyzes the use of NIV in severe fibrosis without practical results, but he concludes for the necessity of prospective studies to identify IPF patients more likely to benefit from MV and NIV. The advantage of the application of NIV in symptomatic therapy of IPF patients has not been demonstrated, and, therefore, NIV is not routinely suggested. Although it is expected that NIV is used in support of a cure or to alleviate breathlessness, utilizing a mask may increase and prolong the difficulty of the patient and limit communication with familiar ones. Therefore, the benefit and disadvantage of NIV in patients with end-stage IPF should be prudently estimated. In contrast to NIV, oxygen therapy is recommended to IPF patients with hypoxemia [23]. Thus, it's not unexpected that the majority of IPF patients received only oxygen. In contrast to the extensive literature that has explored the benefits of palliative care in patients with cancer, few studies have examined factors that influence decisions to provide palliative care referral in patients with advanced lung disease (Table 13.1).

Table 13.1 Factors that influence decisions to provide palliative care referral in patients with advanced lung disease

Author	Aims	Methods	Patients (pt)	Results
Gleeson 2019	Evaluate hospices and specialist palliative care units (SPCUs) in the UK and Ireland in patients with MND using NIV or TV	A 25-item questionnaire developed in SurveyMonkey	185 NMD	A minority of UK and Irish hospices/SPCUs provide support to TV MND patients. Respondents indicated a lack of appropriate expertise and experience
Crimi 2019	Evaluation on survival using NIV in progressive NMD at home	Literature review	NMD, OHS	Monitoring NIV settings through the new built-in ventilator software is recommended. Patient and caregiver education is pivotal for the transition to home since home care programs are rarely available and telemonitoring is a promising resource but still not widespread yet
Cheng 2017	Evaluate the role of the supportive interventions available to patients with MND, the evidence basis for intervention modalities, and highlight areas for future research	Literature review		MDC, NIV, and nutritional support are essential to ensure patients derive the benefits
Brunand 2017	Evaluate end-of-life directive	Literature review		The optimal approach is to have an open, transparent initial discussion with the patient and to continue to discuss the matter incrementally as the disease progresses. Multidisciplinary follow-up and discussions is crucial
Ushikubo 2018	Palliative care in NMD	6 home visiting nurses Individual semistructured interviews	ALS	The circumstances of death of in-home patients with ALS who used NPPV indicated a close relationship between death and the nature of caregiving in the handling of NPPV

Table 13.1 (continued)

Author	Aims	Methods	Patients (pt)	Results
Smith LE 2017	Systematic review on prognostic variables, multivariate score, or models for COPD	Literature review		A number of variables contributing to the prediction of all-cause mortality in COPD were identified. The quality of evidence remains low, such that no single variable or multivariable score can currently be recommended
Duenk 2017	Palliative care for COPD patients was explored	Survey study	256 respondents	Pulmonologists should improve their skills of palliative care, and the members of the SPCT should be better informed about the management of COPD to improve care during hospitalization
Lindell 2017	To explore the perceptions of palliative care (PC) needs in patients with idiopathic pulmonary fibrosis (IPF) and their caregivers	Thematic analysis		early palliative care and regular counselling will allow patients with PF-ILD and their caregivers to obtain better and more effective pharmacological and psychosocial interventions to improve quality of life throughout the disease course
Rush 2018	The utilization of palliative care (PC) in patients with end-stage idiopathic pulmonary fibrosis (IPF) is not well understood	Nationwide Inpatient Sample (NIS)	21,808 patients with IPF	The utilization of PC in patients with IPF who undergo MV has increased dramatically between 2006 and 2012
Faverio 2018	Management ARF in IPF with NIV	Literature search		Nonconclusive data of NIV use in acute IPF
Akgün 2017	PC teams address domains of physical, existential, spiritual, and social suffering and facilitate complex decision-making at any stage of a disease	Literature search		PC specialists can improve symptom management PC interventions have also been associated with improvements in survival for patients living with cancer
Cheung 201	End-of-life (EOL) care preferences, documentation, and communication in patients with various types of advanced neurology diseases	Retrospective chart review		EOL decision-making in patients with advanced neurology disease is often delayed The NPCT can play a valuable role in EOL discussions in patients with advanced neurology diseases under collaboration between the PC and the neurology teams
Ringuier 2017	The objective was to survey pediatricians' opinions and practices regarding NIV in palliative care in France	Mail survey was conducted among pediatric pneumologists		The major criterion for initiating NIV in pediatric palliative care was the presence of dyspnea. In pediatric palliative care, the efficacy of NIV was evaluated primarily clinically in terms of the improvement of the child's comfort level, as well as the child's and family's satisfaction

Many reasons have been suggested to describe the timing of the reference. These include the prognostic uncertainty of IPF, the fear of diminishing hope, clinician discomfort with palliative care discussions, and limited patient and caregiver understanding of potential benefits of palliative care [24].

13.6 Cancer, DNI Context, and Palliative Care

NIV was employed for the first time in an extended group of advanced cancer patients with acute respiratory failure who had been judged by the referring oncologist to be suitable only for palliative care. Subsequently, a randomized controlled study was performed in patients with end-stage cancer presenting acute respiratory failure and severe distress. Symptom burden is substantial for patients with cancer. Fatigue, decreased appetite, pain, and dyspnea are frequently reported and are among the most common symptoms of the patients. Many of these symptoms worsen as patients approach the end of their lives. Respiratory symptoms are among the most common physical symptoms for patients living with cancer. Moderate to severe dyspnea affects approximately 25% of patients with advanced cancer, with prevalence increasing during the last 6 months of life [25].

Akgü analyzes the literature about all the possibilities to treat dyspnea in end-stage neoplastic diseases with high-flow oxygen, and noninvasive ventilation can also be utilized to treat dyspnea and could be opioid sparing for dyspnea management in patients with malignancy. Some authors report similar differences in responses to mechanical ventilation or life-prolonging drugs that may negatively affect the patient's quality of life. Palliative ventilation expresses a field of great potential in a subgroup of patients with dyspnea who start with the acute failure of a specific organ that is not necessarily correlated to the site or progression of cancer [25]. NIV in general wards and after at home has also been used in "not to intubate" patients. "DNI" cannot be considered as an indication for NIV. In patients who can be anticipated to decline as a result of respiratory failure, the introduction of NIV as potentially short-term intervention should be discussed in the outpatient setting, but should not be routinely offered to such patients. In patients with a terminal disease, NIV is aimed at reducing dyspnea, similarly to pain, or as a therapeutic choice to allow to save time and gather consent to diagnostic or therapeutic procedures or communicate the short prognosis when abruptly passing from an intensive to a palliative care setting. In this strictly palliative setting where the main goal is to manage severe respiratory distress in a patient near to death, continuous positive airway pressure (CPAP) alone does not have any role in reducing symptom, because it does not supply respiratory muscles as NIV. Palliative NIV encompasses a range of applications, from symptom-based intervention concurrent with disease-directed treatment to purely palliative treatment delivered at the end of life.

Scala and Esquinas suggested that DNI activities for ancient patients admitted for acute respiratory failure (ARF) (ventilated at home with severe dependence in their daily activities) should be placed in an open or half-open place out of ICU. This issue could be significant in reducing anxiety and depressive symptoms and to improve pain and psychological morbidity "related to DNI and end-of-life context." Furthermore, NIV might improve the end-of-life care in advanced COPD. Old DNI patients with ARF could be treated with NIV in a half-open geriatric ward with trained physicians and nurses. The presence of family members might improve patients' comfort and reduce anxiety levels even at the end of life. In hospital geriatric ward mortality was related to the admission diagnosis. When NIV is applied in a geriatric ward by experienced physicians, and if family members and nurses carefully assisted patients, the mortality was approximately 25% [26]. There are many proposals that NIV might be an alternative option to relieve dyspnea even in patients with advanced disease.

Mercadante in his article affirms that NIV is increasingly used as a palliative strategy when endotracheal ventilation is deemed inappropriate.

Palliative ventilation can either be directed to offer a possibility for survival, with a resolution for acute respiratory failure, particularly in hematologic population, or alleviate the symptoms of respiratory distress in dying patients. Patients in the final stage could be already receiving NIV at home for respiratory disease or for those who have "do not intubate/tracheostomize" order. More commonly, patients with respiratory failure due to the disease or its complications may manifest clinical evidence of severe dyspnea not respondent to standard pharmacological treatment. There is additionally a subgroup of patients, who are primarily treated with palliative ventilation while waiting for further decisions and proper communication of an abrupt switching from an intensive setting to end-of-life care.

For patient treated at home with long-term NIV, the main goal is to optimize their daily quality of life. NIV settings and interfaces should be optimized, and oxygen should be targeted to obtain an SaO_2 around 90%. It is also mandatory to pay particular attention to observe how the patient tolerates NIV. Palliative ventilation should not cause the patient discomfort, and oxygen should be targeted according to patient's dyspnea. Alarm should be put off because they can generate distress and may make the family members even more anxious [27]. The real priority is to make the patient's life comfortable; appropriate sedatives (benzodiazepine) or opioid drugs can be administered if required to facilitate patient's compliance for the first hours until stabilization is achieved. Although NIV is considered a nonaggressive technique, its use in a palliative care setting remains debatable. The pioneer and encouraging studies in palliative care patients near to end of life are inadequate and often of short duration. Further researches focused on quality of life and typical palliative care issues should be performed to provide an additional option in a different clinical context such as respiratory failure with dyspnea. No information exists about the combination of conventional drugs used for relieving dyspnea such as opioids. The appropriateness of palliative ventilation should be described in studies that rely more on qualitative measures (patient comfort, end-of-life process, family burden, and healthcare provider satisfaction) than quantitative strategies (rate of palliative NIV use and mortality). Many patients and their relatives are potentially interested in maximizing comfort in the later stages of the disease. Interestingly, some of them also expressed the desire to maintain cognition and the ability to communicate. However at this very critical stage, the patients are often no longer able to participate, and NIV may be uncomfortable and may cause unacceptable side effects such as skin lesions, irritation of the eyes, abdominal bloating, and in rare cases barotraumatic events. Thus, when possible any palliative ventilation intervention needs to be discussed with patients. Even though palliative ventilation might be beneficial in short-term or long-term conditions, some patients may wish to stop the treatment or simply because palliative ventilation has exhausted his function. More data are necessary to delineate a planned plan for change or discontinuation of palliative ventilation. The discontinuation of any form of palliative ventilation appears to pose considerable challenges to a palliative physician for the emotional, practical, and moral implications. Moral and legal rights to withdrawal from treatment, examination with family and colleagues, experiences of legal advice, and issues contributing to ethical complexity are the most challenging issues to afford.

13.7 Neurologic Disease

NIV is effective and safe in an elderly patient population, many of whom had multiple comorbidities, including significant cognitive impairment and acute delirium, at least in their acute presentations with respiratory insufficiency. However, when long-term domiciliary ventilation in individuals over 75 years of age is considered, early reports did provide favorable testimony outcomes. There is a higher risk of neuropsychological impairment, resulting in more difficulties adapting to the overall burden of NIHMV when compared to a younger individual. Respiratory complications are the highest morbidity and mortality of patients with advanced

neurological conditions. Dementia is a collective term including different types of decline. Alzheimer's disease (AD) is the most common type of dementia; it's a disease, which accounts for an estimated 60% to 80% of cases. The end stage of AD appears at an average of 2 years. In several conditions, such as severe respiratory muscle weakness and central apnea, ventilator has to be prescribed [28]. NIV is the choice for this patient, but we must consider that the patient could not handle the oral secretion, there is vocal cord palsy obstructing the airway, or the patient is unconscious and not capable of breathing spontaneously. Avoiding pressure injury to the face is the top priority in choosing interface. The nasal mask is suitable for those who can close the mouth. Oronasal mask is the most common choice but frequently associated with a nasal bridge pressure injury. A total face mask is as efficient as an oronasal mask, but secretion problem is problematic. For patients who can control the head, mouthpiece attached to the ventilator is the best option [29]. When patients cannot be sustained by NIPPV anymore, or patients have bulbar dysfunction to begin with, invasive ventilation has to be prescribed. For patients using invasive ventilation with regular ventilator, pressure-limited mode is usually preferred because patients feel more natural. However, studies revealed that volume-limited ventilation has the same effectiveness, safety, and patient satisfaction. Clearing the airway with traditional suction is usually not effective, and assisted cough with air stacking helps to prevent chest infection. NIV reduces the need for sedatives, compared with invasive mechanical ventilation, which further contributes to preventing delirium and immobilization. The presence of delirium or dementia was not a barrier for the indication or the administration of NIV; the presence of a pneumo-geriatric team allowed the symptoms to be controlled and the cooperation of the participants to be obtained. Also, NIV in a non-ICU setting will enable relatives to visit more frequently and for a longer time. Given the lack of recognition of AD as a life-threatening disease and of substantial prognostic marker and variability of survival in patients with AD, clinicians do not see AD as a primary cause of death or a disease from which one dies. Not recognizing dementia as a possible cause of death might result in unsatisfactory chance to obtain support or access customized treatment, formal end-of-life care, and healthcare services or might result in receiving care and services on a general basic level not adjusted to their end-of life needs. Identification of dementia as a possible cause of death could have meaningful implications in terms of resource use at the end of life, including palliative care [30].

13.8 Noninvasive Ventilation and Palliative Care in Pediatric Illness

In the last 20 years, there is a progressive increase in the prevalence of pediatric patients on long-term ventilation (LTV) at home (IMV and NIV). In children the benefits of NIV are clear and demonstrated. The current literature produced is not univocal regarding patient's palliative care (PC) or end life assistence. The expected benefits in this context are improving comfort by decreasing the dyspnea, enhancing the quality of sleep and daily capacities, decreasing duration of hospitalization, and increasing time spent at home [31]. Compared with invasive ventilation with a tracheostomy, NIV helps speech and nutrition, and infectious risk is less. Ringuier evaluates DNI in children. In case of acute respiratory failure, 84% of practitioners found NIV appropriate in do-not-intubate (DNI) children, while only 35% of them found it appropriate in comfort-measures-only (CMO) children ($P < 0.0001$). In case of progressive respiratory failure, 68% of the responders found NIV relevant in DNI children, while only 30% in CMO children ($P < 0.0$). The first condition for initiating NIV in pediatric palliative care was the presence of dyspnea. In pediatric palliative care, the efficacy of NIV was evaluated primarily clinically in terms of the improvement of the child's comfort level, as well as the child's and family's satisfaction. Hypercapnia and desaturation were rarely measured to initiate NIV or to assess its efficacy. Sixty percent of the respond-

ing practitioners indicated that referral to NIV was anticipated with children and family before acute events or end-of-life occurred [32].

Rusalen has evaluated the importance of a network model, with constants reference high-level specialized, might offer to these patients and their families overall care and more safe life at home. The severe clinical illnesses of these children cause regular admissions at the hospital for both diagnostics and treatments generally for acute and life-threatening exacerbations requiring the involvement of different specialist pediatricians. The difficulty of these patients' management needs highly specialized expertise, and it is also necessary to confirm permanent global care for this population, either at the hospital or at home. For that, these patients need ad hoc care services with combined multidisciplinary teams and ask for resolutions from different institutional agencies [31].

The place of death that we can consider as an indirect trademark of the quality of care has always been outside the hospital. Indeed, home and pediatric hospice are universally accepted as the better places of end-of-life care for children with an incurable disease. Also, it has already been widely accepted that the home, at first, and the hospice, at second, are considered as the better places of care for patients with life-limiting and life-threatening diseases. Future prospective studies are needed to verify this proposition and more accurately to evaluate possible cost reserves.

13.9 Conclusion

Some barriers prevent widespread NIV use, including perceptions among both patients and clinicians that NIV can prolong suffering during the dying process since the mask can be uncomfortable and claustrophobic and may impede communication with friends and relatives. The intended goals of NIV should, therefore, be established before its use in patients examined to be in the final step of their life with clear language between patients, carers, and healthcare teams. Identification of rationale of therapy, expected response, treatment escalation, and/or withdrawal of therapy should be documented at the initiation of therapy.

References

1. Akgün KM. Palliative and end-of-life care for patients with malignancy. Clin Chest Med. 2017;38(2):363–76.
2. Cortegiani A, Mercadante S, Gregoretti C. Palliative ventilatory support: same knowledge, different goal. J Thorac Dis. 2018;10(3):E236–7.
3. Morelot-Panzini C, Bruneteau G, Gonzalez-Bermejo J. NIV in amyotrophic lateral sclerosis: The 'when' and 'how' of the matter. Respirology. 2019;24(6):521–30.
4. Gleeson A, Johnson F. Assisted ventilation in motor neurone disease during inpatient palliative care: barriers andutilizationn. BMJ Support Palliat Care. 2019. https://doi.org/10.1136/bmjspcare-2018-001672.
5. Crimi C, Pierucci P, Carlucci A, Cortegiani A, Gregoretti C. Long-term ventilation in neuromuscular patients: Review of Concerns, Beliefs, and Ethical Dilemmas. Respiration. 2019;97(3):185–96.
6. Oliver DJ. Palliative care in motorneurone disease: where are we now? Palliat Care. 2019;12: 1178224218813914. https://doi.org/10.1177/1178224218813914.
7. Phelps K, Regen E, Oliver D, McDermott C, Faull C. Withdrawal of ventilation at the patient's request in MND: a retrospective exploration of the ethical and legal issues that have arisen for doctors in the UK. BMJ Supportive & Palliative Care. 2017;7:189–96.
8. Cheng HWB, Chan KY, Chung YKJ, Choi CW, Chan CH, Cheng SC, et al. Supportive & palliative interventions inmotorneurone disease: what we know from current literature?. Ann Palliat Med. 2018;7(3):320–31.
9. Danel-Brunaud V, Touzet L, Chevalier L, Moreau C, Devos D, Vandoolaeghe S, et al. Ethical considerations and palliative care in patients with amyotrophic lateral sclerosis: A review. Rev Neurol. 2017;173(5):300–7.
10. Ushikubo MJ. Circumstances and signs of approaching death in patients with amyotrophic lateral sclerosis undergoing noninvasive ventilation in home care settings. Neurosci Nurs. 2018;50(3):182–6.
11. Janssens JP, Weber C, Herrmann FR, Cantero C, Pessina A, Matis C, et al. Can early introduction of palliative care limit intensive care, emergency and hospital admissions in patients with severe chronic obstructive pulmonary disease? A Pilot Randomized Study. Respiration. 2019;16:1–10.
12. Smith LE, Moore E, Ali I, Smeeth L, Stone P, Quint JK. Prognostic variables and scores identifying the end of life in COPD: a systematic review. Int J Chron Obstruct Pulmon Dis. 2017;12:2239–56.
13. Tavares N, Jarrett N, Hunt K, Wilkinson T. Palliative and end-of-life care conversations in COPD: a systematic literature review. ERJ Open Res. 2017 27;3(2).

14. Harrington SE, Rogers E, Davis M. Palliative care and chronic obstructive pulmonary disease: where the lines meet. Curr Opin Pulm Med. 2017;23(2):154–60.
15. Duenk RG, Verhagen C, Dekhuijzen P, Vissers K, Engels Y, Heijdra Y. The view of pulmonologists on palliative care for patients with COPD: a survey study. Int J Chron Obstruct Pulmon Dis. 2017;12:299–311.
16. Vermylen JH, Szmuilowicz E, Kalhan R. Palliative care in COPD: an unmet area for quality improvement. Int J Chron Obstruct Pulmon Dis. 2015;10:1543–51.
17. Jerpseth H, Dahl V, Nortvedt P, Halvorsen K. Older patients with late-stage COPD: Their illness experiences and involvement in decision-making regarding mechanical ventilation and noninvasive ventilation. J Clin Nurs. 2018;27(3–4):582–92.
18. Mikolasch TA, Garthwaite HS, Porter JC. Update in diagnosis and management of interstitial lung disease. Clin Med. 2017;17(2):146–53.
19. Lindell K, Raghu G. Palliative care for patients with pulmonary fibrosis: symptom relief is essential. European Respiratory Journal. 2018;52:52(6).
20. Lindell KO, Kavalieratos D, Gibson KF, Tycon L, Rosenzweig M. The palliative care needs of patients with idiopathic pulmonary fibrosis: A qualitative study of patients and family caregivers. Heart Lung. 2017;46:24–9.
21. Rush B, Berger L, Anthony CL. Access to palliative care for patients undergoing mechanical ventilation with idiopathic pulmonary fibrosis in the united states. Am J Hosp Palliat Care. 2018;35(3):492–96.
22. Mooney JJ, Raimundo K, Chang E, Broder MS. Mechanical ventilation in idiopathic pulmonary fibrosis: a nationwide analysis of ventilator use, outcomes, and resource burden. BMC Pulm Med. 2017;17:84.
23. Spagnolo P, Tzouvelekis A, Bonella F. The management of patients with idiopathic pulmonary fibrosis. Front Med. 2018;5:148.
24. Faverio P, De Giacomi F, Sardella L, Fiorentino G, Carone M, Salerno F, et al. Management of acute respiratory failure in interstitial lung diseases: overview and clinical insights BMC Pulmonary Medicine. 2018;18:70.
25. Akgün KM. Palliative and end-of-life care for patients with malignancy. Clin Chest Med. 2017;38:363–76.
26. Scala R, Esquinas A. Noninvasive mechanical ventilation for ancient patients with limitations of care: is the ICU the most appropriate setting? Crit Care. 2012;16(3):429.
27. Mercadante S, Giarratano A, Cortegiani A, Gregoretti C. Application of palliative ventilation: potential and clinical evidence in palliative care. Support Care Cancer. 2017;25:2035–9.
28. Faes K, Cohen J, Annemans L. Resource. Use during the last 6 months of life of individuals dying with and of alzheimer's disease. Journal of the American Geriatrics Society. 2018;879–85.
29. Kwok TK. The palliative care needs for those advanced neurology patients on mechanical ventilator support. Ann Palliat Med. 2018;7(3):332–4.
30. Cheung KC, Lau VW, Un KC, Wong MS, Chan KY. Advance care planning for patients with advanced neurology diseases. Ann Palliat Med. 2018;7:349–354.
31. Rusalen F, Agosto C, Brugnaro L, Benini F. Impact of the regional pediatric palliative care network on the care of children on long-term ventilation: Could the availability of a residential solution into the network reduce the duration of intensive care unit staying for these patients?. J Pediatr Intensive Care. 2018;7:75–80.
32. Ringuier B, Troussier F, Boussicault G, Chapotte C, Rachieru P. Non invasive ventilation and pediatric palliative care. A French survey. Arch Pediatr. 2017;24:712–9.

14 Skin Injuries Associated with Noninvasive Mechanical Ventilation: Evidence-Based Synthesis

Ana Luísa Ramos, Ana Margarida Mestre, and Teresa Bastos da Mota

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14.1 Introduction

The skin lesions in the face of contact with the used interface are the most frequent complications in noninvasive ventilation (NIV). The nose lesions, as a complication of the NIV, are present in 50% of individuals after a few hours and virtually in 100% after 48 h [1–4]. Kramer et al. reported that NIV may fail in 18% of patients because of mask discomfort [35].

When an external pressure applied on a tissue is close to the diastolic arterial pressure, the com-

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pensatory mechanism of tissue tolerance will fail, leading to the lesion of the tissue. This sustained compression could induce irreversible lesions on the skin or mucosa or even necrosis [1–3].

Pressure ulcers result from the combination of several internal and external factors, among them the high local pressures, the abrasion, the tissue factors (such as hypoxemia), the hypotension, the concomitant therapy (like corticotherapy), and the long period of NIV, among others [2, 3].

Bony prominences on the face are the ones which are more likely to develop pressure ulcers by the interfaces, being the nasal bridge the most affected region (according to Munckton et al. [4], it is the area of the face where the greatest pressure is applied). Such thing can be explained by the small surface coverage it presents, meaning that all the pressure made will be transmitted to the skin and underlying tissue, culminating in the decrease of the tissue perfusion around this salience [5–8].

Regardless the location, ulcers can be classified, according to the guidelines of the European Pressure Ulcer Advisory Panel, American National Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance [4], from stage I to stage IV. While the first stage can indicate individuals at risk (local erythema), from stage II the loss of skin constituents appears with a crescent risk in parallel to the progression of the stages. Stage IV presents a growing risk of complications due to muscle, tendon, or even bone exposure.

14.2 Methodology

Research was done based on MEDLINE, Cochrane and Web of Science data to reach consensus through an expert panel.

14.3 Internal Factors

14.3.1 Age and Skin Characteristics

The ability of a tissue to redistribute the mentioned pressure dictates its tolerance to pressure. Elastin and collagen are the ones responsible for transmitting more than 70% of the external pressure [9].

Pressure ulcers of the face, in the context of NIV, are a frequent complication at any age group. Still, there are two groups at greater risk such as the premature and the elderly. These two age groups present two common conditions which expose them to the tissue lesion: long- term immobilization and immunosuppression. The long-term immobilization provokes the reduction of the tissue blood flow, leading to the modification of skin trophism. Immunosuppression (by immaturity or deterioration in the context of multiple comorbidities) hampers the repairing mechanism of the wounds [10].

The alterations suffered by the senescence affect all organic systems including the integumental, exposing the elderly to the development of skin lesions. The skin loses elasticity, thickness, and resistance with age, becoming more vulnerable when subjected to pressures or aggressions, increasing the risk of ulcerations. The progressive commitment of cellular activity in the elderly, especially from the fibroblasts, affects the production of local collagen directly, which is the main protein responsible for the formation of the integumental structure and tensile strength. The frequency of cellular restitution decreases which may constitute a contributing factor for increasing the risk of skin lesion [10–13].

To sum up, the advanced age is a factor that is involved in the reduction of the tolerance of a tissue to external pressure and a risk factor for tissue necrosis [1].

According to the results of the latest research, patients that develop a face ulcer present in average a higher age. In the research made by Martins et al. [12], it was possible to verify that patients that developed a face ulcer in the context of NIV presented in average a higher age (76.5 years old) when compared to the average age of the population (74.2 years old) supporting what was previously written [11, 12].

14.3.2 Comorbidities

Comorbidities such as diabetes mellitus, arterial hypertension, anemia, infectious process, cardiovascular and neurological pathology, and respiratory disease are significant factors involved in the development of pressure ulcers [13–15].

Neurological diseases may be a triggering factor for pressure ulcers, since a decrease in the level of consciousness may influence the reduction of sensory perception, mobility, and activity [16].

According to the oxidative hypothesis, arterial hypertension courses with an imbalance between antioxidant substances and oxidants at the endothelium level of the vessels, culminating in the formation of highly oxidative substances that damage vessels. These changes promote ischemia and cellular hypoxia facilitating the onset of pressure ulcers. Also the arterial hypotension, that is caused by low blood flow, decreased blood volume, or decreased vascular resistance, increases muscle relaxation resulting too in cellular hypoxia [13].

A relevant aspect of Furman et al.'s study was the occurrence of pressure ulcers in patients with hypertension, as a significant factor of ulcer formation [13].

In 2016, Martins et al. made a prospective research designated: "Facial pressure ulcers in inpatients undergoing noninvasive ventilation in intermediate care unit." They concluded that individuals with a pressure ulcer were in majority hypertense, contrary to the ones that didn't develop pressure ulcer [12].

14.3.3 Low Weight, Bad Nutrition, and Obesity

According to Martins et al. (2016) patients with a body mass index corresponding to preobesity were more prone to develop face pressure ulcer [12].

There are other investigations that point in the opposite direction: low weight is associated with malnutrition and with a decrease in the percentage of body mass and is presented as a predisposing factor for the development of pressure ulcers [13–15].

14.4 External Factors

14.4.1 Harness and Air Volume

An excessively tight harness and the greater air volume on the interface increase the pressure applied on the nasal bridge. A large quantity of air in the cushion will distend it and make it less complacent. A less complacent facial mask presents a minor contact area between the mask and the nose, increasing the pressure executed over the nasal bridge to the extent that the strength of the compression is distributed through a smaller area. These factors present an additional effect [4].

We should apply the two-finger rule: when the harness is stuck, it should be possible to pass two fingers under [17].

14.4.2 Pressure

Studies have shown that a high level of pressure support or IPAP will increase air leak during noninvasive ventilation, and clinicians may have to decrease air leak by tightening the harness or inflating the face mask cushion. These strategies, while they may be effective in minimizing air leak, can potentially increase the risk of pressure necrosis on the bridge of the nose [4].

14.4.3 Interfaces

An oronasal interface with a larger *cushion* transmits pressure during the inspiration within a wider skin area without affecting the pressure contact. But during the expiration, the force transmitted by the skin will be transmitted to a bigger area resulting in a minor contact pressure (mask cushion pressure is higher in expiration) [18]. The larger cushion surface permits a better seal between the skin and mask at the level of the nasal bridge. This potentially allowed fewer air leaks with less tightening of the mask and avoided the harmful contact between the mask frame and the skin [20].

In general, mask *area* should be kept as low as possible since it is directly proportional to the reduction of lift-up forces and increase of contact pressure during expiration [18].

And yet, if the *size* of the interface is large for the individual, the risk of producing lesions associated with friction and the greater fixation force employed to adapt the mask to the face of the patient is superior [19].

Considering the relationships we described, one can reduce the skin ulcer risk by selecting masks with a small mask area in combination with a large mask cushion [18].

Among the different types of interface, the ones that are most frequently associated with skin lesions of the face are the nasal and oronasal masks since they produce direct pressure on the nasal bridge [5].

Research points to a higher risk of developing pressure ulcers and discomfort with the oronasal mask [20, 21, 24, 26] that, according to Yamaguti et al. [25], is considered an independent risk factor (if its usage is superior to 26 h) to the development of facial lesions. However, the possibility of having a personalized facial mask (total or oronasal) shaped to the individual seems to contribute to the prevention of pressure ulcers and, at the same time, increase the comfort [9, 20, 22, 28]. As for the facial interfaces and helmet, for producing a minor pressure on the face, obtained positive results regarding the increase of the tolerance and reduction of the pressure ulcers so, therefore, are an alternative for the NIV treatment [8, 20, 22–26] (Table 14.1).

Table 14.1 Pressure ulcers and the different interfaces

Authors	Type of research	Conclusions
Gregoretti et al. [20]	Randomized clinical trial	The *prototype total facial mask* significantly reduced the lesions of the skin, the same way it improved the comfort of the patient, when compared to the conventional mask
Antonelli et al. [21]	Prospective clinical trial	The usage of *helmet interface* didn't present complications with skin necrosis, while the group that used the facial mask had an occurrence of 21% ($p = 0.002$)
Fauroux et al. [22]	Transverse retrospective study	The usage of a *personalized mask* shaped for the child was associated with the reduction of the skin breakdown score
Racca et al. [23]	Clinical cases	A nasal ulceration was verified with the usage of the *nasal mask* (3–4 days); the *helmet interface* increased the tolerance of the NIV and allowed the recovery of pressure ulcers
Lemyze et al. [24]	Prospective observational study	It recommends the usage of a *total facial mask* when NIV is extended, so that it decreases the occurrence of facial lesions and obtains better outcomes in comparison to the oronasal facial mask
Yamaguti et al. [25]	Retrospective transversal study	The usage of the *oronasal facial mask for a period* > 26 h was independently associated with the development of facial lesions; *the total facial mask* obtained an occurrence of lesions of the skin much lower to the *oronasal mask*. That's why its usage is recommended, for a greater tolerance and comfort
Schallom et al. [26]	A before-after study	The *total facial mask* significantly reduced the occurrence of pressure ulcers and enhanced comfort in comparison to the *oronasal facial mask*. It is suggested to use total facial mask as soon as possible in order to reduce the ulcers in patients under NIV
Patel et al. [27]	Randomized clinical trial	Statistically, there wasn't a relevant difference in the occurrence of pressure ulcers between the *facial mask group* and the *helmet group*, varying only on the region of the lesion, in the nose in the first group and in the neck in the helmet group
Shikama et al. [28]	Randomized crossover study	The usage of a *personalized oronasal mask* through a 3D scanning mechanism can contribute to the prevention of pressure ulcers in NIV and for a better comfort of the inpatient by increasing the contact area

14.4.4 Drugs

Drugs, mainly of continuous use, can also contribute to the development of pressure ulcers [19].

Sedatives, analgesics, and muscle relaxants are pharmacological classes frequently used in the context of intermediate and intensive care units. These conditions decrease the sensory perception and impair mobility making them less reactive to excessive pressure and more susceptible to injury. In the study by Furman et al. [13], it was found that more than half of the patients with pressure ulcers were under analgesic therapy [12, 13, 19].

Hypotensive agents reduce blood flow and tissue perfusion making them more susceptible to pressure [19].

Corticosteroid treatment is a risk factor that has been reported to decrease "tissue tolerance" for pressure. It was also reported to be a risk factor for pressure necrosis [10].

14.4.5 Humidity and Dehydration

Several researches show humidity of the skin as a factor involved in the increase of the risk of pressure ulcer [13, 14]. The excess of humidity macerates the skin, leaving the more superficial layers weaker and more vulnerable to the occurrence of lesions [13].

On the other hand, other research states that dehydration can also be a risk factor associated with the risk of skin ulcer. In the research of Furman et al. [13], the dry skin, present in 73.1% of the inpatients, was identified as a factor associated with skin ulcers, probably due to dehydration. Dehydration is characterized by the reduction of water and total electrolytes of the organism making them susceptible to rupture due to a reduced elasticity as well as a lower tolerance to friction. In the research made by Silva et al. [11], a higher frequency of pressure ulcers on the face of inpatients with an integral, dry skin was verified (16.7%). This factor can be associated with the dehydration that inpatients in a critical state present, as it is highlighted in another research of Campos et al. [13, 15].

Dehydration is a factor involved in the reduction of the tolerance of a tissue to the external pressure and a risk factor for tissue necrosis [4].

14.4.6 Duration

Interface-related pressure ulcers are medical device-related pressure ulcers and the longer treatment lasts, the more likely they are to develop [2].

Nasal skin lesions (erythema, ulcers) at the site of mask contact increase with longer NIV durations. According to Martins et al. study, patients submitted to more NIV hours per day and for a greater number of NIV days presented higher frequency of ulcers [12].

14.5 Prevention and Treatment

There is a variety of interventions that can be used to minimize the risk of skin breakdown in patients doing NIV. The most common are protection coatings (tapes, foams, and others) placed on the skin in places of higher pressure, being soaked in hydrocolloid, which present better results in several studies [1–4]. However, there is also the option of hyper-oxygenated fatty acids [5] and the transparent film tape [2], which present promising results in the recovery and prevention of facial pressure ulcers.

In 2003, Lloys et al. presented positive results related to the sealing of the facial mask with water, allowing a delay on the appearance of pressure ulcers [6]. Other measures, such as rotation or alteration of the interface and the interruption of usage periods, can also be relevant in the prevention and delay of the occurrence of skin lesions [7–12].

These types of measures should be introduced during the therapy with NIV, especially in patients with higher risk or that present any sign of vulnerability of the skin during the treatment.

Caring for wounds associated with NIV, as with those with other causes, starts with preparing the base, then involving the control both of

non-viable tissue and the infection or inflammation and the exudate, as well as stimulating the epithelial edges, through various interventions: cleaning, debridement, managing infections, and use of dressings. It is important to note the treatment of this damage is complex since it had to be compatible with care and the continued use of the equipment that caused it [36].

In the management of facial skin breakdown related with the use of NIV devices, we performed daily disinfection and application of topical cream containing hyaluronic acid sodium salt on pressure ulcers [10] (Table 14.2).

14.6 Key Recommendations

- Knowledge of the risk factors associated with pressure ulcer development is the key to the success of prevention strategies. The risk of developing pressure ulcers should be assessed in patients in all care settings within the first 6 h after patient admission.
- Most of the patient-dependent risk factors cannot be changed, but if interface fitting, regular assessment, and skin protection are considered from the beginning of therapy and adapted to the individual patient's needs, skin

Table 14.2 Prevention strategies of skin lesions in NIV users

Authors	Type of research	Conclusions
Protection coating and topical agents		
Callaghan et al. [29]	Randomized clinical trial	The Granuflex group (*hydrocolloid coating*) presented, throughout the study, a minor occurrence of skin lesions in comparison to the Spenco Dermal group (*adhesive film coating*). It also revealed a great coating effect when compared to the control group (no coating)
Weng et al. [30]	Observational cohort study	A significant reduction on stage I pressure ulcers of the nasal bridge in both groups that used protection coating was verified (*hydrocolloid* and *transparent adhesive film*) when compared to the control group (no intervention)
Tai et al. [31]	Randomized clinical trial	The *foam* and *hydrocolloid* coatings obtained positive results in the prevention of pressure facial lesions
Bishopp et al. [32]	Quasi experimental study before-after	There was a significant reduction, statistically speaking, in the occurrence of stage II pressure ulcers in group 2 (*hydrocolloid coating*) when compared to the control group (no intervention)
Pena-Otero et al. [33]	Randomized clinical trial	The group that used the *hyper-oxygenated fatty acid (HOFA) solution* presented a significant decrease of the occurrence of facial pressure ulcers when compared to the remaining groups. The groups that used polyurethane coatings obtained a greater occurrence of pressure ulcers than the control group
Lloys et al. [34]	Randomized prospective study	The usage of water in the *facial mask sealing* NIV delayed in average 847 min the occurrence of facial pressure ulcers, when compared to air sealing
Alteration/rotation of the interface		
Fauroux et al. [22]	Transversal retrospective study	The usage of a personalized mask to the child's face was associated with the reduction of skin lesions' score, being suggested the *alteration of the interface* as a correction measure
Racca et al. [23]	Clinical cases	The alteration of the nasal mask to a *helmet* type one increased the tolerance of the NIV and allowed the recovery of pressure ulcers. It is suggested the rotation or alteration of the interfaces for the recovery and prevention of ulcers
Yamaguti et al. [25]	Retrospective transversal study	In patients under an extended interrupted NIV, for a better prevention of pressure facial ulcers, it is suggested the *rotation and alteration* of the interface
Schallom et al. [26]	A before-after study	It is suggested the *rotation* of the total facial mask, as soon as possible, as a way to reduce ulcers in inpatients doing NIV
Interruption of the usage periods		
Fauroux et al. [22]	Transversal retrospective study	The *reduction of the daily usage* of NIV with positive pressure is referred as a preventive measure of the occurrence of skin breakdown
Silva Martins et al. [11]	Prospective study	The *number of hours with NIV* increases the frequency of pressure ulcers. It is suggested the interruption of usage periods

breakdown can be avoided or at least reduced in many cases.

- The first few hours of acute NIV are extremely important, and time spent fitting the mask is well invested. When interface does not fit appropriately, friction or shearing force may be induced between the devices and skin, thus causing wound deterioration.
- Routine assessment of the skin (check every 3–4 h) and risk of pressure ulcers, regular pressure relief, and skin-protective strategies should be included in the routine application of NIV to reduce discomfort and the occurrence of soft tissue damage.
- Usage of interfaces with a small area of interface and a big cushion.
- Total facial masks and helmet can be good alternatives in cases of NIV for long periods.
- Hydrocolloid coatings/dressings and hyperoxygenated fatty acid solutions should be considered and used for the prevention and treatment of pressure ulcers.
- Rotation or alteration of the interface and the interruption of usage periods of NIV may help to prevent face lesions.

References

1. Defloor T. The risk of pressure sores: a conceptual scheme. J Clin Nurs. 1999;8:206–16.
2. Brill A. How to avoid interface problems in acute noninvasive ventilation. Breathe. 2014;10:230–42.
3. Romanelli M, Clark M, Cherry G, Colin D, Defloor T. Science and practice of pressure ulcer management. London: Springer; 2006. p. 11–26. ISBN 978-1-84628-134-1
4. Munckton K. Ho KM, Dobb GJ, Das-Gupta M, Webb SA. The pressure effects of facemasks during noninvasive ventilation: a volunteer study. Anaesthesia. 2007;62:1126–31.
5. National pressure ulcer advisory panel, european pressure ulcer advisory panel and pan pacific pressure injury alliance. Prevention and treatment of pressure ulcers: Quick reference guide. Emily haesler (Ed.). Cambridge Media: Perth, Australia; 2014.
6. Worsley PR, Prudden G, Gower G, Bader DL. Investigating the effects of strap tension during noninvasive ventilation mask application: a combined biomechanical and biomarker approach. Med Devices (Auckl). 2016;9:409–17.
7. Barros LS, Talaia P, Drummond M, Natal-Jorge R. Facial pressure zones of an oronasal interface for noninvasive ventilation: a computer model analysis. J Bras Pneumol. 2014;40:652–7.
8. Holanda M, Reis R.C, Winkeler G. F. P, Fortaleza S. C. B, Lima J. W. O, Pereira E. D. B. Influence of total face, facial and nasal masks on short-term adverse effects during noninvasive ventilation. J Bras Pneumol. 2009;35(2):164–73.
9. Kosiak M. Etiology of decubitus ulcers. Arch Phys Med Rehabil. 1961;42:19–29.
10. Maruccia M, Ruggieri M, Onesti MG. Facial skin breakdown in patients with non-invasive ventilation devices: report of two cases and indications for treatment and prevention. Int Wound J. 2015;12:451–5.
11. Silva M, Oliveira S, Diniz E, Fernandes M. Úlcera por compressão em pacientes hospitalizados: Análise da prevalência, fatores de risco e lesões instaladas. Fiep Bulletin. 2014;84 (esp. ed.).
12. Martins M, Ribas PSC, Sousa JRA, Silva NAP, Preto LSS, Correia TIG. Face pressure ulcers in patients undergoing ventilation noninvasive hospitalized in intermediate care. Nursing Rev Ref. 2016;10.
13. Furman G, Rocha AF, Guariente MHD, Barros SKS, Morooka M, Mouro D. Pressure ulcers: incidence and association of risk factors in patients of a university hospital. Nursing Rev UFPE. 2010;4(3):1506–14.
14. Rogenski NMB and Santos VLCG. Incidence of pressure ulcers at a university hospital. Rev Latino-am Nursing. 2005;13(4):474–80.
15. Campos SF, Chagas ACP, Costa ABP, França REM, Jansen AK. Factors associated with the development of pressure ulcers: the impact of nutrition. J Nutr. 2010;23(5):703–14.
16. Jorge SAJ and Dantas SRPE. Abordagem multiprofissional do tratamento de feridas. Atheneu Ed., São Paulo; 2005; ISBN 8573795751.
17. Meduri GU, Abou-Shala N, Fox RC, Jones CB, Leeper KV, Wunderink RG. Noninvasive face mask mechanical ventilation in patients with acute hypercapnic respiratory failure. Chest. 1991;100:445–54.
18. Dellweg D, Hochrainer D, Klauke M, Kerl J, Eiger G, Kohler D. Determinants of skin contact pressure formation during non-invasive ventilation. J Biomech. 2010;43:652–7.
19. Ramos P. Non invasive mechanical ventilation. 2007, XI Monographs.
20. Gregoretti C, Confalonieri M, Navalesi P, Squadrone V, Frigerio P, Beltrame F, et al. Evaluation of patient skin breakdown and comfort with a new face mask for non-invasive ventilation: a multi-center study. Intensive Care Med. 2002;28:278–84.
21. Antonelli M, Conti G, Pelosi P, Gregoretti C, Pennisi MA, Costa R, et al. New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet—a pilot controlled trial. Crit Care Med. 2002;30(3):602–8.
22. Fauroux B, Lavis JF, Nicot F, Picard A, Boelle PY, Clément A, et al. Facial side effects during noninva-

sive positive pressure ventilation in children. Intensive Care Med. 2005;31(7):965–9.
23. Racca F, Appendini L, Berta G, Barberis L, Vittone F, Gregoretti C, et al. Helmet ventilation for acute respiratory failure and nasal skin breakdown in neuromuscular disorders. Anesth Analg. 2009;109:164–7.
24. Lemyze M, Mallat J, Nigeon O, Barrailler S, Pepy F, Gasan G, et al. Rescue therapy by switching to total face mask after failure of face mask-delivered noninvasive ventilation in do-not-intubate patients in acute respiratory failure. Crit Care Med. 2013;41:481–8.
25. Yamaguti WP, Moderno EV, Yamashita SY, Gomes TG, Maida AL, Kondo CS, Salles IC, Brito CM. Treatment-related risk factors 3-6. for development of skin breakdown in subjects with acute respiratory failure undergoing noninvasive ventilation or CPAP. Respir Care. 2014;59:1530–6.
26. Schallom M, Cracchiolo L, Falker A, Foster J, Hager J, Morehouse T, Watts P, Weems L, Kollef M. Pressure ulcer incidence in patients wearing nasal-oral versus full-face noninvasive ventilation masks. Am J Crit Care. 2015;24:349–56.
27. Patel BK, Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA. 2016;315(22):2435–41.
28. Shikama M, Shikama M, Nakagami G, Noguchi H, Mori T, Sanada H. Development of personalized fitting device with 3-dimensional solution for prevention of NIV oronasal mask-related pressure ulcers. Respir Care. 2018;63(8):1024–32.
29. Callaghan S, Trapp M. Evaluating two dressings for the prevention of nasal bridge pressure sores. Prof Nurse. 1998;13(6):361–4.
30. Weng M. The effect of protective treatment in reducing pressure ulcers for non-invasive ventilation patients. Intensive Crit Care Nurs. 2008;24(5):295–9.
31. Hu LZZ. Preventing facial pressure injuries in patients who use noninvasive positive pressure ventilators: the efficiency of dressings. 2016;63(5):86–94.
32. Bishopp A, Oakes A, Antoine-Pitterson P, Chakraborty B, Comer D, Mukherjee R. The preventative effect of hydrocolloid dressings on nasal bridge pressure ulceration in acute non-invasive ventilation. Ulster Med J. 2019;88(1):17–20.
33. Otero DP, Domínguez DV, Fernández LH, Magariño AS, González VJ, Klepzing JV, Montesinos JV. Preventing facial pressure ulcers in patients under non-invasive mechanical ventilation: a randomised control trial. J Wound Care. 2017;26(3):128–36.
34. Lloys A, Madrid C, Solà M, Segura M, Tarré E, Mas A. The use of water to seal facial mask for non invasive ventilation reduces the incidence of pressure ulcers. Enferm Intensiva. 2003;14(1):3–6.
35. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized prospective trial of non-invasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med. 1995;151:1799–806.
36. Raurell-Torredà M, Romero-Collado A, Rodríguez-Palma M, Farrés-Tarafa M, Martí JD, Hurtado-Pardos B, et al. Prevention and treatment of skin lesions associated with non-invasive mechanical ventilation. Recommendations of experts. Enferm Intensiva. 2017;28(1):31–41.

Noninvasive Ventilation and Pulmonary Rehabilitation

15

Paolo Buonpensiero

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Abbreviations

AE	Acute exacerbation
COPD	Chronic obstructive pulmonary disease
EPAP	Expiratory positive airway pressure
IPAP	Inspiratory positive airway pressure
NIV	Noninvasive ventilation
PS	Pressure support
RR	Respiratory rate
VT	Tidal volume
WOB	Work of breathing

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15.1 Introduction

Reduced exercise tolerance and quality of life are commonly reported in chronic obstructive pulmonary disease (COPD) patients, and key elements of their pulmonary rehabilitation (PR) programmes are also represented from exercise training programmes that improve exercise tolerance (less fatigue and less dyspnoea) and quality of life of COPD patients [1] as well as reduction in healthcare use [3]. These well-proven and measurable effects have been demonstrated in stable COPD patients as well as in COPD during or after an acute exacerbation (AE) [4]. To date, publications attributable to such programmes unequivocally demonstrate the effectiveness of physical exercise in this patient population. From these considerations and from the level of scien-

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tific publications, until now produced, exercise training programmes can be considered a cornerstone of PR in COPD. Exercise practice and prescription has nowadays different scopes justified from multiple complex and coexisting physiopathological backgrounds in COPD: cardiovascular and ventilatory limitation gas exchange dysfunctions, respiratory and peripheral muscle changes and not least a permanent oxidative stress status [2]. Furthermore comorbidities often present in COPD population (obesity, diabetes, neurological conditions) play a negative role in planning and then in reaching effective and long-term results [3]. Poor motivation anxiety and depression also can play an additional negative factor in the success of PR programmes. General accepted rules regarding the main outcomes for physical training in COPD patients (but also in healthy population) indicate that total training load must exceed the load encountered during daily life improving the aerobic capacity and muscle strength always reflecting the *individual* general features [5].

The most relevant mechanism of action of these conditioning strategies passes through morphological and biochemical modifications (at the same time) of muscles responsible for locomotion (as well as postures) as the quadriceps.

The ability (capacity) to work in the aerobic regime is improved by reducing the accumulation of lactates, the ventilatory load and the related feeling of dyspnoea at a given a submaximal workload.

Although training has been shown to be an essential component of comprehensive rehabilitation programmes, some patients do not always benefit to the same extent (apart coexisting comorbidities), and a proportion of COPD patients do not substantially benefit from training programmes therefore not improving their performance and exercise capacity (so-called nonresponders). Due to the severity of the pathology (severe airflow obstruction and deep ventilator limitation during exercise), these "nonresponders," i prefer to call them "diversely responders," are not able to reach optimal targets of training intensity necessary to produce "the expected" adaptation to "exercising stimulus" at the level of the peripheral muscles [6].

The ventilatory derangement, at given workload, responds with expiratory flow limitation, increased respiratory frequency and abnormal expiratory lung emptying time with dynamic hyperinflation, greater mechanical disadvantage, greater intrinsic PEEP, dyspnoea worsening and early termination of exercise.

An alternative strategy to overcome the effects of the characteristic physiopathology of the most severe forms of COPD (or not responders) to physical exercise is represented from the use of NIV.

The use of NIV during exercise belongs to a series of strategic approaches (complementary) developed inside PR programmes with main aim to overcome intrinsic limitation of COPD to exercise.

Some of these strategies appear more common to use and may be more easy; other one as noninvasive ventilation seems to be less frequently used because it may appear (until now) difficult to implement in everyday clinical practice.

Using NIV during exercise has been suggested in COPD from more than 15 years and that adding NIV to exercise is a useful way to improve the whole response to COPD patients to physical exercise.

In a comprehensive way NIV during exercise in COPD acts with different mechanisms (by IPAP and EPAP administration):

- Reduction in work of breathing.
- Respiratory muscle unloading.
- Blood flow switch from respiratory to limb muscles.
- Anti-inflammatory activity.
- Changes in vegetative status.
- Dynamic hyperinflation reduction.

The aim of the work is to provide, in a narrative way, useful (I hope) reviewed informations arising from physiological studies, clinical trials and meta-analysis in order to animate discussions on the clinical utility of NIV applied to exercise as well as its potential application fields.

15.2 Using NIV During Exercise (Rationale and Different Ventilation Modes)

One of the first reports (showing the proof of concept about NIV application during exercise in COPD) of a pressure noninvasive support during exercise in a COPD population explicitly demonstrated the effects of this intervention to reduce respiratory muscle effort and dyspnoea at equivalent exercise workloads improving and increasing exercise tolerance [7]. Another element of physiological rationale inherent in the use of NIV during exercise in COPD patients derives from experiences conducted on healthy subjects subjected to high levels of exercise.

In these subjects the respiratory work secondary to the stimulus is inversely correlated with the blood flow of the peripheral (limb) muscles [8]. From these observations could be argued that in COPD during leg exercise at a given workload, were WOB increases, such switch could predispose peripheral muscle to severe fatigue with exercise interruption. In support of this rationale in subsequent studies, the preventive role of the unloading strategies in diaphragmatic fatigue induced by physical exercise has been demonstrated in COPD subjects [9].

Assisted ventilation should reduce WOB by unloading inspiratory muscle and therefore reducing their blood flow requirements in favour of an enhanced limb blood flow.

On previous hypothesis that inspiratory muscle performance determines exercise endurance, O′ Donnell et al. demonstrated that CPAP reduces dyspnoea by unloading respiratory muscle [10].

Most recently these previous results were not confirmed (Walterspacher et al. [11]) in COPD patients using CPAP during exercise (climbing stairs). The results showed no benefits for the patient, and major outcomes such as hyperinflation, oxygenation, hypoventilation and blood lactate production did not improve in the patients supported by CPAP [11]. Similar studies also (in CPAP group) reported less leg discomfort.

Generally CPAP titration (on individual basis) is suggested, but this would involve the measurement of the intrinsic PEEP intervention practically unrealistic in daily clinical practice. High pressures could increase respiratory effort [12].

15.2.1 Pressure Support

Inspiratory pressure support is a mode of ventilatory assistance designed to maintain a constant preset positive airway pressure during spontaneous inspiration. The respiratory rate (RR), tidal volume (VT) and inspiratory time are regulated by the patient, and the work performed by the inspiratory muscles, especially the diaphragm, is substantially reduced [13]. First physiological evidence showed that PS (in COPD during cycling) increased ventilation (VE) through changes to both VT and RR. Physiologically this was unrelated to reductions in inspiratory effort, evidenced by oesophageal and transdiaphragmatic pressure-time intervals [14]. Pressure support ventilation has a role in unloading respiratory muscles, and this action was better demonstrated by kyroussis et al. [14] investigating the effects of PS ventilation in severe COPD patients during treadmill exercise. Oesophageal and transdiaphragmatic pressures arose early during exercise (in unsupported patients) showing constantly pressures until dyspnoea was so high to cause patients to stop exercise. With the same workload (same distance) but supported with NIV inspiratory and expiratory time products, results decreased [14]. Another sensitive outcome at this type of intervention is the lactate behaviour. Severe COPD patients show, if supported with PS, also at high levels of exercise a delay in lactate levels while walking on a treadmill [15].

This physiology-related concept assumes more scientific and clinical weight if we look at the studies of Harms et al. [8] in which in normal subjects supplemental NIV during exercise had improved blood flow distribution. Improving

blood flow distribution in COPD by unloading respiratory muscles has a direct less lactate and better response to exercise. It means less leg fatigue perceived and better oxygenation.

The improvement in inspiratory muscle strength during NIV in this study could be responsible for the decrease of mechanical load and pause on the beginning of the fatigue with a consequent less metaboloreflex activity of the respiratory muscles.

Borghi and Silva [9] showed an improvement of lactate/speed ratio (ratio of lactate concentration to walk speed oxygen uptake VO_2) in stable COPD after 6 weeks of training NIV (PS) supported. This could be related to a better oxidative muscle capacity. During the last decades, evidence supporting a pro-inflammatory behaviour of COPD (also in response to exercising stimuli) patients has raised attention to clinicians. Hannink et al. found a protective action of NIV during exercise in COPD patients during exercise and especially in IL6 production [16].

Utility of NIV by means of PAV has also been investigated during unsupported upper arm exercises (also present as routine exercise in PR programmes for COPD patients).

During exercise NIV improved endurance upper arm exercise by means of decreased dyspnoea and perceived exertion although muscles are involved to a respiratory and postural task (in the same time), and some of the work is shifted to diaphragm and abdominal muscles. Upper arm exercises (elevation) increase respiratory muscle work in chronic respiratory failure so the NIV support could work in unloading respiratory muscles.

15.2.2 Proportional Assist Ventilation

Proportional assist ventilation (PAV) delivers assisted ventilation in proportion to patient effort and is developed to enhance ventilator responsiveness. PAV uses very sensitive triggers and response not by means of a preset inspiratory pressure but with flows and pressures in proportion to the patient's effort [16]. Bianchi et al. [17] in a randomized short-term crossover trial (2 consecutive days) compared the effects of CPAP, IPS and PAV in COPD patients exercising at four endurance tests (80% max workrate). In comparison to sham ventilation, PAV, PSV and CPAP were able to increase the endurance time (from 7.2 ± 4.4 to 12 ± 5.6, 10 ± 5.2 and 9.6 ± 4.6 min, respectively) and to reduce dyspnoea and oxygen flow to the nasal mask. However, the greatest improvement was observed with PAV [17]. In patients with IPF, PAV produced better submaximal test with lower heart rate compared with CPAP, during exercise in the presence of constant nonchanging systolic and diastolic pressures among tests [18]. In a cohort of obese patients (BMI >34), PAV applied during exercise showed to improve exercise endurance (31%) and reduction of dyspnoea with 50% of the subject responders. In this study, although some methodology caveats regarding post hoc analysis are subjected to bias, probable learning effects, the authors suggest this mode of NIV applied to exercise in obese patient a further possible novel technique to enhance PR in obese patients [19]. Utility of NIV by means of PAV has also been investigated during unsupported upper arm exercises (also present as routine exercise in PR programmes for COPD patients). During upper arm exercise, NIV improved endurance and decreased dyspnoea and perceived exertion although the muscles are involved in a respiratory and postural task (in the same time) and some of the work is shifted to diaphragm and abdominal muscles. Upper arm exercises (elevation) increase respiratory muscle work in chronic respiratory failure so the NIV support could work in unloading diaphragm respiratory task [20].

15.2.3 Controlled Mechanical Ventilation

In the assisted-control ventilation, the device delivers a positive pressure breath at a preset tidal volume in response to the patient's respiratory effort. Preset rate breath is present if no rate effort occurs in the preselected time period. This modal-

ity was first described from Tsuboi et al. [21] in patients with pulmonary tuberculosis and lately in 2002 from Highcock [22] in patients with kyphoscoliosis.

Applying NIV in the latter modality via nasal mask during exercise resulted in improvement of exercise endurance and breathlessness.

15.3 Suggestions from the Evidences

Proposing NIV as an alternative strategy to overcome COPD pathology, limiting effects on exercise and cardiovascular performance, has been supported by a good number of studies in the last decade. These show in most of them immediate improvement in the main outcomes subjected to investigation. All the different devices used in the studies cited in the previous pages of this chapter in relation to different types of exercise testing in patients with mild or severe COPD create an immediate positive variation of the main outcome studied, satisfying (clearly in most of the cases) specific physiological background and suggesting a clinical application in this area of respiratory care and creating expectations which may be better clinical outcomes in our patients.

In 2014 the Cochrane review of Menadue [23] after more than a decade of clinical studies tried to summarize the best clinical effects in order to answer the question regarding the clinical utility of NIV applied alongside PR in affecting HRQL and PA in COPD patients. Not surprisingly in the work of Menadue, the total number of patients subjected to the six intervention studies was quite low ($n = 126$).

Population of COPD ranged from severe to very severe (mean forced expiratory volume in 1 s (FEV1) ranged from 26% to 48% predicted). The participant's mean age ranged from 63 to 71 years, and cycling or treadmill exercise was performed in the studies for a period ranging from 6 to 12 weeks.

The participant showed an increase in percent delta peak and endurance exercise capacity with NIV during training (mean difference in peak exercise capacity 17%, 95% confidence interval (CI) 7% to 27%, 60 participants, low-quality evidence; mean difference in endurance exercise capacity 59%, 95% CI 4% to 114%, 48 participants, low-quality evidence) with no significant improvement in other outcomes.

Also measures of HRQL (St George's Respiratory Questionnaire) didn't show any significant modification.

Surprisingly physical activity measures were not conducted in the studies so the effects measured are limited to a physiological effect for this reason we don't know if the interventions were able to modify functional everyday activities of the patients; furthemore no follow-up measures or were taken after the studies.

Most of the studies included in the work of Menadue showed (apart allocation method) some (expected) criticism about the risk of bias.

In all the study the personnel who trained the participants was not blinded to group allocation nor to the participants to the study.

Only in one study [24], a sham NIV (IPS cmH_2O) was used also if the same authors in a precedent study demonstrate an equivalent exercise effect on performance of the participants [25].

Half of the studies reported blinded assessors to evaluate clinical outcomes [24, 26, 27].

Two studies [28, 29] did not use blinded assessors. One study did not report whether outcome assessors were blinded [30].

Considering the number of the studies and the number of the participants, bias from incomplete data for dropouts was relatively high and intolerance to NIV was the main reason.

These data about dropout for intolerance highlight some until now not resolved problems about technical problems than can affect patients' adherence to the training NIV supported (interfaces choice, circuit and ventilator efficiency).

The results about the improvement in adding NIV to exercise (to achieve a greater percentage improvement in lower limb peak and endurance exercise capacity, to exercise at a higher training intensity and to gain a greater physiological training effect) could have been overestimated, and differences in the outcomes were found only when

percentage change from baseline values rather than post-intervention values was used in analyses.

Large interindividual or intergroup baseline differences were present, and the use of change from baseline values rather than post-intervention analysis could provide greater statistical significance to detect treatment effects. Due to the lack of consistency of the outcomes produced from the participants, to the error bias reported that may be influenced by the results, clear indication of a *extensive* use of NIV in clinical practice during PR cannot be suggested. From the studies evidence can be provided that the use of NIV during exercise allows people with COPD to exercise to a higher level of intensity and achieve physiological training effects greater than exercise alone. Ricci et al. [25] in a meta-analysis attempted to evaluate the effectiveness of supporting exercise training with NIV in terms of physiological effects after the completion of a pulmonary rehabilitation programme in patients with COPD and investigate the dose-response relationship between physical improvement and total training time in the NIV arm. The search strategy looked at the presence of a proper description of the training modules of PRP meta-analysis, and meta-regressions were performed using random effects models. From 107 studies only 8 were selected because of a proper description of the training modules, and all the studies were controlled trials (2 consecutive and other used randomization). At the end of the training protocol, the sample size in each study varied between 7 and 15 patients, and the number of dropouts varied between zero and the 50% reported by Bianchi et al. [28]. Quality scores of almost all of the studies examined from Ricci et al. with PEDro scale was satisfactory (minimum score 6, maximum 8; see Table 15.1). The duration of the programmes is homogeneous although the individual sessions were heterogeneous (20–60 min). Exercise training also consisted of treadmill training, cycling with a cycle ergometer or endurance walking. The declared ventilation protocol in the NIV arm was extremely heterogenous. In the studies comparing NIV vs placebo (also if not statistically significant), Costes et al. and Toledo notified same differences about HR as outcome between NIV and placebo group. The behaviour of this outcome showed better in the NIV group with a reduction, respectively, of 5.0 and 5.8 beats/min. Bianchi et al. [28] and Hawkins [29] used PAV and other used PSV. In the studies evaluated, the NIV arm clearly shows significant post-training modifications, considering the prevalence of the variables under the interventions (especially HR and lactate modifications). Heart rate at iso time improved by 6 beats/min (95% CI 0.98–11.01, *P*_0.02) after training, as did workload (fixed effect mean change 9.73 [95% CI 3.78–15.67], *P*_0.001) and $V\dot{O}_2$ (fixed effect mean change 242.11 [95% CI154.93–329.9], *P* 0.001). There is important change also in lactate production after training exercise (fixed effect mean change 0.21–*P* 0.025 [95% CI 0.1 to 0.54]. Total training time also plays a determinant role in the variable modifications with a positive interrelationship. The slopes in the meta-regressions utilized in the work of Ricci et al. [25] were 0.015 (95% CI 0.008 to 0.02) for HR and for workload slope 0.01 (95% 0.0002–0.0215). NIV shows beneficial effects on HR and V_o; the same treatment seems to have similar effects (as the controls) on workload and lactate production, but the element that seems really effective in influencing the effect of the PR is the training duration and not NIV, but considering the effects of NIV on HR and V_o (the arm patients had lower HR, higher workload and improved VO_2), this could, for instance, play a concurrent role in the better performance of PR. NIV settings and mode in the studies resulted in different approaches, and maybe the ventilators used at the time of the studies were not able to fulfill patient ventilatory demand resulting indeed in problems of patient-ventilator synchrony. NIV settings utilized from authors were low IP that could not produce significant *physiological* effects able to *assist the participants during the efforts. No studies declared PEEP adjustments related to PEEPi calculations routinely difficult or a mission impossible in the routine care setting*.

Adding NIV in patients not confident with the ventilators' physical effects and interfaces could be difficult, and physiological effects of the tech-

Table 15.1 Summary of findings from exercise programs

Author-year	Subjects	Mean age_SD year (range)	Mean FEV1_SD %	Training protocol	Quality score
Borghi-Silva (2010) NIV group Oxy group	12 12	68 ± 9 67 ± 7	34 ± 10 37 ± 7	18 sessions (30 min) 6 weeks	7 7
Toledo (2007) BPAP group Control group	9 9	68 ± 9 67 ± 11	33 ± 10 34 ± 8	36 sessions (30 min) 12 weeks	8 8
van't Hul (2006) NIV group Control group	14 15	70 ± 5 71 ± 4	41 ± 10 38 ± 9	24 sessions (45 min) 8 weeks	8 8
Reuveny (2005) BPAP group Control group	9 10	64 ± 9 63 ± 9	32 ± 4 33 ± 9	16 sessions (45 min) 8 weeks	6 6
Costes (2003) NIV group Control group	7 7	60 ± 7 67 ± 6	31 ± 12 32 ± 7	24 sessions (30 min) 8 weeks	6 6
Jhonson (2002) NIV group HT group UT group	11 10 11	69 ± 9 62 ± 9 67 ± 8	32 ± 9 34 ± 13 31 ± 11	12 sessions (20 min) 6 weeks	6 6 6
Hawkins (2002) PAV Control group	10 9	68 ± 9 66 ± 7	26 ± 7 28 ± 7	18 sessions (30 min) 6 weeks	6 6
Bianchi (2002) PAV group Control group	9 10	64 (61–67) 65 (61–69)	48 ± 19 40 ± 12	18 sessions (60 min) 6 weeks	

nique could be more evident in the presence of hypercapnia if NIV mode and settings are better adjusted. Vitacca et al. reported a significant improvement in endurance time in patients with CVF on home nocturnal NIV and long-term oxygen therapy [31]. The patients in the arm group received NIV during exercise (as add-on) with same interfaces and ventilators used at home at the start of exercise (mean values IPAP, 17.4 cmH_2O; EPAP 6.5 cmH_2O; inspiratory time 1.2 s). The control group received exercise programme without add-ons. Improvement in endurance time was significantly greater in the NIV group compared with the non-NIV training group (754 ± 973 vs 51 ± 406 s, $P = 0.0271$); dyspnoea improved in both groups, while respiratory muscle function and leg fatigue improved only in the NIV ET group. MRF-28 improved only in the group training without NIV. Gloekl et al. added high-pressure NIV in a randomized controlled crossover trial ($n = 20$) in CVF patients with NIV pressures (mean 27 ± 3 cmH_2O) and with oxygen supplementation [32–34]. Compared to the control group, patients in the arm group improved by 39% endurance time showing other interesting behaviour outcomes without side effects. When applying NIV in COPD (CVF) during exercise, some considerations must be done because until now the effects of intrathoracic pressures during exercise in these patients are still unknown. Preliminary evaluation of lung and cardiac function should be performed for safety and ethical issues (Table 15.1).

15.3.1 Problem-Solving in the Practice and Safety Issues

Interfaces: during high-intensity exercise (or for some patients also during simple walking or upper arm exercise), the choice of a full-face mask or a mouthpiece could help to prevent air leak but especially in naïve patients could reduce adherence or performance or both.

In more severe COPD patients, consider the use of a plateau valve to avoid rebreathing in single circuit.

Cardiac comorbidities in CVF have a high prevalence rate; NIV during to exercise could predispose to a mechanical doping because the relief of dyspnoea due to NIV adding [35].

Patients with unknown cardiac ischemia could exercise at higher intensity level of their ischemic cardiac threshold.

Consider careful clinical assessment of the patient before practicing.

Consider personnel-staff availability due to the need of one-to-one approach and the time required for the comprehensive procedure.

Consider patient need and comfort due to high risk of dropouts.

Consider location, logistics and strategic technologies that help support home exercise with NIV.

15.4 Final Remarks

As in other fields of respiratory care, application of NIV during exercise in the comprehensive approach of PR seems to need other well-conducted RCTs approaching the methodology of the research with more specific outcomes, with better phenotipization of the patient and why not of the devices and mode of ventilations.

The evidence from published studies, the experience and confidence of staff and the presence of basic technological resources can help us to make this complementary therapy a positive reality for many patients otherwise not treated.

References

1. Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigaré R, et al. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;189(9):e15–62.
2. Koechlin C, Couillard A, Cristol JP, Chanez P, Hayot M, Le Gallais D, Préfaut C. Does systemic inflammation trigger local exercise-induced oxidative stress in COPD? Eur Respir J. 2004;23:538–44. https://doi.org/10.1183/09031936.04.00069004.
3. McNamara RJ, McKeough ZJ, McKenzie DK, Alison JA. Physical comorbidities affect physical activity in COPD: a prospective cohort study. Respirology. 2014;19(6):866–72.
4. Parekh PI, Blumenthal JA, Babyak MA, Merrill K, Carney RM, Davis RD, Palmer SM, INSPIRE Investigators. Psychiatric disorder and quality of life in patients awaiting lung transplantation. Chest. 2003;124:1682–8.
5. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;15;188:e13–64.
6. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training inpatients with obstructive lung disease. Am Rev Respir Dis. 1991;143(1):9–18.
7. Maltais F, Hajo KR, Gottfried SB. Pressure support reduces inspiratory effort and dyspnea during exercise in chronic airflow obstruction. Am J Respir Crit Care Med. 1995;151(4):1027–33.
8. Harms CA, Babcock MA, McClaran SR, Pegelow DF, Nickele GA, Nelson WB, Dempsey JA. Respiratory muscle work compromises leg blood flow during maximal exercise. J Appl Physiol (1985). 1997;82(5):1573–83.
9. Borghi-Silva A, Oliveira CC, Carrascosa C, Maia J, Berton DC, Queiroga F Jr, Ferreira EM, Almeida DR, Nery LE, Neder JA. Respiratory muscle unloading improves leg muscle oxygenation during exercise in patients with COPD. Thorax. 2008;63(10):910–5. https://doi.org/10.1136/thx.2007.090167.
10. O'Donnell DE, Sanii R, Younes M. Improvement in exercise endurance in patients with chronic airflow limitationusing continuous positive airway pressure. Am Rev Respir Dis. 1988;138(6):1510–4.
11. Walterspacher S, Walker DJ, Hans-Joachim K, Windisch W, Dreher M. The effect of continuous positive airway pressure on stair-climbing performance in severe COPD patients. J Chron Obstruct Pulmon Dis. 2013;10(2):193–9.
12. Rossi A, Polese G, Brandi G, Conti G. Intrinsic positive end-expiratory pressure (PEEPi). Intensive Care Med. 1995;21(6):522–36.
13. Brochard L, Harf A, Lorino H, Lemaire F. Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. Am Rev Respir Dis. 1989;139(2):513–21.
14. Kyroussis D, Polkey MI, Hamnegard CH, Mills GH, Green M, Moxham J. Respiratory muscle activity in patients with COPD walking to exhaustion with and without pressure support. Eur Respir J. 2000;15(4):649–55.
15. Polkey MI, Hawkins P, Kyroussis D, Ellum SG, Sherwood R, Moxham J. Inspiratory pressure sup-

port prolongs exercise induced lactataemia in severe COPD. Thorax. 2000;55(7):547–9.
16. Hannink JD, van Hees HW, Dekhuijzen PN, van Helvoort HA, Heijdra YF. Non-invasive ventilation abolishes the IL-6 response to exercise in muscle-wasted COPD patients: a pilot study. Scand J Med Sci Sports. 2014;24(1):136–43. https://doi.org/10.1111/j.1600-0838.2012.01484.x.
17. Bianchi L, Foglio K, Pagani M, Vitacca M, Rossi A, Ambrosino N. Effects of roportional assist ventilation on exercise tolerance in COPD patients with chronic hypercapnia. Eur Respir J. 1998;11(2):422–7. PubMed PMID: 9551748.
18. Moderno EV, et al. Effects of proportional assisted ventilation on exercise performance in idiopathic pulmonary fibrosis patients. Respir Med. 2010;104(1):134–41.
19. Dreher M, Kabitz H-J, Burgardt V, Walterspacher S, Windisch W. Proportional assist ventilation improves exercise capacity in patients with obesity. Respiration. 2010;80:106–11. https://doi.org/10.1159/000245272.
20. Menadue C. Bilevel ventilation during exercise in acute on chronic respiratory failure: a preliminary study. Respir Med. 2010;104(2):219–27.
21. MTsuboi T, Ohi M, Chin K, Hirata H, Otsuka N, Kita H, Kuno K. Ventilatory support during exercise in patients with pulmonary tuberculosis sequelae. Chest. 1997;112:1000–7.
22. Highcock MP, Smith IE, Shneerson JM. The effect of noninvasive intermittent positive-pressure ventilation during exercise in severe scoliosis. Chest. 2002;121:1555–1560.
23. Menadue C, Piper AJ, van 't Hul A, Wong KK. Non-invasive ventilation during exercise training for people with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014;5:CD007714.
24. van 't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G. Training with inspiratory pressure support in patients with severe COPD. Eur Respir J. 2006;27:65–72.
25. Ricci C, Terzoni S, Gaeta M, Sorgente A, Destrebecq A, Gigliotti F. Physical training and noninvasive ventilation in COPD patients: a meta-analysis. Respir Care. 2014;59:709–17.
26. Reuveny R, Ben-Dov I, Gaides M, Reichert N. Ventilatory support during training improves training benefit in severe chronic airway obstruction. Isr Med Assoc J. 2005;7:151–5.
27. Toledo A, Borghi-Silva A, Sampaio LM, Ribeiro KP, Baldissera V, Costa D. The impact of noninvasive ventilation during the physical training in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). Clinics (Sao Paulo). 2007;62:113–20.
28. Bianchi L, Foglio K, Porta R, Baiardi R, Vitacca M, Ambrosino N. Lack of additional effect of adjunct of assisted ventilation to pulmonaryrehabilitation in mild COPD patients. Respir Med. 2002;96:359–67.
29. Hawkins P, Johnson LC, Nikoletou D, Hamnegård CH, Sherwood R, Polkey MI, Moxham J. Proportional assist ventilation as an aid to exercise training in severe chronic obstructive pulmonary disease. Thorax. 2002;57:853–9.
30. Johnson JE, Gavin DJ, Adams-Dramiga S. Effects of training with heliox and noninvasive positive pressure ventilation on exercise ability in patients with severe COPD. Chest. 2002;122:464–72.
31. Vitacca M, Kaymaz D, Lanini B, Vagheggini G, Ergün P, Gigliotti F, Ambrosino N, Paneroni M. Noninvasive ventilation during cycle exercise training in patients with chronic respiratory failure on long-term ventilatory support: A randomized controlled trial. Respirology. 2018;23:182–9.
32. Gloeckl R, Andrianopoulos V, Stegemann A, et al. High-pressure non-invasive ventilation during exercise in COPD patients with chronic hypercapnic respiratory failure: A randomized, controlled, crossover trial. Respirology. 2019;24:254–61.
33. van't Hul A, Gosselink R, Hollander P, Postmus P, Kwakkel G.Eur Respir J. Acute effects of inspiratory pressure support during exercise in patients with-COPD. 2004;23:34–40.
34. Duiverman ML, Maagh P, Magnet FS, Schmoor C, Arellano-Maric MP, Meissner A, et al.Impact of High-Intensity-NIV on the heart in stable COPD: a randomised cross-over pilot study. Respir Res. 2017;18:76.
35. Ambrosino N. Assisted ventilation as an aid to exercise training: a mechanical doping? Eur Respir J. 2006;27:3–5.

16 Bronchodilation and Humidification During Noninvasive Mechanical Ventilation

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16.1 Introduction

Nowadays noninvasive ventilation (NIV) represents the standard of care for the treatment of patients suffering from exacerbation of chronic obstructive pulmonary disease (COPD) and other respiratory insufficiencies, such as cystic fibrosis (CF) and asthma [1].

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NIV is widely used in patients hospitalized and in emergency room affected by acute or chronic respiratory failure for preventing intubation and for reducing morbidity and mortality.

Successful application of NIV often requires the exploitation of other accompanying treatments, such as inhalation therapy with bronchodilators and corticosteroids to treat acute respiratory failure (ARF) in patients with COPD, in order to relieve airway obstruction [2]. In addition to the latter, other inhaled drugs can be employed in patients receiving NIV, including antibiotics, prostaglandins, surfactant, immunomodulators and mucolytic agents [3].

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The advantages of inhaled therapy for treating respiratory disorders are well known and include a rapid onset of drug effect, due to the direct delivery to its site of action, the need of lower doses of the drug than if administered systemically and a lower incidence of adverse effects.

Accordingly, efforts have been made in recent years to put together both the therapies [4, 5], assuming that the simultaneous administration of both these treatments could be more effective for each of them [5].

When the patient's conditions allow brief periods of discontinuation of ventilation, one option is to interrupt NIV, remove the interface and administer the aerosolized drug; otherwise, there is the possibility of combining NIV with simultaneous aerosol delivery. In clinical practice, the preferable option is often to continue NIV without interruption, especially in hypoxaemic or acutely dyspnoeic patients; nevertheless, even though the therapeutic efficacy of the combination has been widely shown [4], more studies would be needed to find the best setting for the combined NIV and aerosol devices [6].

Indeed, whereas the treatment with bronchodilators has been set up and its efficacy widely verified during invasive mechanical ventilation, its employment and the choice of the best performing devices for aerosol therapy coupled with NIV is more controversial [6, 7].

There is a broad spectrum of aerosol-generating devices: pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs) and nebulizers, all generating particles with a mass median aerodynamic diameter between 1 and 5 μm^3 [5].

Nebulizers are the most common choice to administer aerosol therapy when it is combined with mechanical ventilation. The main advantages of the nebulizers on pMDI are the possibility of choosing freely the drug dosage and of adopting drug formulations or drug combinations that are not commercially available in pMDIs.

There are three types of nebulizers: jet, ultrasonic and vibrating mesh. They differ for the mechanism transforming the liquid solution or suspension into small droplets.

The vibrating mesh nebulizers (VMN) incorporate a mesh or plate with multiple apertures to produce aerosol; they are powered by electricity and do not add additional flow into the circuit; thus they do not interfere significantly with the ventilator setting and functioning.

In jet nebulizers (JN), a high-velocity gas flow passes through a narrow opening near the tip of a capillary tube, whose base is immersed in the drug solution to be nebulized [8, 9].

Ultrasonic nebulizers generate the aerosol by sound waves generated by high-frequency vibrations of a piezoelectric crystal that are transferred to the surface of the solution to be aerosolized; they have not been routinely employed due to their high cost and relative inefficiency [8].

In normal physiological conditions, inspired gas is heated and humidified during its transit through the human airway; consequently, humidification is mandatory when invasive mechanical ventilation bypasses the normal mechanisms of heating and humidification. Even though NIV does not use invasive artificial airway, humidification may be useful, in particular for long-term treatments, in order to prevent NIV-induced airway dryness and patient's distress [10, 11].

During mechanical ventilation, the air should be conditioned with the physiological level of humidity and temperature, which would be 100% relative humidity at 37 °C. However, since in NIV the delivered gas must first pass through the nasal cavity, the temperature of 37 °C may cause the patient's discomfort; therefore the temperature is usually set at 34 °C and 100% relative humidity [10, 12].

Humidification and warming of the inspired gases during NIV can be delivered either by passive humidifiers, such as heat and moisture exchangers (HME), or by active humidifiers. Passive humidifiers are based on the principle that they retain heat and humidity during expiration to deliver most of them at the following inspiration. There are different kinds of active humidifiers, but all of them are composed of an electric heater that warms the water, which is used to humidify and to warm the gas being inspired [12].

However, there is lack of studies concerning the level of humidification required and how it affects the success of the NIV treatment in relation to the patient pathology [11].

The aim of this review is to examine the available literature on bronchodilation and humidification coupled with NIV treatment and to discuss the related advantages and problems, with particular attention to the advances gained in the last 2 years.

16.2 Methods

For all the involved topics, our aim was the description of current issues concerning inhalation therapy and humidification during noninvasive mechanical ventilation; specific attention was devoted to find and review the in vitro and in vivo studies published during the last 2 years.

Discussion was based on the most recent randomized controlled trials (RCTs) and interventional or observational studies. We applied standard filters for the identification of these studies using the PUBMED search engine, from inception to March 2019, focusing on the studies published from January 2017 to March 2019.

Our search included the following keywords: noninvasive ventilation, aerosol, inhalation therapy, humidification and bronchodilation (Table 16.1).

Table 16.1 Summary of the last 2 years (2017–2019) in vitro and in vivo studies concerning the combination between NIV and aerosol therapy

First author/ year	Type of study	Main topic of the study	Key results
Michotte [13]	In vivo	Different nebulization modes (continuous vs inspiratory synchronized) in healthy volunteers: effects on lung deposition	Enhanced lung deposition with inspiratory synchronized nebulization mode
Saeed [14]	In vitro	Effects of the type of nebulizer (VMN vs JN) and fill volume on drug delivery	Enhanced drug delivery with VMN Minor impact of fill volume on VMN compared to JN (JN should be diluted to increase delivery)
Harb [15]	In vivo	Preliminary drug dose with pMDI before nebulization Three different connections (T-piece, large spacer and large spacer with pMDI)	Higher short-term bioavailability due to the preliminary dose; effect disappeared after 24 h No difference in the efficiency of drug delivery between T-piece and large spacer
Bodet-Contentin [16]	In vivo	Improvement of forced expiratory volume in 1 s (FEV1) due to nebulization of salbutamol in COPD patients	FEV1 did not change immediately after the end of nebulization, but increased significantly 40 min after Best nebulizer position just after the Y-piece
Xu [17]	In vitro	Effects of JN on NIV applied in ICU ventilators and noninvasive ventilators	In noninvasive ventilators, JN only affected the tidal volume monitored In ICU ventilators, JN also affected the triggering performance
Peng [18]	In vitro	Effects of six different nebulizer positions on drug delivery efficiency and ventilator performance during NIV	Lower delivery efficiency with the nebulizer close to the exhalation valve or the ventilator No difference in ventilator performance between different positions

(continued)

Table 16.1 (continued)

First author/ year	Type of study	Main topic of the study	Key results
Saeed [19]	In vivo	Effects of fill volume and humidification on lung deposition using different types of nebulizer (VMN vs JN) in patients with COPD	VMN improved lung deposition regardless of the fill volume Greater lung deposition with 2 ml fill volume vs 1 ml fill volume with JN No effect of humidification on lung deposition
Harb [20]	In vitro	Drug delivery with VMN using Combihaler and T-piece, with and without pMDI, in single-limb NIV	No difference in drug delivery between T-piece and Combihaler pMDI pre-nebulization may affect aerodynamic characteristics
Walenga [21]	In vitro	Excipient enhanced growth (EEG) as a technique for improving the lung-dose with VMN during NIV	EEG improved the lung penetration fraction Connect an in-line DPI device to the NIV mask to deliver rapidly an EEG aerosol
Rabea [22]	In vitro	Comparison between different types of VMN	Similar emitted dose for the different VMN
Hassan [23]	In vitro/in vivo	Efficiency of different types of aerosol devices (pMDI + spacer, JN, VMN) and effects in COPD patients	Higher drug delivery with VMN than with JN Greater efficiency with pMDI + spacer than nebulizers
Hussein [24]	In vitro	Comparison between different types of spacers	No significant difference in the emitted dose independently on the three spacers
Sutherasan [25]	In vitro	Effects of the ventilator settings, of the interface, of the leak port position and of the nebulizer on drug delivery	No significant difference in drug delivery between NIV and CPAP Nebulizer should be placed between an unvented mask and the leak port In BIPAP 15/5 cmH_2O provide better delivery than 10/5 or 20/10 cmH_2O

16.3 Bronchodilators

Aerosol delivery has been shown to be improved when performed coupled with NIV in terms of tidal volume, decreased respiratory rate and reduced particle size. These advantages may be impaired, on the other hand, by the adverse effect of the high flow rate produced by NIV on the deposition of the drug particles in the lung.

Since the effectiveness of bronchodilation relies on the correct placement of the drug at the action site in the lung, it is important to optimize the drug delivery by taking account of the multiple factors influencing the appropriate deposition of the drug in the mechanical ventilated patient.

Based on both in vitro and in vivo experiments, in particular those published in the last 2 years, the aerosol-generating device, the ventilator and its circuit, the interface, the humidifier and their clinical applications are the issues being discussed.

16.4 The Aerosol-Generating Device

Among all the available devices, only pMDIs and nebulizers have been investigated in combination with NIV, but there is a limited amount of available data concerning pMDIs.

The nebulizers are the most common choice to administer aerosol therapy, when it is combined with mechanical ventilation, due to the possibility of the administration of drugs and drug combinations that are not commercially available as pMDI. However, in a study combining in vivo

and ex vivo experiments, an equivalent or improved efficiency of pMDI compared to VMN and even more to jet nebulizer was demonstrated depending on the position of the leak port in the circuit or on the mask [23]. Obviously, to improve the efficiency of lung deposition, it is essential their administration during inspiration, rather than during expiration.

Among the nebulizers, all the most recent articles available in the literature recognize vibrating mesh nebulizers definitely superior to both the jet and ultrasonic nebulizers in terms of reliability, effectiveness and deposition on the treated tissues.

A single trial investigated the use of ultrasonic nebulizers during NIV, showing that they lost the highest dose of inhaled drug, compared with four other different nebulizers; moreover they are expensive, and consequently, they should not be recommended [8].

Regarding the jet nebulizers, their main problems are high drug losses [13] and driving an additional 6–8 l/min of gas into the ventilator circuit, which may affect the ventilation of the patient [4, 8, 9]. Moreover, they are influenced by the fill volume, because greater dilutions provide a better lung deposition. This topic has been investigated by Saeed et al. on COPD patients treated with NIV: two groups were nebulized using a VMN and two groups with a jet nebulizer, and, among each group, the nebulizer was filled either with 1 or 2 ml of salbutamol solution. The higher fill volume was essential for increasing the amount of inhaled drug when using the jet nebulizer, whereas the amount of salbutamol administered with the VMN was less affected by the fill volume. Therefore, the VMN nebulization produced a higher lung deposition and systemic absorption than the jet nebulizer, regardless of the fill volume [19].

Only Xu et al. considered jet nebulizers superior to VMN in terms of cost and safety [17].

Compared with the other ones, vibrating mesh nebulizers (VMN), which are the most recently developed devices, have a smaller residual volume, are quieter and produce a higher respirable fraction, and consequently their popularity is increasing [9].

The superior performance of the VMN devices was also shown by Galindo-Filho et al., who compared the deposition of radiolabelled aerosol in the lungs of ten healthy subjects using either a VMN or a jet nebulizer during NIV. The distribution of the radioaerosol particles within and outside the target organ was detected by scintigraphy. The subjects nebulized using the VMN apparatus showed a dose of radiolabelled aerosol deposited into the lungs that was more than twice the dose detected in the subjects nebulized with the jet nebulizer [26].

There may be differences between various models of VMN, but they are insubstantial [8, 22].

The higher efficiency and lower drug displacement of the vibrating mesh nebulizers is important both for the correct dosage of the drug deposited on the site of action and for reducing the drug loss, which can be a critical issue when the nebulized drugs are expensive and/or toxic, such as for antibiotics [6].

Anyway, in the clinical practice pMDIs and nebulizers are not mutually exclusive and can be used in co-administration, for example, using pMDIs to predose a bronchodilator in COPD patients before nebulization.

Regarding this issue, Harb et al. verified the effect of predosing 12 COPD subjects with salbutamol, which was administered using a pMDI before the subsequent dose nebulized during NIV. The rationale of the experiment was that the preliminary bronchodilation using the pMDI would improve the distribution of the following nebulization with salbutamol using a VMN during NIV performed with a single-limb bilevel ventilator. Three different settings of the connection were tested in the study: T-piece, large spacer and large spacer with pMDI [15]. The same authors had previously tested these same settings in an in vitro experiment [20]. The results of the different tested experimental configurations were evaluated by detecting the salbutamol content deposited in a collecting filter and by dosing the drug content in the subjects' urine samples. The experiment showed that there were not significant differences in the efficiency of salbutamol delivery between T-piece

and large spacer connections. The preliminary dose of salbutamol administered with the pMDI device determined a higher bioavailability of the bronchodilator after half an hour, but this effect disappeared after 24 h, becoming irrelevant for long-term treatments. However, the short-term effect of the prenebulization with pMDI could be useful to maximize the drug delivery in severely ill patients [20].

16.5 Interface and Position of the Aerosol-Generating Device

In order to obtain the best drug deposition results in aerosol treatment during NIV, several published researches, even in recent years, evaluated the influence of the nebulizer position in the NIV ventilator circuit, which was compared with the corresponding settings during invasive mechanical ventilation.

During invasive ventilation, the ventilator circuit works as a spacer allowing aerosol accumulation between inspirations; consequently the nebulizer should be placed at a distance from the endotracheal tube [3]. Conversely, during NIV the "spacer function" of the circuit is less effective, due to the gas leakage and flow through the circuit with leak compensation.

Peng et al. carried out a specific in vitro experiment on this subject; they evaluated the effect of six different positions of VMN during NIV performed with a respiratory simulation system. The lowest efficiency of aerosol delivery of salbutamol solution was detected when the VMN was positioned closer either to the exhalation valve or to the ventilator [18].

Michotte et al. compared in vitro five different nebulizers during NIV with a single-limb circuit bilevel ventilator. The three vibrating mesh nebulizers, the jet nebulizer and the ultrasonic nebulizer were filled with a solution of amikacin antibiotic and were positioned before and after the exhalation port. The best results in terms of high efficiency of drug delivery and less lost dose were obtained with the vibrating mesh nebulizers positioned before the exhalation port [8].

In a further in vitro study, an inspiratory synchronized vibrating mesh nebulizer (VMN) was compared with a continuous VMN during NIV using a single-limb circuit bilevel ventilator. The nebulizer was placed either between the artificial lung and the exhalation port or between the ventilator and the exhalation port. Regardless of the nebulizer position, the inspiratory synchronized VMN produced the highest inhaled dose and lowest expiratory waste dose. The best position for the VMN was between the lung simulator and the exhalation port [27].

Based on both in vitro and in vivo experiments, it seems that the best aerosol efficiency is obtained when the nebulizer is placed between the exhalation port and the mask.

The unvented masks, rather than the masks incorporating a leak port, appear as the best interfaces for providing an efficient drug delivery using nebulizers, since they cause lower leakages during both breathing phases [25]. Oronasal masks should be preferred to full-face masks, in particular when using some drugs, such as ipratropium bromide, which could cause eye irritation or acute angle closure. Nasal masks can be used in patients with massive expectoration.

The single study that compared aerosol delivery with helmet and full-face mask in children did not find any difference as regards adverse effect related to nebulization between the two examined interfaces [28].

16.6 Delivery Technique

Many studies have shown the importance of synchronizing the administration of aerosol therapy during inspiration phase, with either pMDIs or nebulizers.

For instance, Michotte et al. compared the pulmonary drug delivery using either continuous or inspiratory synchronized VMN during NIV in six healthy volunteers. Since there were not commercially available inspiratory synchronized VMNs, it was used as an experimental apparatus. The six healthy volunteers were ventilated by NIV and treated with an aerosol of amikacin administered either during the only inspiratory

phase or continuously. The extent of drug delivery of both aerosol systems was evaluated by measuring the amikacin content in urine samples taken for the following 24 h. The subjects treated with the inspiratory synchronized VMN showed higher urinary excretion of amikacin, more constant elimination, and longer nebulization time than the subjects treated with the continuous nebulization [13]. This was in agreement with the results previously reported in intubated and mechanically ventilated patients [29]. The study of Michotte et al. was the first clinical study concerning the use of inspiratory synchronized VMN in NIV and confirmed previously experiments performed in vitro.

Furthermore, new perspectives can be provided from recent studies on excipient enhanced growth (EEG) aerosol delivery, which may reduce the extreme dose variation in drug lung deposition. Walenga et al. used an in vitro approach, based on the use of two nasal cavity models obtained by 3D printing, to study the EEG as a technique for improving the lung-deposited dose of aerosol delivery through VMN during NIV. The EEG aerosol delivery resulted to improve the lung penetration fraction in comparison to conventional sized aerosol. Moreover, they showed that the most convenient method to administer rapidly an EEG aerosol was to connect an in-line DPI device to the NIV mask [21].

16.7 The Ventilator

NIV settings also impact lung deposition of the aerosolized drugs. Increase in inspiratory positive airway pressure (IPAP) improves lung deposition, while increase in expiratory positive airway pressure (EPAP) results in decrease in the nebulizer efficiency.

A recent bench study by Sutherasan et al. [25], which compared the effects on albuterol jet nebulization of the following ventilator settings, BIPAP mode (IPAP/EPAP of 10/5, 15/10, 15/5 and 20/10 cmH_2O) and CPAP mode with pressure levels of 5 and 10 cmH_2O, confirmed the results observed in previous researches [30]. They did not find any difference in the amount delivered in CPAP and BIPAP modes. In BIPAP, the best results in terms of efficiency of drug delivery were obtained with IPAP/EPAP set on 15/5 cmH_2O, compared to 10/5 and 20/10 cmH_2O, whereas the pressure level did not affect the drug delivery in CPAP.

Conversely, in a recent study performed on a paediatric NIV model, Velasco et al. reported that IPAP increasing did not improve aerosol efficiency. These conflicting results may be explained by the fact that they were both in vitro experiments, while in the clinical practice pressures are usually adjusted according to the mechanical properties of the lung and to the patient's tolerance, both parameters that are impossible to reproduce in a bench model [31].

Therefore, we can assume that more studies in vivo have to be performed to determine the relationship between inspiratory and expiratory airway pressures and aerosol delivery efficiency.

As long as NIV setting can influence aerosol delivery, one can easily infer that nebulization may affect the functioning of NIV ventilators. The occurrence of this situation depends on the types of nebulizer and ventilator employed.

The effect of jet nebulization on NIV is different from that on invasive ventilation. In contrast to the latter, during NIV air leak is always present and noninvasive ventilators or ICU ventilator with noninvasive modes are designed to compensate air leak through automatic adjustment of flow, up to 60 l/min. Driving flow during jet nebulization is between 2 and 10 l/min, which would result in automatic adjustment of flow in noninvasive ventilators.

Accordingly, a recent study of Xu et al. showed that tidal volume and control performance of seven models of noninvasive ventilators and four ICU ventilators were not significantly affected by jet nebulization, but detected different effects of aerosol delivery between ICU and noninvasive ventilator settings. Indeed, jet nebulization affected the monitored tidal volume and the triggering performance in the ICU ventilators, but affected only the monitored tidal volume in noninvasive ventilators. Anyhow, the greater

the driving flow, the stronger the impact on the monitored tidal volume [17].

16.8 Clinical Applications

The benefits of aerosol therapy during noninvasive ventilation in patients with COPD, asthma and cystic fibrosis are well known and have been investigated in many clinical studies. COPD and acute asthma exacerbations are very similar, because they are both characterized by airway obstruction, dynamic hyperinflation and necessity to overcome the intrinsic positive end-expiratory pressure (iPEEP).

Compared to aerosol therapy during spontaneous breathing, the administration of bronchodilators with BIPAP ventilation in patients with COPD or acute asthma exacerbations results in improvement of spirometric parameters (peak expiratory flow rate, forced expiratory volume in the first second, forced vital capacity), reduced bronchial obstruction and relief of symptoms [9, 32, 33].

However, the improvement in pulmonary function does not seem to be associated with an increase of lung deposition, as demonstrated in the scintigraphic study by Galindo-Filho et al. [26].

These findings were supported by a recent randomized controlled trial by Bodet-Contentin et al., who studied the effect of salbutamol nebulization with VMN during NIV in 43 patients diagnosed with exacerbated COPD. The amount of drug potentially reaching the trachea was determined by a preliminary in vitro experiment using a lung model. The FEV1 values taken by spirometry did not differ significantly between the patients nebulized with salbutamol and those receiving the placebo immediately after nebulization, whereas the FEV1 of the salbutamol-treated patients was significantly higher than that of the control group [16].

These results suggest that the clinical improvement could be explained by the physiological benefit of NIV in these categories of patients, but additional studies in larger experimental populations would be needed to confirm these findings.

16.9 Humidification

Whereas heating and humidification of the ventilated gas is mandatory when using invasive mechanical ventilation, air conditioning seems less important in case of NIV, when the gas is heated and humidified during the passage through the natural airways. However, humidification may affect patient's comfort and work of breathing, especially during long-term NIV treatments.

Skin damages or even ulcers could represent a potential serious problem, especially during winter, when there is higher condensation, due to the increased humidity at the mask interface.

Many papers about humidification in NIV compared different humidifiers, in particular the heated humidifiers (HH) and the heat and moisture exchangers (HME).

Boyer et al. compared the performance of HH and HME humidifiers in patients with acute respiratory failure (ARF), using different device configurations. The parameters of ventilation and the arterial blood gases were not modified using small dead space HME rather than HH, both in patients treated with NIV for ARF and in hypercapnic patients. Also the insertion of a flex tube between either the HH or HME humidifier and the Y-piece did not alter the results. They concluded that the HME humidifiers with sufficiently reduced dead space might be used during NIV in different patient categories [34].

Lellouche et al. studied the short-term effects of HH and HME humidifiers on respiratory pattern and arterial blood gases during NIV. They subdivided 81 subjects into three groups: hypercapnia and respiratory acidosis, hypercapnia only and hypoxaemic non-hypercapnic. In all three monitored groups, HME produced a small but significant increase in $PaCO_2$, in particular in hypercapnic patients. CO_2 removal improved with HH but not with HME humidifiers. The different results obtained by Boyer et al. were explained by the small difference of dead space between HME and HH and by the high pressures used during NIV. The authors showed the negative impact of the HME dead space in terms of CO_2 elimination and minute ventilation [35].

Conversely, a subsequent randomized controlled study by Lellouche et al. did not find any difference between the effects of HME or HH on a pragmatic clinical outcome [36].

In the last 2 years, only few authors have released studies about humidification during noninvasive ventilation. Among them, Nilius et al. studied the influence of ambient temperature, heated humidification and heated tubing on the mask humidity. The experiment was performed on 18 patients with obstructive sleep apnoea syndrome (OSAS) and consisted of three different CPAP treatments, delivered with a nasal mask: without humidification, standard heated humidification and heated humidification with a heated tube climate line. The patients treated during winter reported more undesirable effect than those treated during summer, suggesting that ambient temperature and humidity affect mask humidity. In fact, clinically relevant reductions of absolute humidity were detected during winter CPAP. The use of a heated tube for avoiding condensation increased the absolute humidity and could improve the conditions of the patients complaining of nose and throat symptoms [37].

Also Alqahtani et al. studied the potential damages of humidification during noninvasive ventilation on 15 healthy volunteers treated with humidified and non-humidified CPAP for 30 min through an oronasal mask. Skin integrity was evaluated by several parameters. The humidified CPAP increased significantly the local humidity at the skin interface and the transepidermal water loss, inducing skin alterations and potentially disrupting the barrier function of facial skin. Moreover, the subjects reported elevated nasal discomfort during non-humidified CPAP [38].

Humidification can also affect aerosol drug delivery, since the humidity produces an increase of the particle size and consequently may reduce the lung deposition due to their lower respiratory delivery, compared to a dry circuit [29]. The effect of fill volume and humidification on aerosol delivery during single-limb NIV was investigated by Saeed et al. on four groups of COPD patients treated with NIV, showing that the dose of delivered drug was not affected by the humidification, and consequently would not be necessary to switch off the humidifier during the aerosol therapy [19]. The hypothesis of the authors about these results is that the possible adverse effects of humidification on the nebulized drug might have been avoided positioning the nebulizer in single-limb circuit proximal to the patient.

Table 16.2 Main conclusions/future perspective

Main topic	Conclusions/future perspectives
Aerosol-generating device	Better efficiency of VMN compared to other nebulizers Usefulness of pMDI for preliminary bronchodilation
Interface	Unvented mask preferable to vented mask Oronasal mask preferable to full-face mask Only one study on helmet in children
Position of the nebulizer	Better position of nebulizer between the leak port and the mask
Delivery technique	Better efficiency synchronizing nebulization with inspiration Future perspective offered by EEG
NIV settings	Optimal setting with high IPAP and low EPAP Need for further studies in vivo
Clinical applications	Reduction of bronchial obstruction and improvement of spirometric parameters in asthma/COPD patients
Humidification	No clinically relevant differences between HH and HME Lack of studies on the effects of humidification on aerosol delivery

Considering the lack of studies, especially in recent years, it should be further evaluated the effect of humidification on the administration and deposition of bronchodilators during NIV (Table 16.2).

16.10 Conclusions

NIV has replaced, whenever possible, invasive mechanical ventilation for treating patients affected by COPD or other respiratory insufficiencies. In spite of its growing importance, the effect of the simultaneous administration of drugs has been investigated less extensively than in

invasive mechanical ventilation. Moreover, the effect of humidification during NIV has been even less analysed.

On the basis of both in vitro and in vivo experiments, it seems that nebulizers and, among others, the vibrating mesh nebulizers should be preferred over pMDI.

The oronasal unvented mask seems to be the best interface for the administration of bronchodilators during NIV, the nebulizer should be placed between the leak port and the mask and the optimal settings involve the use of high IPAP and low EPAP.

In the last decades many issues about aerosol delivery during NIV have been investigated with the help of bench studies; however many of these findings still need confirmation in human clinical studies. Further comprehensive and extended randomized experiments would be needed in order to evaluate the most suitable devices and settings for the coupled treatments.

Studies concerning humidification in patients treated with NIV are even less represented in the medical literature. Humidification decreases oronasal symptoms, facilitates secretions removal and may improve patient's tolerance and compliance during NIV, even though skin damages could represent a potential serious problem. The addition of substantial dead space with HMEs might be problematic in patients with COPD or asthma, in whom hypercapnia or increased WOB is of concern.

Eventually, it should be further evaluated the effect of humidification on the administration and deposition of bronchodilators during NIV.

References

1. Hess DR. Noninvasive ventilation for acute respiratory failure. Respir Care. 2013;58(6):950–72.
2. Rzepka-Wrona P, Skoczynski S, Wrona D, Barczyk A. Inhalation techniques used in patients with respiratory failure treated with noninvasive mechanical ventilation. Can Respir J. 2018;2018:8959370.
3. Dhand R. Aerosol therapy in patients receiving noninvasive positive pressure ventilation. J Aerosol Med Pulm Drug Deliv. 2012;25(2):63–78.
4. Galindo-Filho VC, Brandão DC, de Ferreira R C, et al. Noninvasive ventilation coupled with nebulization during asthma crises: a randomized controlled trial. Respir Care. 2013;58(2):241–9.
5. Mukhopadhyay A, Dela Pena E, Wadden B, Procyshyn M, Lim TK. Effects of inhalational bronchodilator treatment during noninvasive ventilation in severe chronic obstructive pulmonary disease exacerbations. J Crit Care. 2009;24:474.e1–5.
6. Reychler G, Michotte JB. Development challenges and opportunities in aerosol drug delivery systems in non-invasive ventilation in adults. Expert Opin Drug Deliv. 2019;16(2):153–62.
7. Esquinas Rodriguez AM, BaHammam A, Scala R, Soroksky A, Nasilowski J, Siekmeier R, Koksal GM, Celikel T, Shah PS, Mukhopadhyay A, Cosentini R, Papadakos PJ. Aerosol therapy during non-invasive mechanical ventilation. Review of key technical factors and clinical implications. Can J Respir Ther. 2013;49(1):11–7.
8. Michotte JB, Jossen E, Roeseler J, Liistro G, Reychler G. In vitro comparison of five nebulizers during noninvasive ventilation: analysis of inhaled and lost doses. J Aerosol Med Pulm Drug Deliv. 2014;27(6):430–40.
9. Dhand R. How should aerosols be delivered during invasive mechanical ventilation? Respir Care. 2017;62(10):1343–67.
10. Esquinas Rodriguez AM, Scala R, Soroksky A, BaHamman A, de Klerk A, Valipour A, Chiumello D, Martin C, Holland AE. Clinical review: humidifiers during non-invasive ventilation—key topics and practical implications. Crit Care. 2012;16(1):203, 7 pgs.
11. Branson RD, Gentile MA. Is humidification always necessary during noninvasive ventilation in the hospital? Respir Care. 2010;35(2):209–16.
12. Plotnikov GA, Accoce M, Navarro E, Tiribelli N. Humidification and heating of inhaled gas in patients with artificial airway. A narrative review. Rev Bras Ter Intensiva. 2018;30(1):86–97.
13. Michotte JB, Staderini E, Aubriot AS, Jossen E, Dugernier J, Liistro G, Reychler G. Pulmonary drug delivery following continuous vibrating mesh nebulization and inspiratory synchronized vibrating mesh nebulization during noninvasive ventilation in healthy volunteers. J Aerosol Med Pulm Drug Deliv. 2018;31(1):33–41.
14. Saeed H, Ali AMA, Elberry AA, Eldin AS, Rabea H, Abdelrahim MEA. Modeling and optimization of nebulizers' performance in non-invasive ventilation using different fill volumes: comparative study between vibrating mesh and jet nebulizers. Pulm Pharmacol Ther. 2018;50:62–71. https://doi.org/10.1016/j.pupt.2018.04.005.
15. Harb HS, Elberry AA, Rabea H, Fathy M, Abdelrahim ME. Performance of large spacer versus nebulizer T-piece in single-limb noninvasive ventilation. Respir Care. 2018;63(11):1360–9.
16. Bodet-Contentin L, Guillon A, Boulain T, Frat JP, Garot D, Le Pennec D, Vecellio L, Ehrmann S, Giraudeau B, Tavernier E, Dequin PF. Salbutamol nebulization during noninvasive ventilation in exacerbated chronic obstructive pulmonary disease patients:

a randomized controlled trial. J Aerosol Med Pulm Drug Deliv. 2019;32(3):149–55.
17. Xu MJ, Dai B, Peng Y, Su J, Tan W, Zhao HW. Effect of jet nebulization on noninvasive positive-pressure ventilation administered with non-invasive or intensive care unit ventilators: a bench study. Respiration. 2018;13:1–8.
18. Peng Y, Dai B, Hu CX, Su J, Tan W, Zhao HW, Kang J. Which nebulizer position should be avoided? An extended study of aerosol delivery and ventilator performance during noninvasive positive pressure ventilation. Respiration. 2018;95(3):145–53.
19. Saeed H, Mohsen M, Salah Eldin A, Elberry AA, Hussein RRS, Rabea H, Abdelrahim MEA. Effects of fill volume and humidification on aerosol delivery during single-limb noninvasive ventilation. Respir Care. 2018;63(11):1370–8.
20. Harb HS, Elberry AA, Rabea H, Fathy M, Abdelrahim ME. Is combihaler usable for aerosol delivery in single limb non-invasive mechanical ventilation? J Drug Deliv Sci Technol. 2017;40:28–34.
21. Walenga RL, Longest PW, Kaviratna A, Hindle M. Aerosol drug delivery during noninvasive positive pressure ventilation: effects of intersubject variability and excipient enhanced growth. J Aerosol Med Pulm Drug Deliv. 2017;30(3):190–205.
22. Rabea H, Ali AM, Salah Eldin R, Abdelrahman MM, Said AS, Abdelrahim ME. Modelling of in-vitro and in-vivo performance of aerosol emitted from different vibrating mesh nebulisers in non-invasive ventilation circuit. Eur J Pharm Sci. 2017;97:182–91.
23. Hassan A, Salah Eldin R, Abdelrahman MM, Abdelrahim ME. In-vitro/in-vivo comparison of inhaled salbutamol dose delivered by jet nebulizer, vibrating mesh nebulizer and metered dose inhaler with spacer during non-invasive ventilation. Exp Lung Res. 2017;43(1):19–28.
24. Hussein RRS, M A Ali A, Salem HF, Abdelrahman MM, Said ASA, Abdelrahim MEA. In vitro/in vivo correlation and modeling of emitted dose and lung deposition of inhaled salbutamol from metered dose inhalers with different types of spacers in noninvasively ventilated patients. Pharm Dev Technol. 2017;22(7):871–80.
25. Sutherasan Y, Ball L, Raimondo P, Caratto V, Sanguineti E, Costantino F, Ferretti M, Kacmarek RM, Pelosi P. Effects of ventilator settings, nebulizer and exhalation port position on albuterol delivery during non-invasive ventilation: an in-vitro study. BMC Pulm Med. 2017;17(1):9.
26. Galindo-Filho VC, Ramos ME, Rattes CS, Barbosa AK, Brandão DC, Brandão SC, Fink JB, de Andrade AD. Radioaerosol pulmonary deposition using mesh and jet nebulizers during noninvasive ventilation in healthy subjects. Respir Care. 2015;60(9):1238–46.
27. Michotte JB, Staderini E, Le Pennec D, Dugernier J, Rusu R, Roeseler J, Vecellio L, Liistro G, Reychler G. In vitro comparison of a vibrating mesh nebulizer operating in inspiratory synchronized and continuous nebulization modes during noninvasive ventilation. J Aerosol Med Pulm Drug Deliv. 2016;29(4):328–36.
28. Rodriguez Garcia L, Medina A, Modesto I, Alapont V, Palacios Loro ML, Mayordomo-Colunga J, Vivanco-Allende A, Rey C. Safety of aerosol therapy in children during noninvasive ventilation with helmet and total face mask. Med Intensiva. 2018;27:pii: S0210-5691(18)30184-0.
29. Miller DD, Amin MM, Palmer LB, Shah AR, Smaldone GC. Aerosol delivery and modern mechanical ventilation: in vitro/in vivo evaluation. Am J Resoir Crit Care Med. 2003;168:1205–9.
30. Chatmongkolchart S, Schettino GP, Dillman C, Kacmarek RM, Hess DR. *In vitro* evaluation of aerosol bronchodilator delivery during noninvasive positive pressure ventilation: effect of ventilator settings and nebulizer position. Crit Care Med. 2002;30(11):2515–9.
31. Velasco J, Berlinski A. Albuterol delivery efficiency in a pediatric model of noninvasive ventilation with double-limb circuit. Respir Care. 2018;63(2):141–6.
32. Pollack CV Jr, Fleisch KB, Dowsey K. Treatment of acute bronchospasm with beta-adrenergic agonist aerosols delivered by a nasal bilevel positive airway pressure circuit. Ann Emerg Med. 1995;26(5):552–7.
33. Brandao DC, Lima VM, Filho VG, Silva TS, Campos TF, Dean E, de Andrade AD. Reversal of bronchial obstruction with bi-level positive airway pressure and nebulization in patients with acute asthma. J Asthma. 2009;46(4):356–61.
34. Boyer A, Vargas F, Hilbert G, Gruson D, Mousset-Hovaere M, Castaing Y, Dreyfuss D, Ricard JD. Small dead space heat and moisture exchangers do not impede gas exchange during noninvasive ventilation: a comparison with a heated humidifier. Intensive Care Med. 2010;36:1348–54.
35. Lellouche F, Pignataro C, Maggiore SM, Girou E, Deye N, Taillé S, Fischler M, Brochard L. Short-term effects of humidification devices on respiratory pattern and arterial blood gases during noninvasive ventilation. Respir Care. 2012;57(11):1879–86.
36. Lellouche F, L'Her E, Abroug F, et al. Impact of the humidification device on intubation rate during noninvasive ventilation with ICU ventilators: results of a multicenter randomized controlled trial. Intensive Care Med. 2014;40:211–9.
37. Nilius G, Domanski U, Schroeder M, Woehrle H, Graml A, Franke K-J. Mask humidity during CPAP: influence of ambient temperature, heated humidification and heated tubing. Nat Sci Sleep. 2018;10:135–42.
38. Alqahtani JS, Worsley P, Voegeli D. Effect of humidified noninvasive ventilation on the development of facial skin breakdown. Respir Care. 2018;63(9):1102–10.

Noninvasive Mechanical Ventilation in Elderly

17

Nicola Vargas and Loredana Tibullo

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Abbreviations

ARF	Acute respiratory failure
DNI	Do not intubate
DNR	Do not resuscitate
ECCO2R	Extracorporeal CO_2 removal
FOB	Flexible bronchoscopy
HFCWO	High-frequency chest wall oscillation
HFNC	Figh-flow nasal cannula
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
NIV	Noninvasive ventilation

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17.1 Introduction

The demographic changes determined a significant increase in the percentage of adults who are very elderly and the proportion of their hospital admissions. In this group, the invasive mechanical ventilation (IMV) use decreased significantly even after adjustment for DNR (do not resuscitate) status. The poor prognosis and the subsequent belief that IMV and intensive care unit (ICU) care could be harmful are two conditioning factors in daily clinical practice. The IMV may be "a questionable option" in some (do not intubate) DNI-related clinical scenarios, for example, in an older patient, bedridden, who cannot perform ADLs independently, and with multimorbidity and acute respiratory failure, in the absence of advance directives [1]. Over time the use of NIV has increased significantly among patients (of all classes of age) hospitalized for

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acute exacerbations of COPD, whereas the need for intubation and in-hospital mortality has declined. Age did not imply a lower response [2]. In the same way many investigations straightened the use of NIV as a comfort measure at the end of life and DNI older patients. For this reason, the NIV use has become a primary therapeutic option in the management of acute or acute-on-chronic respiratory failure in older patients. In this chapter, the authors reviewed the evidence about the use of NIPPV in the elderly focusing on criticisms and the positive effects on the outcome.

17.2 The Use of NIV to Avoid IMV in Very Old Patients

The admission in ICU and the IMV may be not by itself associated with poor outcome for older patients without preceding respiratory diseases [3]. Despite this evidence in 2006, Garrouste-Orgeas et al. showed that in the 50% of patients the factor age influenced the decision-making process and the choice of admission in ICU even in the presence of an accurate indication [4]. In the emergency department, the initial inappropriate treatment such as the decision to not intubate when there is the indication may impact on the patient's survival. Birolleau et al. in his study noted that inadequate treatment was present in 32% of the patients. The mortality was higher in this group [5].

Furthermore, behind the inclination of not admitting the elderly patients in ICU, there is evidence that age and invasive mechanical ventilation are strongly associated with in-hospital mortality. The risk increased progressively with every age increment [6]. On the other hand, Nava et al. revealed the importance of using NIPPV not only as a palliative measure but also as preferential treatment when intubation is either not wanted by the patient or questionable for the physicians. Compared with standard medical therapy, NIPPV decreased the rate of meeting the endotracheal intubation criteria and the mortality rate of very old patients [7]. The questionable context refers to an older patient, bedridden, who cannot perform ADLs independently, and with multimorbidity and acute respiratory failure, in the absence of advance directives. For these patients the prognosis of ICU admission is poor. The possibility of avoiding endotracheal intubation and preventing acute respiratory failure becomes the main reason for using NIPPV in the elderly [8]. The outcome and the mortality in the very old (>85 years) group were not statistically different from the younger group when physicians used NIPPV in the emergency department. The observed mortality was significantly lower than the expected death in both groups. In both age groups, patients treated with NIV for chronic obstructive pulmonary disease (COPD) had lower mortalities than those treated for other illnesses, although this was statistically significant only in the younger group. In very old patients, when used with correct indications, NIV was associated with mortality similar to younger patients. Patients receiving NIPPV had lower than expected mortality in all age groups [9].

17.3 The DNI and NIV

Curtis et al. [10] identified the use of NPPV in three categories of patients with acute respiratory failure: (1) NPPV as life support with no preset limitations on life-sustaining treatments, (2) NPPV as life support when patients and families have decided to forego endotracheal intubation, and (3) NPPV as a palliative measure when patients and families have chosen to forego all life support, receiving comfort measures only. The second and third category refers specifically to DNI order. The decision for the patients to forego the endotracheal intubation presumes that the elderly have valid decision-making capacity (DCM). The most of very old patients have a limited DCM. The possibility of family members to take a decision is very variable in the different European and not European countries [11]. When physicians use NIV in DNI patients, they should take into account that the patients and family members may change idea during an acute phase of respiratory failure. Furthermore, Schortegen et al. [12] showed that NIV used for the management of acute respiratory failure

(ARF) in very old patients (≥80 years), often in the context of a do-not-intubate order (DNI), has an overall satisfactory 6-month survival and functional status, except for endotracheal intubation after NIV failure. Vilaca et al. [13] noted that the survival rate was 49% among DNI status patients, and NIV did not provide significant relief of symptoms in more than half the patients who receive it for that purpose. The ethical dilemmas of using NIV in a palliative context as comfort care are related to the balance between benefits and discomfort [14].

17.4 Failure of NIV Use in Elderly and Integrative Therapies

The possible causes of immediate failure (within minutes to <1 h) are a weak cough reflex, excessive secretions, hypercapnic encephalopathy, intolerance, agitation, and patient-ventilator asynchrony. The risk factors for early failure (within 1–48 h) may differ for hypercapnic and hypoxaemic respiratory failure. However, most cases of early failure are due to poor arterial blood gas (ABGs) and an inability to promptly correct them, increased severity of illness, and the persistence of a high respiratory rate. Despite a satisfactory initial response, late failure (48 h after NIV) can occur and may be related to sleep disturbance [15].

In addition, older patients with anxiety symptoms and a high bicarbonate level at NIV initiation are potentially good responders in terms of an improvement in hypercapnia. Also, higher inspiratory ventilator pressures are associated with a larger reduction in $PaCO_2$. However, the improvement in hypercapnia does not seem to be associated with improved survival [16].

The integration of NIV with other less invasive supports (e.g. high-flow nasal cannula (HFNC), mechanical cough assistance devices such as high-frequency chest wall oscillation (HFCWO), flexible bronchoscopy (FOB) with toilette of abundant secretion, and low-flow CO_2-removal systems such as extracorporeal CO_2 removal (ECCO2R) could reduce the rate of NIV failure and may be especially feasible in the elderly in which IMV is not desirable [8]. Many studies showed the feasibility, efficacy, and tolerance of HFNC in hypoxaemic ARF of different aetiologies with the aims of reducing the escalating ventilatory therapy in "DNI patients" as an alternative to NIV, in "end-stage" chronic cardiopulmonary diseases with ARF. Some investigations demonstrated that acute-on-chronic respiratory patients with bronchial hypersecretions of different aetiologies showed improvement of PaO_2 and $PaCO_2$ values when NIV was associated with HFCWO applications [17, 18]. The results are still controversial because of some meta-analysis not confirming this positive outcome. Scala et al. [19] revealed an encouraging result with the use of FOB in patients with copious hypersecretions and hypercapnic encephalopathy. ECCO2R, which developed from the traditional ECMO, has been recently proposed as an alternative or an integrated therapeutic option in patients with acute hypercapnic acidotic respiratory failure who are "non-responder" to an NIV trial. While ECMO is a "total extracorporeal support" which can oxygenate severely hypoxaemic patients and remove up to 50% of the total body CO_2 production, ECCO2R works as a "partial extracorporeal support" capable of removing the lower amount of CO_2 without substantial effects on the oxygenation [8]. Furthermore, with this technique, ECCO2R plus NIV experienced adverse events related to extracorporeal CO_2 removal. Bleeding episodes and vein perforation were observed.

17.5 Setting

Over the last years, much more elderly patients are managed with NIV outside of ICU [22]. Until now the criterion to guide the choice of setting according to pH value is still valid. A pH < 7.25 the better setting is ICU or a respiratory unit [20]. With a pH > 7.3 and experienced staff, the patients may be treated also in a general ward [21]. According to disease in the case of acute cardiogenic oedema, the NIV may be used in the ambulance too. In the case of palliative context for DNR and DNI and end of life outside of ICU,

the presence of the family members may improve the comfort [22].

17.6 Conclusion

The NIV in elderly should be used with the correct indications. In choosing the setting, the physicians should take into account the safety of patients. The early identifications of the predictors of failure should lead to integrative therapy practice when available. The DNI status requires an accurate evaluation and in a palliative context may be treated outside of ICU.

References

1. Vargas N, Esquinas AM. The reduced use of intubations in elderly patients in the emergency department: many insights behind a historical trend. Am J Emerg Med. 2018;36(12):2321.
2. Chandra D, Stamm JA, Taylor B, et al. Outcomes of NIV for acute exacerbations of COPD in the United States, 1998–2008. Am J Respir Crit Care Med. 2012;185:152–9.
3. Esteban A, Anzueto A, Frutos-Vivar F, et al. Outcome of older patients receiving mechanical ventilation. Intensive Care Med. 2004;30:639–46.
4. Garrouste-Orgeas M, Timsit JF, Montuclard L, et al. Decision-making process, outcome, and 1-year quality of life of octogenarians referred for intensive care unit admission. Intensive Care Med. 2006;32:1045–51.
5. Ray P, Birolleau S, Lefort Y, et al. Acute respiratory failure in the elderly: etiology, emergency, diagnosis and prognosis. Crit Care. 2006;10:R82.
6. Farfel JM, Franca SA, do Carmo Sitta M, Filho WJ, Carvalho CRR. Age, invasive ventilatory support and outcomes in elderly patients admitted to intensive care units. Age Ageing. 2009;38(5):515–20. https://doi.org/10.1093/ageing/afp119.
7. Nava S, Grassi M, Fanfulla F, Domenighetti G, Carlucci A, Perren A, Dell'Orso D, Vitacca M, Ceriana P, Karakurt Z, Clini E. Non-invasive ventilation in elderly patients with acute hypercapnic respiratory failure: a randomised controlled trial. Age Ageing. 2011;40(4):444–50. https://doi.org/10.1093/ageing/afr003.
8. Scala R. Challenges on non-invasive ventilation to treat acute respiratory failure in the elderly. BMC Pulm Med. 2016;16:150. https://doi.org/10.1186/s12890-016-0310-5.
9. Montoneri G, Noto P, Trovato FM, et al. Outcomes of non-invasive ventilation in 'very old' patients with acute respiratory failure: a retrospective study. Emerg Med J. 2019;36:303–5.
10. Curtis JR, Cook DJ, Sinuff T, White DB, Hill N, Keenan SP, Benditt JO, Kacmarek R, Kirchhoff KT, Levy MM, Society of Critical Care Medicine Palliative Noninvasive Positive Ventilation Task Force. Noninvasive positive pressure ventilation in critical and palliative care settings: understanding the goals of therapy. Crit Care Med. 2007;35(3):932–9.
11. Tibullo L, Esquinas AM, Vargas M, Fabbo A, Micillo F, Parisi A, Vargas N. Who gets to decide for the older patient with a limited decision-making capacity: a review of surrogacy laws in the European Union. Eur Geriatr Med. 2018;9:759. https://doi.org/10.1007/s41999-018-0121-8.
12. Schortgen F, Follin A, Piccari L, et al. Results of noninvasive ventilation in very old patients. Ann Intensive Care. 2012;2(1):5. https://doi.org/10.1186/2110-5820-2-5.
13. Vilaça M, Aragão I, Cardoso T, Dias C, Cabral-Campello G. The role of noninvasive ventilation in patients with "do not intubate" order in the emergency setting. PLoS One. 2016;11(2):e0149649. https://doi.org/10.1371/journal.pone.0149649.
14. Quill CM, Quill TE. Palliative use of noninvasive ventilation: navigating murky waters. J Pall Med. 2014;17:657–61.
15. Ozyilmaz E, Ugurlu AO, Nava S. Timing of non-invasive ventilation failure: causes, risk factors, and potential remedies. BMC Pulm Med. 2014;14:19.
16. Raveling T, Bladder G, Vonk JM, et al. Improvement in hypercapnia does not predict survival in COPD patients on chronic noninvasive ventilation. Int J Chron Obstruct Pulmon Dis. 2018;13:3625–34. https://doi.org/10.2147/COPD.S169951RESULTS.
17. Al-Saady NM, Fernando SS, Petros AJ, Cummin AR, Sidhu VS, Bennett ED. External high frequency oscillation in normal subjects and in patients with acute respiratory failure. Anaesthesia. 1995;50(12):1031–5. https://doi.org/10.1111/j.1365-2044.1995.tb05945.x.
18. Takeda S, Nakanishi K, Takano T, Nejima J, Takayama M, Ishikawa G, Ogawa R. The combination of external high-frequency oscillation and pressure support ventilation in acute respiratory failure. Acta Anaesthesiol Scand. 1997;41(6):670–4. https://doi.org/10.1111/j.1399-6576.1997.tb04765.x.
19. Scala R, Naldi M, Maccari U. Early fiberoptic bronchoscopy during non-invasive ventilation in patients with decompensated chronic obstructive pulmonary disease due to community-acquired-pneumonia. Crit Care. 2010;14(2):R80.
20. Martin TJ, Hovis JD, Costantino JP, Bierman MI, Donahoe MP, Rogers RM, Kreit JW, Sciurba FC, Stiller RA, Sanders MH. A randomized, prospective evaluation of noninvasive ventilation for acute respi-

ratory failure. Am J Respir Crit Care Med. 2000;161(3 Pt 1):807–13.
21. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet. 2000;355(9219):1931–5.
22. Vargas N, Vargas M, Galluccio V, Carifi S, Villani C, Trasente V, Landi CA, Cirocco A, Di Grezia F. Non-invasive ventilation for very old patients with limitations to respiratory care in half-open geriatric ward: experience on a consecutive cohort of patients. Aging Clin Exp Res. 2014;26(6):615–23. https://doi.org/10.1007/s40520-014-0223-1.

Telemedicine for Noninvasive Mechanical Ventilation

18

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18.1 Telemedicine

Telemedicine tools enable the communication and sharing of medical information in electronic form and thus facilitate access to remote expertise and knowledge [1]. A physician located far from a reference center can consult his colleagues remotely in order to solve a difficult case, follow a continuing education course over the Internet to improve his knowledge, or access medical information from digital libraries. These same tools can also be used to facilitate the exchange between centers of medical expertise at a national or international level and have been performed many times [2–5].

Today the telemedicine field is changing faster than ever before. As technology advances at exponential levels, so does the widespread affordability and accessibility to basic telemedicine tools. For example, not only do we now have the technology for live video telemedicine, but much of the worldwide population has experience using online videochat apps and access to a computer or mobile device to use them.

Telemedicine was originally created as a way to treat patients who were located in remote places, far away from local health facilities or in areas with shortages of medical professionals. While telemedicine is still used today to address these problems, it's increasingly becoming a tool for convenient

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medical care. Today's connected patient wants to waste less time in the waiting room at the doctor and get immediate care for minor but urgent conditions when they need it [4, 5].

This expectation for more convenient care, combined with the unavailability of many overburdened medical professionals, has led to the rise of telemedicine companies. Many offer patients 24/7 access to medical care with an on-call doctor contracted by that company. Others offer hospitals and larger health centers access to extra clinical staff and specialists, for outsourcing of special cases (common model among teleradiology companies). Still others provide a telemedicine platform for physicians to use to offer virtual visits with their own patients. Increasingly, telemedicine is becoming a way to give medical practices an edge in a competitive healthcare landscape where it's difficult to stay independent or maintain a healthy bottom line.

Also impacting the rise of telemedicine today is the growing mobile health field. With the wide variety of mobile health apps and new mobile medical devices that are consumer-friendly, patients are starting to use technology to monitor and track their health. Simple home-use medical devices that can take vitals and diagnose ear infections, monitor glucose levels, or measure blood pressure let patients gather needed medical information for a doctor's diagnosis, without going into the doctor's office [4, 5].

18.2 Types of Telemedicine and Delivery Mechanisms

According to our literature review in telemedicine, we can classify the exchanged data among telemedicine systems in four main categories [6]:

- Textual data, e.g., the results of biomedical examinations, performed by analysis laboratories, and diagnostic reports which can be transferred using Portable Document Format (PDF).
- Audiovisual data based on the MPEG format, which are transferred during a videoconferencing session using the H 320 standard.
- Imaging data, i.e., X-ray, magnetic resonance imaging (MRI), and ultrasounds, which are transferred using DICOM2, the HL73 standard, or other standards of CEN/TC 251 WG4.
- Physiological signals, i.e., ECG, EEG, etc., provided in their own standard interchange format, for example SCP-ECG4 for the ECG, which has been set up by the European normalization committee (CEN).

Telemedicine information may be delivered in different ways [6]:

- Networked programs link tertiary care hospitals and clinics with outlying clinics and community health centers in rural or suburban areas through either hub-and-spoke or integrated networked systems. The links may use dedicated high-speed lines or the Internet for telecommunication links between sites.
- Point-to-point connections using private networks are used by hospitals and clinics that deliver services directly or contract out (out sourced) specialty services to independent medical service providers at ambulatory care sites.
- Health provider to the home connections involves connecting primary care providers, specialists, and home health nurses with patients over single-line phone-video systems for interactive clinical consultations. Such services can also be extended to a residential care center such as nursing homes or assisted living facility.
- Direct patient to monitoring center links are used for pacemaker, cardiac, pulmonary, or fetal monitoring and related services and provide patients the ability to maintain independent lifestyles. Web-based e-health patient service sites provide direct consumer outreach and services over the Internet.

18.3 Telemedicine Benefits [7]

- *Inexpensive*: You can add on telemedicine services for as low as $2.00 per employees making it the perfect solution for rising healthcare costs for employees.

- *Time savings*: The technology-based communication allows a doctor and patient to communicate without being in the same physical space, eliminating the need to physical travel to a doctor's office. Wait times are also reduced from 30 min to an hour to just minutes, with no time spent in a waiting room. Employees can access this quickly and easily without missing big chunks of work.
- *Easy to use*: You can access telemedicine anywhere you are, on-demand. This works well for common ailments including allergies, cold/flu symptoms, bronchitis, sinus infections, sore threats, and many more illnesses. Most of the time a doctor can assess your symptoms and provide antibiotics if needed or refer to a specialist if need be.
- *Privacy*: Your information will still receive the same level of privacy as if you were to attend a doctor's office in person. Telemedicine systems abide by all HIPAA guidelines.

18.4 Telemedicine Cons [7]

- *Limitations exist*: While telemedicine is great for more common ailments, there are still times where seeing a doctor in person can prove to be more beneficial. Routine physical exams are a prime example of this, where establishing a good relationship with your doctor has proven to be very effective.
- *Not all doctors use telemedicine*: Many people have an established relationship with a doctor they trust. Using the telemedicine services limits your options, and it is unlikely you will be able to speak with a doctor you know. While good doctors do use telemedicine services, the limited availability of choices may make consumers skeptical.

18.5 Telemedicine in Intensive Care Unit

Telemedicine in critical care areas is a specialty subset of the overall field of telemedicine.

Tele-ICU systems are composed of technology (hardware and software) and personnel that collect, analyze, and transmit information back and forth between the physical ICU and the tele-ICU command center. These systems can track, analyze, and document patient data and allow ICU and tele-ICU clinicians to intervene in patient care. Analyses and descriptions of tele-ICU systems have largely focused on the technology, but consideration of the personnel components may be even more important. We will briefly describe both. There are three core technology components of all tele-ICU systems. Firstly, the system relays all available patient data to the tele-ICU center. This includes nearly real-time physiological data, laboratory results, radiographic results, electronic patient records, and the medication record. Secondly, a user interface software application organizes the patient data in the tele-ICU center, in an indexed manner so that the data can be easily retrieved and viewed. Finally, a communication network is established between the physical ICUs and the tele-ICU center [9, 10]. While these functions appear simple, making them work is established between the physical ICUs and the tele-ICU center [9, 10].

ICU telemedicine typically involves specialists located at a dedicated central hub providing care to patients in multiple, remotely located ICUs [8]. Staff located at the hub may include a physician intensivist, critical care nurses, nurse practitioners, hospitalists, or other members of the multidisciplinary team such as pharmacists or respiratory therapists, as well as associated administrative staff. Staffing and coverage models may vary with individual circumstances.

Studies that focused on ICU and hospital mortality and LOS showed mixed results [8–14]. Rosenfeld conducted a 16-week before and after study of the implementation of tele-ICU in a 10-bed surgical ICU [15]. Analysis of severity-adjusted hospital mortality before and after the institution of remote intensivist monitoring showed a 30% decrease in hospital mortality and a decrease in LOS in the ICU. Breslow et al. conducted a before and after analysis study of the introduction of a tele-ICU in both a surgical and a medical ICU [8]. ICU and hospital mortality

decreased significantly in the medical ICU but not in the surgical ICU. ICU LOS decreased significantly in both ICUs by 16%, while overall hospital LOS was unchanged [8]. Thomas et al. did not find an overall difference in ICU and hospital mortality or LOS, although tele-ICU was associated with improved survival and shorter ICU LOS in sicker patients (SAPS score > 44) [12]. In a recent study of more than 4000 patients in 2 large suburban community hospitals, a difference in ICU and hospital mortality was not found after the institution of tele-ICU. Hospital LOS was unaffected and ICU LOS increased after the institution of tele-ICU [13]. Both hospitals had a very high quality of care before the institution of tele-ICU, with a baseline mortality of 81% of predicted and virtually no ventilator-associated pneumonia (VAP) and catheter-related bloodstream infections (CRBI) [13]. The reasons for the negative results in the studies by Morrison and Thomas could be the low percentage (30% in Thomas et al.) of attending physicians that allowed the remote team to work as a category 3 team [12, 13].

Another component of tele-ICU is checking the daily care plan of the ICU patient for adherence to guidelines by the remote intensivist. Most programs assign the responsibility for best practice compliance to the remote team. The technicians of the tele-ICU can very easily generate daily reports on adherence to guidelines concerning: prevention of VAP, insulin regulation, early sepsis management, and lung protective ventilation [8]. Shaffer et al. found a significantly reduced amount of cardiopulmonary resuscitations in the ICU and outcome was slightly—but not statistically significantly—improved [16].

18.6 Telemedicine in Respiratory Care

Chronic obstructive pulmonary disease (COPD), asthma, and lung transplantation have been, by far, the respiratory diseases or conditions more studied, in terms of telemedicine. However, the interest of telehealth providers in new areas also related to neurologic conditions, such as neuromuscular diseases in need of home noninvasive ventilation (NIV) due to chronic respiratory failure, or sleep-related breathing disorders, has arisen in recent years. Existing evidence reveals promising results regarding reliability and validity of measures across all pulmonary conditions, and patients usually show a positive attitude toward telecare technologies.

It is now consensually agreed that an estimated number of 328 million people have COPD worldwide, that is, 168 million men and 160 million women. Moreover, COPD causes the death of 2.9 million people annually, and it is projected to be the third cause of mortality by 2020 [17]. There is moderate evidence of the benefit of telemedicine in COPD, in terms of increasing quality of life and reducing hospital admissions. Basically, the problem has been that in previous years the studies included in systematic reviews were underpowered, had heterogeneous populations, and had lack of detailed intervention descriptions and of the care processes that accompanied telemonitoring [18]. Another issue is the clinical scenario where patients are usually recruited. For instance, telemedicine can be offered to those patients prone to exacerbations that are in stable condition [19] or right after admission regardless of the number of previous exacerbations or FEV1 obstruction severity [20].

Telemedicine has been used to support self-management of long-term conditions such asthma. Positive results have been reported [21–23]. A systematic review and meta-analysis from three randomized controlled trials using different technologies showed an improvement of asthma control, though the clinical effectiveness of the used apps, typically incorporating multiple features, varied [23].

Telemedicine has been studied as a feasible instrument for retrieving daily spirometric data in lung transplanted patients. Earlier works determined the telemonitored spirometry as feasible, valid, reliable, and repeatable, when compared to the regular in-clinic functional testing [24–26], although these studies were clearly underpowered due to the small samples included. While on earlier works the objective is to determine the technical aspects of collecting acceptable spi-

rometries, recent works have carried out clinical trials to demonstrate that a computerized rule-based decision support algorithm for nursing triage of potential acute bronchopulmonary events is effective [27] or the identification of these events taking decision rules developed using wavelet analysis of declines in spirometry and increases in respiratory symptoms [28].

18.7 Telemedicine for Noninvasive Ventilation

Mechanical ventilation is the use of a mechanical ventilator to assist breathing when a person is not capable of breathing sufficiently on their own, typically because of respiratory failure caused by impairment in the lungs or in the pump mechanism. A mechanical ventilator provides a controlled flow of gas into the patient's lungs, with a certain differential pressure temporal pattern and with a certain value of temperature. In intensive hospital care unit, ventilation parameters are monitored by physicians and nurses in order to evaluate patients' physical conditions. Patients who have acute respiratory failure and who have not responded to other treatment options can benefit from using a treatment, called home mechanical entilation (HMV), performed by means of a mechanical ventilator at the patient's home. However, during the treatment of HMV, it is difficult for a physician to continuously monitor ventilation parameters and to evaluate the physical conditions of a patient.

In the last few years, several tele-monitoring systems have been proposed for hospital or home MV.

In first-generation systems for tele-monitoring, data from sensors are usually transferred via a telephone system to a database and relayed to the clinical team [29]. Second-generation tele-monitoring systems comprise a non-immediate or analytical decision system in which the data transfer is synchronous with an automated algorithm [29]. The clinical team recognizes important changes in the patient's condition, but response is delayed if the system is monitored only at certain times. Third-generation systems [29] have constant analytical and decision-making support in which monitoring centers are physician-led and staffed by specialist nurses and have full authority to effect therapy changes 24 h per day, 7 days per week.

Future generation of tele-monitoring for non-invasive ventilation may include:

- The transfer of data about ventilatory settings.
- The evaluation of vital parameters.
- The chance for patients to communicate with help desk 24/7.

References

1. Perednia DA, Allen A. Telemedicine technology and clinical applications. J Am Med Assoc. 1995;274(6):461–2.
2. Ganapathy K. Telemedicine and neurosciences in developing countries. Surg Neurol. 2002;58:388–94.
3. Graham LE, Zimmerman M, Vassallo DJ, Patterson V, Swinfen P, Swinfen R, et al. Telemedicine-the way ahead for medicine in the developing world. Trop Dr. 2003;33:36–8.
4. Sarbadhikari SN. The state of medical informatics in India: a roadmap for optimal organization. J Med Syst. 2005;29(2):125–41.
5. Wright D. Telemedicine and developing countries. A report of study group 2 of the ITU Development Sector. J Telemed Telecare. 1998;4 Suppl 2:1–85.
6. An ATA issue paper. Telemedicine, Telehealth, and Health Information Technology. The American Telemedicine Association; 2006.
7. Hjielm NH. Benefits and drawbacks of telemedicine. J Telemed Telecare. 2005;11:60–70.
8. Breslow MJ. ICU telemedicine: organization and communication. Crit Care Clin. 2000;16(4):707–22.
9. Breslow MJ. Remote ICU care programs: current status. J Crit Care. 2007;22(1):66–76.
10. Breslow MJ, Rosenfeld BA, Doerfler M, Burke G, Yates G, Stone D. Effect of a multiple-site intensive care unit telemedicine program on clinical and economic outcomes: an alternative paradigm for intensivist staffing. Crit Care Med. 2004;32(1):31–8.
11. Marcin JP, Nesbitt TS, Kallas HJ, Struve SN, Traugott CA, Dimand RJ. Use of telemedicine to provide pediatric critical care inpatient consultations to underserved rural Northern California. J Pediatr. 2004;144:375–80.
12. Morrison JL, Cai Q, Davis N, Yan Y, Berbaum ML, Ries M, et al. Clinical and economic outcomes of the

electronic intensive care unit: results from two community hospitals. Crit Care Med. 2010;38:2–8.
13. Thomas EJ, Lucke JF, Wueste L, Weavind L, Patel B. Association of telemedicine for remote monitoring of intensive care patients with mortality, complications, and length of stay. JAMA. 2009;302:2671–8.
14. Zawada ET Jr, Herr P, Larson D, Fromm R, Kapaska D, Erickson D. Impact of an intensive care unit telemedicine program on a rural health care system. Postgrad Med. 2009;121:160–70.
15. Rosenfeld BA, Dorman T, Breslow MJ, Pronovost P, Jenckes M, Zhang N, et al. Intensive care unit telemedicine: alternate paradigm for providing continuous intensivist care. Crit Care Med. 2000;28:3925–31.
16. Shaffer JP, Breslow MJ, Johnson JW, Kaszuba F. Remote ICU management improves outcomes in patients with cardiopulmonary arrest. Crit Care Med. 2005;33:A5.
17. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease study 2010. Lancet. 2012;380:2163–96.
18. Bolton CE, Waters CS, Peirce S, Elwyn G, EPSRC and MRC Grand Challenge Team. Insufficient evidence of benefit: a systematic review of home telemonitoring for COPD. J Eval Clin Pract. 2011;17:1216–22.
19. Segrelles Calvo G, Gómez-Suárez C, Soriano JB, Zamora E, Gónzalez-Gamarra A, González-Béjar M, et al. A home telehealth program for patients with severe COPD: the PROMETE study. Respir Med. 2014;108:453–62.
20. Gottlieb M, Marsaa K, Andreassen H, Strømstad G, Godtfredsen N. Feasibility of a telecare solution for patients admitted with COPD exacerbation: screening data from a pulmonary ward in a university hospital. Eur Clin Respir J. 2014;1:24193.
21. McLean G, Murray E, Band R, Moffat KR, Hanlon P, Bruton A, et al. Interactive digital interventions to promote self-management in adults with asthma: systematic review and meta-analysis. BMC Pulm Med. 2016;16:83.
22. Himes BE, Weitzman ER. Innovations in health information technologies for chronic pulmonary diseases. Respir Res. 2016;17:38.
23. Hui CY, Walton R, McKinstry B, Jackson T, Parker R, Pinnock H. The use of mobile applications to support self-management for people with asthma: a systematic review of controlled studies to identify features associated with clinical effectiveness and adherence. J Am Med Inform Assoc. 2016; https://doi.org/10.1093/jamia/ocw143.
24. Finkelstein SM, Snyder M, Edin-Stibbe C, Chlan L, Prasad B, Dutta P, et al. Monitoring progress after lung transplantation from home patient adherence. J Med Eng Technol. 1996;20:203–10.
25. Lindgren BR, Finkelstein SM, Prasad B, Dutta P, Killoren T, Scherber J, et al. Determination of reliability and validity in home monitoring data of pulmonary function tests following lung transplantation. Res Nurs Health. 1997;20:539–50.
26. Wagner FM, Weber A, Park JW, Schiemanck S, Tugtekin SM, Gulielmos V, et al. New telemetric system for daily pulmonary function surveillance of lung transplant recipients. Ann Thorac Surg. 1999;68:2033–8.
27. Finkelstein SM, Lindgren BR, Robiner W, Lindquist R, Hertz M, Carlin BP, et al. A randomized controlled trial comparing health and quality of life of lung transplant recipients following nurse and computer-based triage utilizing home spirometry monitoring. Telemed J E Health. 2013;19:897–903. https://doi.org/10.1089/tmj.2013.0049.
28. Wang W, Finkelstein SM, Hertz MI. Automatic event detection in lung transplant recipients based on home monitoring of spirometry and symptoms. Telemed J E Health. 2013;19:658–63.
29. Koehler F, Anker SD. Noninvasive home telemonitoring: the Trans-European Network-Home-Care management system. J Am Coll Cardiol. 2006;48:850–1.

Part II

Sleep Section

Giuseppe Insalaco

Importance of Interface in the Effectiveness of CPAP

19

Ana Margarida Mestre and Ana Luísa Ramos

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19.1 Introduction

Obstructive sleep apnea (OSA) is a chronic disorder caused by repeated upper-airway collapse during sleep resulting in recurrent nocturnal wake-ups, fragmented sleep, increased sympathetic nervous system activity with associated increased cardiovascular risk [1], and great impact in daily life including excessive daytime somnolence, reduced quality of life and increased risk of motor vehicle, as well as incident heart failure and stroke [2–5]. Given that only a few attempts have been made to screen the general population its real prevalence remains unknown. Last time it was revised was around 34% in men aged 30–70 years and 17% in women aged 30–70 years [1]. Continuous positive airway pressure (CPAP) is considered the gold-standard therapy for OSA and remains the most effective treatment [3, 5, 6]. CPAP can effectively reduce sleep-disordered breathing events, improve objective and subjective sleepiness, and enhance quality of life [2]. CPAP therapy in patients with OSA is also associated with a significant reduction in the cardiovascular risk [6]. Despite huge technology progress and the wide variety of masks available in the

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market, as the success of this treatment depends on the prolonged use of the CPAP, it is essential to have a good adherence and commitment with the treatment. The lack of patient acceptance and inadequate adherence remain the major causes of treatment failure. One of the most important factors contributing to patient's acceptance of CPAP therapy is the selection of the proper interface. This fact makes it extremely important to find a mask with which the patient feels comfortable, which makes good sealing and associated with few side effects [2, 6].

There are three main groups of CPAP interfaces to deliver pressure to the patient: nasal, oral, and oronasal, although oral masks have not found widespread acceptance and are rarely used [3]. Many interface models have been released in the market these last years; however, it lacks guidelines and scientific knowledge to support decision-making. Moreover, there is a growing concern that oronasal interface may compromise CPAP effectiveness to treat OSA [7, 8]. A prior systematic review comparing CPAP interfaces has been published; however, because of limited available data at that time, the results were not clear [9].

The aim of this work was to perform a systematic review to better understand the role of interface in CPAP treatment efficacy, adherence, side effects, comfort, and sleep quality in patients with OSA.

19.2 Methodology

The literature search began on February 2019 and consisted of a systematic review of common database, mainly PubMed and Medline. The keywords used in this search were "sleep apnea," "CPAP adherence," "interface and CPAP," "nasal mask," and "oronasal mask." The criteria followed for publication inclusion were based on publication date (between 2017 and 2019, mainly), whether, or not, they reported original findings, scientific knowledge, and background information or contained relevant theoretical speculation about the role of different interfaces on the areas addressed in this review. The reference lists of identified articles were also searched for any additional sources.

19.3 Interface Characteristics

As mentioned before, CPAP is the first-line treatment for OSA treatment. The importance of selection of the right mask for each patient is also more than established as a determinante factor in the compliance and efficacy of the treatment. The availability of several types of interface and the lack of studies supporting and guiding the decision-making process make the choice of the appropriate interface for patients with OSA a great challenge.

There are available a vast number of interfaces in the market, each one with its features. They can be arranged into six main categories of masks used to deliver CPAP therapy (Table 19.1) [6, 10]:

Human beings are obligate nose breathers during wakefulness. During sleep, humans also breathe mainly through the nose. Besides, in normal subjects, nasal breathing is not affected neither by sleep stage nor by body position [6, 11].

In patients with OSA and snoring, a multilevel anatomic obstruction is often present. Nasal obstruction may contribute to sleep disordered breathing (SDB) as it's the first anatomical boundary of the upper airway. One of the pathophysiological mechanisms that can potentially explain the role of nasal pathology in SDB is the Starling resistor model. Through this model we can also understand the assumptions of CPAP therapy. The Starling resistor model consists of a tube passing through a sealed box. The tube consists of two rigid segments with a collapsible segment interposed in between corresponding to the muscular pharynx of the human's airway. The fundamental concept of treating OSA with nasal CPAP is that nasal CPAP increases the pressure inside the pharynx above the pharyngeal critical closing pressure and thereby keeps the pharynx open (Fig. 19.1) [6].

Table 19.1 Categories and main features of masks used to deliver CPAP therapy available in the market

Mask model	Characteristics
Nasal masks 	This type of mask sits around the nostrils and rests against the nasal bridge and on the upper lip to form a contained area for delivery of airflow down the nasal airway. They are recommended for use with patients who dominantly nasal breathe and are limited in their application with oral breathers or those with deviated septum.
Nasal pillows 	This type of mask has a contact area through two small cushions designed to insert into the patient nares, minimalizing facial contact. They rest on the inside rim of the nostrils. They are a good option for people who find nasal or oronasal mask too intrusive or uncomfortable and who have skin breakdown on nasal bridge. The extremely localized delivery of pressured air directly to the nostrils is associated with increased dryness and a "jetting" sensation.
Oral masks 	This type of mask fits in the mouth between the gums and lips. It also has a tongue guide to prevent obstruction of the passage of air by the tongue. These are appropriate in those intolerant of nasal breathing. This type is not common in practice.
Hybrid masks 	These masks integrate characteristics of oral and nasal pillow masks to supply airflow to both airways while being less obtrusive than oronasal masks and with significantly reduced dead space. They are however more difficult to secure in space, making them unsuitable for patients with high nocturnal activity levels, and suffer from the same jetting sensation as nasal pillow models.
Oronasal masks or full-face masks 	These masks are the most commonly used in a hospital setting where reliable airflow delivery takes precedence over patient comfort. A cushion is used to create a contained environment, and it encompasses both the oral and nasal orifices while resting on the chin, sides of the nose and mouth, and on the nasal bridge.

(continued)

Table 19.1 (continued)

Mask model	Characteristics
Total face masks 	This type of mask covers the entire face. The skin contact areas are shifted away from the nasal bridge and mouth areas, potentially improving comfort depending on patient facial structure. It is a comfortable alternative for patients who may not be able to obtain a good seal with other masks such as nasal masks, nasal pillows, and full-face masks, and is preferably indicated for those with facial deformities and those suffering from skin breakdown around the facial area. User vision is increased but there is significant dead space within the mask, the effects of which should be taken in account during CPAP therapy.

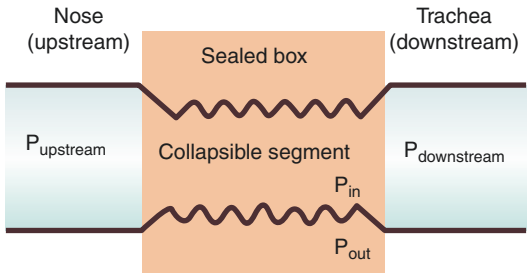

Fig. 19.1 The Starling resistor model consists of a tube passing through a sealed box. The tube consists of two rigid segments with a collapsible segment interposed in between. In humans, the rigid tube is represented by the nose and trachea and the collapsible segment corresponds to the muscular pharynx of the human's airway. As long as the pressure inside the pharynx (P_{in}) is greater than the pressure outside of the surrounding tissue pressure (P_{out}), the pharynx does not collapse [6]

The presence of nasal obstruction, either due to anatomical factors, inflammatory diseases, or nasal valve incompetence, may also lead to mouth breathing during daytime or mouth opening at night due to increased nasal resistance, changing upper airway dynamics, and increasing the propensity to develop OSA [6].

Interestingly, the mask of choice for patients with OSA with nighttime mouth opening should not be necessarily the oronasal mask. Actually, nasal CPAP mask seems to be very efficient in decreasing mouth opening episodes as well as the amplitude of mouth opening movements in patients with OSA [6]. Ruhle et al. had already demonstrated a reduction in mouth opening events and a decrease in the number of oral breaths with nasal CPAP [12]. Moreover, nasal CPAP enhances the Starling resistor model by increasing the pressure inside the pharynx, above the pharyngeal critical closing pressure, thereby keeping the pharynx open, while oronasal mask violates the Starling resistor model as pressure applied simultaneously through the mouth and nose may lead to a collapse of the upper airway. In Fig. 19.2 is represented the same patient without and under CPAP therapy, with nasal mask and with oronasal mask.

Another study achieved similar findings. Andrade et al. investigated the effect on upper airway of CPAP therapy with nasal and oronasal routes in patients with severe OSA. When the CPAP flow route was shifted from the nasal to the oronasal or oral route, there was a significant and progressive reduction in the distance between epiglottis and tongue base and the retroglossal area, respectively. They also realized that patients had upper airway obstruction during oronasal CPAP, despite maintaining predominant breathing through the nose preceding the obstructive event [6, 7]. But does this mean all patients should be advised to use nasal masks?

19.3.1 Adherence

Rowland et al. conducted a prospective study where they compared among other things CPAP adherence. In this study there was no statistically significant difference in CPAP adherence between interfaces. However, patient satisfaction and quality of sleep were higher with the nasal mask and nasal mask with chinstrap than with the oronasal mask. When they were asked about their preference, most chose nasal mask over the nasal mask

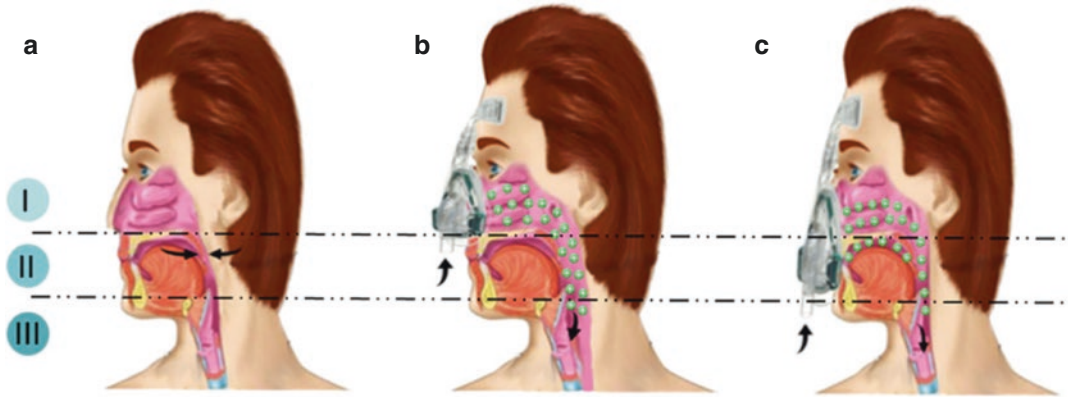

Fig. 19.2 This illustration demonstrates the relationship between the Starling model and mask type. There are two rigid segments (nose and trachea) with a collapsible segment interposed in between (pharynx). Level I, the nose (upstream); level II, the pharynx (collapsible segment); and level III, the trachea (downstream). (**a**) Upper airway obstruction during inhalation due to negative airway pressure. (**b**) The use of CPAP through a nasal mask enhances the Starling resistor model by increasing the pressure inside the pharynx above the pharyngeal critical closing pressure and thereby keeping the pharynx open. (**c**) The use of CPAP through an oronasal mask violates the Starling resistor model as pressure applied simultaneously through the mouth and nose may lead to displacement of the tongue and soft palate posteriorly and obstruction of the upper airway [6]

with chinstrap and oronasal masks, as that was perceived to be easier to fit and keep in place, leak less, be quieter, and provide a more restful sleep [3].

The efficacy of intra-nasal compared with nasal interfaces for improving adherence to CPAP therapy was evaluated using meta-analyses of two crossover randomized controlled trials (RCTs) of 3- to 4-weeks duration [13, 14] involving newly treated participants with a range of CPAP pressures and one RCT [15] for 1-week periods in participants previously established on nasal CPAP treatment at ≥12 cmH_2O for >6 months. There was no clinically significant difference in mean adherence and percent of nights of CPAP use with intra-nasal interfaces compared with nasal interfaces [16].

The efficacy of oronasal compared with nasal interfaces for improving adherence was evaluated in meta-analyses of three crossover RCTs of 3- to 4-week duration [3, 17] which demonstrated a clinically significant improvement in adherence of 0.6 h/night (95% CI: −0.2 to 1.3 h/night) with nasal interface compared with oronasal interface [16]. Another meta-analysis was performed of three nonrandomized studies in which participants were predominantly male without major medical comorbidities, with previously untreated moderate to severe OSA, treated for at least 3 weeks up to 24 months [18–20]. A clinically significant difference in adherence was also demonstrated with an improve of 0.7 h/night (95% CI: 0.2–1.2 h/night) in adherence of nasal interfaces. There was insufficient evidence to perform meta-analysis for the effects on adherence for oral versus nasal interfaces. Although it's worth mentioning that the American Academy of Sleep Medicine commissioned a task force of content experts to conduct this review and accordingly to their clinical experience, most patients have difficulties using an oral interface over the long term [16].

19.3.2 Positive Pressure and Apnea Hypopnea Index (AHI)

An observational study conducted by Borel et al. associated oronasal mask use with higher treatment pressures when compared with nasal masks [18]. In contrast, observational crossover studies by Bakker et al., Teo et al., and Ebben et al. have demonstrated no differences between nasal and oronasal masks and the pressure prescribed. The interpretability of these studies is somewhat limited by their small sample sizes which not only limits the ability to explore relationships between mask types and pressure requirements but also

reduces the array of craniofacial structures examined. Also, subjects were followed during a short number of nights for each mask type, making the results susceptible to night-to-night variability. Moreover, each study dictated a specific oronasal mask to be used in the study, so the lack of differences in therapeutic pressures may be unique to these particular models of masks. Shirlaw et al. conducted a randomized, crossover trial design with a greater number of subjects using both a nasal mask and an oronasal mask for a longer period of time (4 weeks). They found an equal proportion of noncompliance at time of recruitment, with 26% and 23% of subjects noncompliant with CPAP therapy (threshold of 4 h per night) for oronasal mask and nasal mask interfaces, respectively [2]. Actually, in their work, parameters such as positive airway pressure requirements (median and 95th percentile pressures), leak, and residual AHI were not statistically different between oronasal and nasal masks [2]. It should be emphasized that these similarities in pressure requirements between nasal and oronasal masks were not universal. Indeed, four subjects in this last study showed much higher pressures when using an oronasal mask. This would suggest that there are specific aspects that predispose them to higher pressure requirements while using an oronasal mask. As already mentioned, decreases in either the retroglossal or retropalatal area with use of an oronasal mask may explain this occurrence, but only partially [2]. Still, higher pressure requirement was not isolated to oronasal mask use. Some subjects required higher therapeutic pressures with a nasal mask compared to the oronasal mask [2].

Patil et al. analyzed the efficacy of intra-nasal compared to nasal interfaces for the treatment of OSA in adults which was evaluated using a meta-analysis of three crossover RCTs. Of those, two studies of 3- to 4-week duration [13, 14] involve newly treated participants with a range of CPAP pressures. The other study analyzed a 1-week period [15] in participants previously treated with nasal CPAP treatment at $\geq$12 cmH_2O for >6 months. There was no clinically significant difference in AHI in neither group. The authors also compared the efficacy of oronasal and nasal interfaces for the treatment of OSA in previously untreated adults. This was evaluated through a meta-analysis of two crossover RCTs: one of 3-week duration [17] and one of 4-week duration [3]. Concordantly with previous data, they found that residual AHI was higher with oronasal than with nasal interfaces, although this difference was not clinically significant. There was insufficient evidence to perform a meta-analysis on OSA severity for oral versus nasal interfaces, perhaps because it is not often used. Even though, one RCT employing a 4-week crossover design demonstrated no clinically significant differences in AHI with oral compared with nasal interfaces [16]. Further studies are needed to elucidate other contributory factors.

19.3.3 Leaks

It is possible to try to reduce mouth leaks by using a chinstrap that supports and restricts jaw movements, but there is limited data supporting the efficacy of this approach [3]. The oronasal mask covers both the nose and the mouth and allows the patient to breathe through the mouth while maintaining therapeutic CPAP pressure which, in theory, would eliminate mouth leaks [3]. However, theses masks, as they have a wider surface, can be more difficult to adapt to patients' face, resulting in more leaks, patient discomfort, and reduced adherence [3, 18].

More recently, some studies have analyzed the relationship between mouth opening and body position, showing that mouth opening, and consequently leak, was more influenced by sleep stage than by body position [9, 21]. Lebret et al., in their work, found that lateral and prone positions increased the risk of unintentional leak, probably because of mask displacement or traction on the CPAP tube in these positions. Nasal obstruction may also be an independent determining factor of mouth opening that can lead to the use of an oronasal mask, although in their study, nasal obstruction and mouth opening were significantly greater in patients who used an oronasal mask. Moreover, the oronasal mask itself may promote mouth opening by displacing the jaw backward and downward [22–25]. Once more, the specific indications for oronasal masks are still debated and more studies are necessary. But, accordingly to Lebret et al.'s

work, there is an overall equivalence between oronasal and nasal masks except for the specific situations of mouth opening and REM sleep, in which there were fewer leaks with oronasal interfaces. This suggests that oronasal masks could be an effective solution to reduce unintentional leak in such cases [23]. There was insufficient data comparing other interface models.

19.3.4 Sleepiness

Regarding self-reported sleepiness, once more there are insufficient data and are contradictory. BaHammam et al. reported that the use of nasal pillow mask was associated with less adverse effects and better perceived sleep quality in the first 3 weeks of CPAP treatment [6]. Later on the efficacy of intra-nasal was compared with nasal interfaces using a meta-analysis of two crossover studies, one employing a 3-week duration [13] and one employing a 4-week duration [14]. There was no clinically significant difference in self-reported sleepiness between intra-nasal and nasal interfaces as assessed with the Epworth Sleepiness Scale (ESS). The efficacy of oronasal versus nasal interfaces was evaluated using a meta-analysis of two RCTs [3]. The meta-analysis demonstrated no clinically significant difference in self-reported sleepiness between the interfaces as assessed with the ESS. There was insufficient evidence to perform meta-analysis for the effects on self-reported sleepiness for oral versus nasal interfaces. Actually, in concern of self-reported sleepiness no meta-analyses were able to demonstrate clinically significant differences in self-reported sleepiness between the different mask interfaces [16].

19.3.5 Quality of Life

When looking to quality of patient life accordingly to the type of interface used, there was insufficient evidence to perform a meta-analysis. Only one RCT [13] was identified that met inclusion criteria which assessed the effect of intra-nasal versus nasal interfaces on quality of life. The study took place over a period of 3 weeks each in a crossover RCT and accessed the effect of interface in quality of life with a questionnaire, but no clinically significant difference in quality of life was found comparing intra-nasal versus nasal interfaces [13, 16].

19.3.6 Other Side Effects

Since this is a therapy based in the delivery of positive pressure during a long period of time on a daily basis, side effects are expected and have been reported with all interfaces and, of course, may adversely impact adherence. Side effects may differ between interface type and between individuals for a given interface. A well-sealed interface is necessary for effective delivery of CPAP, and mask and/or mouth leak may adversely impact treatment efficacy. Improvements of air leak and other side effects through interface selection may have beneficial effects on treatment adherence and efficacy.

The nasal mask is most commonly used, although some studies report a high rate of side effects, sometimes in over 50% of individuals. In those, mouth and mask leaks are common and are associated with drying of the nasal and the oral mucosa, sore eyes, irritating noises and airstreams, and even increased arousals of patients [3].

For intra-nasal versus nasal interfaces, side effect data were reported from two crossover RCTs of 3-week and 4-week duration [13, 14] involving newly treated participants with a range of CPAP pressures or for 1-week periods [15] in participants previously established on nasal CPAP treatment at $\geq$12 cmH_2O for >6 months. An overall multi-item side effect score favored intra-nasal interfaces in one study of newly treated participants, but there were no clinically significant differences in overall side effects between interfaces for the other two studies. Individual side effects including pressure sensation on the face, skin irritation, claustrophobia, and obtrusiveness were in general less for intra-nasal interfaces in the three studies, while nasal interfaces were scored as being less obtrusive. There were no clinically significant differences between interfaces for nasal or oral congestion or dryness. In one study, overall mask satisfaction scores were significantly higher for intra-nasal interfaces, while in the other two studies there was no clinically significant dif-

ference in preference between intra-nasal and nasal interfaces either for newly treated or previously treated participants. Overall, differences in side effects between the two interfaces were not clinically significant.

In a non-RCT of 2311 participants in whom 62% were using nasal and 26% oronasal interfaces, there were greater reports in symptoms of eye irritation, dry mouth, choking sensation, and psychologically perceived inconvenience with oronasal interfaces, while there were no clinically significant differences between oronasal and nasal interfaces in nasal congestion, headache, aerophagia, or family tolerance of treatment. [16]. In these non-RCT cohorts, oronasal interfaces were least often chosen by participants for long-term treatment compared with nasal and intra-nasal interfaces [18, 19]. Borel et al. also demonstrated lower compliance (based on average hours used per night) and a greater risk of noncompliance (based on the proportion of nights with 4 h or more usage) with oronasal masks compared with nasal masks [2]. Rowland et al. obtained similar results. Nasal interface was reported as more comfortable although it was associated with more complaints of nasal and throat dryness, nasal congestions, and rhinitis but not nasal stuffiness. In the other hand, self-reported mask leak, sore eyes, claustrophobia, and difficulty exhaling were clinically significant and more predominant with the oronasal interface. In their study mask noise and leak were also greater with oronasal masks which were also reported to be harder to fit and hold in place [3].

More recently in Shirlaw's work, nasal masks generally appear to be more preferable than oronasal masks, based on the greater number of subjects withdrawing during the study because of intolerance of the oronasal mask and the preference for the nasal mask in the majority of subjects completing the trial [2].

In Patil et al. review, there were clinically important differences in side effects with oronasal compared with nasal interfaces, and these increased side effects appear to result in a patient preference for nasal over oronasal interfaces and ultimately in a significant reduction in adherence to CPAP with oronasal when compared to nasal CPAP [16].

Advantages and disadvantages of the three main types of interfaces are presented in Table 19.2:

As already mentioned above, the correct mask fitting is an essential step for the success of CPAP therapy. BaHammam et al. proposed a flow chart to support and guide the choice of the correct interface for each patient (Fig. 19.3).

Table 19.2 Different types of CPAP masks: advantages/disadvantages based on Dibra's work [26]

	Advantages/indications	Disadvantages
Nasal pillow masks	• Patients with claustrophobia • Intractable air leak into eyes with a nasal mask • Difficulty obtaining a seal over upper nasal bridge with a nasal mask • No upper teeth or mustache (makes obtaining a seal with a nasal mask difficult)	• Sensation of higher pressure in some patients • Nasal irritation (saline gel may help) • May not be tolerated in patients requiring high pressure
Nasal masks	• Smaller area to obtain a seal • In some, a lower pressure than with a full-face mask may be effective	• Mouth leak (chin strap) • Nasal congestion (medications and adequate humidification) • Air leak into eyes
Oronasal masks	• Patients with mouth leak or nasal congestion	• Large area to obtain a seal (often associated with higher leak) • May be challenging in edentulous patients or those with facial creases • May worsen claustrophobia • May require higher treatment pressure than a nasal mask in some patients

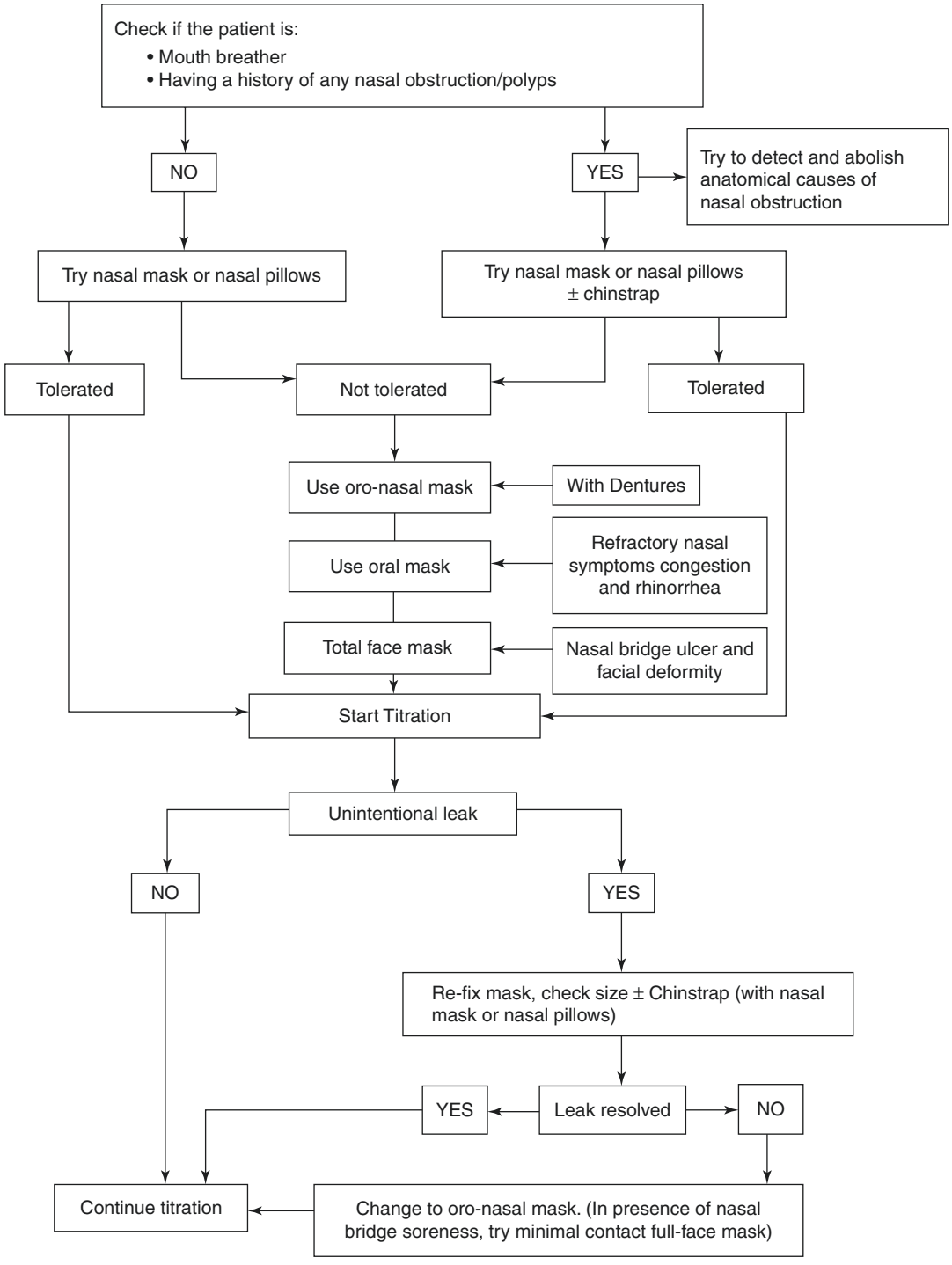

Fig. 19.3 Algorithm proposed by BaHammam et al. for the choice of interface during CPAP therapy in patients with OSA

19.4 Conclusions

The effectiveness of CPAP depends on the numbers of hours the patient really is under positive pressure therapy. Interface selection is a key factor to CPAP compliance and should be based on individual patient preference and tolerance. It is important to let the patient try different types of masks and to choose the most suitable. Published data suggest that unless patients have significant nasal problems, OSA therapy may be better tolerated and more effective if initially commenced with nasal mask. There is also increasing recognition about the different phenotypes underlying OSA and the route of breathing as important factors to be accounted for when choosing an interface. Further studies are needed to guide and substantiate medical decision. Nowadays, there are a huge number of interfaces available in the market. Their characteristics, advantages, and disadvantages should be compared. New studies should be developed, stronger studies with bigger samples and a longer duration. It is well known that as time goes on, the number of people who fail to comply CPAP therapy raises. Finally, studies should also be developed including hybrid masks, to help to clarify its position in interface choice algorithm.

19.5 Key Recommendations

- The fundamental concept of CPAP therapy is that nasal CPAP increases the pressure inside the pharynx above the pharyngeal critical closing pressure maintaining the pharynx open.
- Despite different airway delivery routes having little impact on CPAP efficacy, compatibility with a specific patient's preferred method of breathing constitutes a significant factor in patient adherence.
- There is no difference in therapeutic pressures when using either a nasal or oronasal mask.
- There is no difference in the residual AHI between nasal and oronasal mask use.
- Nasal masks are preferable based on better tolerability and compliance with therapy.
- Oronasal mask itself may promote mouth opening by displacing the jaw backward and downward.
- In specific situations of mouth opening and REM sleep, oronasal interfaces demonstrated fewer leaks when compared to nasal masks.
- Regarding sleepiness no meta-analyses were able to demonstrate clinically significant differences in self-reported sleepiness between interfaces.
- Difficulty with mask interface is common and none proved to be clearly superior.
- An oronasal mask may be useful in patients with mouth leak or severe nasal congestion.
- Changing mask type or improving fit can dramatically improve adherence and satisfaction.

References

1. Heinzer R, Andries D, Bastardot F, et al. Prevalence of sleep disordered breathing in middle-aged general population: the HypnoLaus study. Lancet Respir Med. 2015;3(4):310–8.
2. Shirlaw T, Duce B, Milosavljevic J, et al. A randomised crossover trial comparing nasal masks with oronasal masks: no differences in therapeutic pressures or residual apnea-hypopnea indices. J Sleep Res. 2019;28(5):e12760.
3. Rowland S, Aiyappan V, Hennessy C, et al. Comparing the efficacy, mask leak, patient adherence, and patient preference of three different CPAP interfaces to treat moderate-severe obstructive sleep apnea. J Clin Sleep Med. 2018;14(1):101–8.
4. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165(9):1217–39.
5. Gay P, Weaver T, Loube D, Iber C. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep. 2006;29(3):381–401.
6. BaHammam A, Singh T, George S, et al. Choosing the right interface for positive airway pressure therapy in patients with obstructive sleep apnea. Sleep Breath. 2017;21(3):569–75.
7. Andrade R, Madeiro F, Piccin V, et al. Impact of acute changes in CPAP flow route in sleep apnea treatment. Chest. 2016;150(6):1194–201.
8. Andrade R, Madeiro F, Genta P, Lorenzi-Filho G. Oronasal mask may compromise the efficacy of continuous positive airway pressure on OSA treat-

ment: is there evidence for avoiding the oronasal route? Curr Opin Pulm Med. 2016;22(6):2016.
9. Chai CL, Pathinathan A, Smith B. Continuous positive airway pressure delivery interfaces for obstructive sleep apnoea. Cochrane Database Syst Rev. 2006;4:CD005308.
10. Doyle C. The engineering of masks for application in continuous positive airway pressure (CPAP) therapy. Newcastle upon Tyne: New Castle University; 2017.
11. Gleeson K, Zwillich C, Braier K, White D. Breathing route during sleep. Am Rev Respir Dis. 1986;134(1):115–20.
12. Ruhle K, Nilius G. Mouth breathing in obstructive sleep apnea prior to and during nasal continuous positive airway pressure. Respiration. 2008;76(1):40–5.
13. Massie C, Hart R. Clinical outcomes related to interface type in patients with obstructive sleep apnea/hypopnea syndrome who are using continuous positive airway pressure. Chest. 2003;123(4):1112–8.
14. Ryan S, Garvey J, Swan V, Behan R, McNicholas W. Nasal pillows as an alternative interface in patients with obstructive sleep apnoea syndrome initiating continuous positive airway pressure therapy. J Sleep Res. 2011;20(2):367–73.
15. Zhu X, Wimms A, Benjafield A. Assessment of the performance of nasal pillows at high CPAP pressures. J Clin Sleep Med. 2013;9(9):873–7.
16. Patil S, Ayappa I, Caples S, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of sleep Medicine systematic review, meta-analysis, and GRADE assessment. J Clin Sleep Med. 2019;15(2):301–34.
17. Ebben M, Narizhnaya M, Segal A, et al. A randomised controlled trial on the effect of mask choice on residual respiratory events with continuous positive airway pressure treatment. Sleep Med. 2014;15(6):619–24.
18. Borel J, Tamisier R, Dias-Domingos S, et al. Type of mask may impact on continuous positive airway pressure adherence in apneic patients. PLoS One. 2013;8(5):e64382.
19. Beecroft J, Zanon S, Lukic D, Hanly P. Oral continuous positive airway pressure for sleep apnea: effectiveness, patient preference, and adherence. Chest. 2003;124(6):2200–8.
20. Bachour A, Vitikainen P, Virkkula P, Maasilta P. CPAP interface: satisfaction and side effects. Sleep Breath. 2013;17(2):667–72.
21. Mador MJ, Krauza M, Pervez A, Pierce D, Braun M. Effect of heated humidification on compliance and quality of life in patients with sleep apnea using nasal continuous positive airway pressure. Chest. 2005;128(4):2151–8.
22. Lebret M, Arnol N, Martinot J, et al. Determinants of unintentional leak during CPAP treatment in obstructive sleep apnea syndrome. Chest. 2017;S0012-3692(17):31435–6.
23. Lebret M, Arnol N, Contal O, et al. Nasal obstruction and male gender contribute to the persistence of mouth opening during sleep in CPAP-treated obstructive sleep apnoea. Respirology. 2015;20(7):1123–30.
24. Borel J-C, Gakwaya S, Masse J-F, Melo-Silva CA, Sériès F. Impact of CPAP interface and mandibular advancement device on upper airway mechanical properties assessed with phrenic nerve stimulation in sleep apnea patients. Respir Physiol Neurobiol. 2012;183(2):170–6.
25. Andrade R, Viana F, Nascimento J, et al. Nasal vs oronasal CPAP for OSA treatment: a meta-analysis. Chest. 2018;153(3):665–74.
26. Dibra M, Berry R, Wagner M. Treatment of obstructive sleep apnea. Choosing the Best Interface Sleep Med Clin. 2017;12:543–9.

20 Pathophysiology of Adult OSA: A Dynamic Look to Upper Airway Obstruction

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Abbreviations

CPAP	Continuous positive airway pressure
EELV	End-expiratory lung volume
EFL	Expiratory flow limitation
NED	Negative effort dependence
OSA	Obstructive sleep apnea
PSG	Polysomnography

20.1 Search Methodology

A PubMed search was performed from 2017 to March 2019 with the following keywords: "airflow shape," "upper airway obstruction," and "sleep apnea." Full-text publications were screened to fit the search criteria. For each selected work, the execution methodology and the results obtained were reported. This critical review of the literature explores the impact on the daily clinical practice of airflow analysis of the airflow shape recorded with nasal cannulas to define the site of pharyngeal airway obstruction in subjects with OSA and the possible consequent relapses for the treatment of different phenotypes.

20.2 Introduction

The pathophysiological mechanism underlying the obstruction of the upper airways have received considerable attention in recent years, and the

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most in-depth knowledge has underlined the relevance of signal analysis recorded during a nocturnal diagnostic examination in order of better phenotyping the subjects and choosing therapy. The analysis of the various morphologies of airflow shape, recorded during polysomnography or cardiorespiratory monitoring, can provide us accurate information on different anatomical and functional mechanisms of airway obstruction, without performing further instrumental examinations. In line with this approach, direct vision of the upper airways during natural sleep allowed us to understand the different morphologies of the airflow curves recorded with the nasal cannulas.

Postural muscle tone decreases during sleep. In all subjects, the decrease in upper airway's muscle tone during sleep leads to an increase in resistance with a relative reduction in ventilation, which is usually, at least in part, offset by the increase in respiratory muscle activity. The non-snoring subjects compensate for the reduced muscle tone with a relatively low respiratory drive, while the loud snorers require a higher respiratory drive to overcome the increased resistance of the upper airways and the consequent obstructive hypoventilation during sleep. Patients with obstructive sleep apnea (OSA) fail to maintain the upper airway patency during sleep, and arousal is often necessary to restore muscle tone and patency. Conventionally, the severity of the OSA is defined in terms of apnea/hypopnea index, which is based on the analysis of changes in the respiratory effort by thoracoabdominal bands and the semiquantitative change of airflow measured with nasal cannulas.

However, only a few methods are available to monitor the behavior of the collapsible structure of the upper airway during sleep. The critical pressure of the upper airways is a measure of the collapse of the upper airway under static conditions, with blockage of the airflow. The phasic activity of the upper airway dilator muscles can be evaluated by electromyography, but this method provides us with information on the central drive but not on the effect on airflow dynamics. We know that the size of the upper airways during the respiratory cycle undergoes significant changes in size [1]. They are significantly smaller in apneic compared to healthy subjects, especially in the retro-palatal and back of the tongue level. Furthermore, in apneic patients, the airways may have a major anteroposterior axis instead of the more common lateral-lateral axis. Both in healthy and apneic subjects there is a small narrowing of the airways during inspiration when the action of the dilator muscles balances the effects of negative intraluminal pressure. However, in apneic patients, there is a more considerable enlargement of the respiratory tract in the initial phase of inspiration, which presumably reflects a higher activity of the dilating muscles. The positive pressure inside the upper airways in the expiratory phase leads, in OSA patients, to a more significant expansion compared to controls, indicating that the airways in these subjects are more extensible. At the end of the exhalation, the upper airways narrow to a maximum at the end of the exhalation [2].

20.3 Upper Airway Obstruction and Airflow Shape

During inspiration, the airway is subjected to more forces that influence its behavior and its patency. These forces are the phasic activity of the dilator muscles (activated at the beginning or before the beginning of inspiration), the negative inspiratory pressure in the airways (which has the maximum effect halfway through the airflow peak), and the support dependent on tracheal downward traction (maximum effect at the end of inspiration with high lung volumes). The combined action of these different forces results in specific changes of inspiratory flow shape commonly observed in polysomnographic traces. The type and severity of airway alteration can be identified by analyzing changes from the normality of the airflow shape. The interpretation of the inspiratory flow curves is based on the shape of the inspiratory flow determined by muscle activ-

ity, tracheal downward traction, and the central respiratory drive that is different during the various sleep stages. The deficiency or excess of one force can alter the balance and determine the change of the inspiratory flow shape of the upper airway from that of the sinusoidal wave; therefore, the analysis of the inspiratory flow curves could help in the identification of the specific dysfunction of the upper airways and help to identify the most appropriate therapy [3].

A collapsible upper airway or "compromised anatomy" is the main cause of OSA although the anatomic contribution to OSA can vary widely and may be modest in about 20% of patients. Thus, non-anatomical factors or "phenotypes" that modulate pharyngeal patency are essential determinants of OSA for most patients. These include reduced control and function of pharyngeal dilator muscles during sleep, increased propensity to awaken during narrowing of the airways (low arousal respiratory threshold), and unstable respiratory control (high loop gain).

The structure of the pharynx lacks rigid bone support; it follows that the patency of the upper airways is firmly based on the activity of the muscles that constitute its structure. A modifiable structure controlled by the muscles is functional for the upper airway to perform its roles of speech, swallowing, and breathing. There are essential aspects to consider the potential role of pharyngeal dilator muscles in the pathogenesis of OSA: nervous control, muscular reactivity, and muscle efficacy. These characteristics must be kept in mind because they can be identified on the patient's breathing pattern and respiratory airflow shapes.

The most considerable dilator muscle of the upper airway located at the base of the tongue is the genioglossus, which can have up to six different patterns of activation during quiet breathing. This muscle is fan-shaped, receiving activation from the brainstem neurons, reflex input from mechanoreceptors sensitive to pressure changes in the upper airway, and from the chemical drive sensitive to increases in CO_2 and hypoxia. The sum of the different drives leads to greater activation of the genioglossus, even before the activation of the diaphragm. This pre-activation model acts to prevent airway narrowing during inspiration [4]. In contrast, the sum of the neural drive for another dilator muscle such as the tensor veli palatini typically generates a constant level of activation (tonic activity) during quiet breathing, even if the muscle can increase its activity in response to respiratory stimuli. The sleep-wake system strongly influences the neural drive to the genioglossus and the tensor veli palatini. Indeed, there are critical sleep-dependent changes in pharyngeal reflexes and neural control [5].

The nervous stimulus to genioglossus muscle progressively decreases from slow-wave sleep to N_2 and REM sleep. In contrast, the activity of the tensor veli palatini decreases significantly during the onset of sleep but remains relatively constant through the phases of sleep under these conditions. Despite the onset of sleep and the phase-dependent changes, the pharyngeal muscles increase their activity when they undergo to respiratory stimuli during sleep (changes in pharyngeal pressure and CO_2). More than one-third of people with OSA do not increase the EMG activity of genioglossus or increase it by only a small amount (<0.1% of maximum EMG per-cmH_2O) before arousal when exposed to narrowing of the airways during the sleep. Regardless of the mechanisms, weak muscular reactivity during sleep combined with an anatomic compromise of the upper airways is likely the main cause of OSA in these subjects. Muscle efficacy is the effectiveness to commute upper airway muscles' neural drive to upper airway dilation and increase airflow in response to hypopnea or apnea. People with OSA who have weak muscle reactivity (an insufficient increase of the neural drive to narrowing of the airways during sleep) also have reduced muscular effectiveness. However, some OSA generate significant increases in pharyngeal muscle activity (good muscle responses) when the airway is reduced during sleep. Pharyngeal muscle activity can sometimes reach levels of activation far beyond those generated during wakefulness, but this does not translate into an adequate pharyn-

geal dilatation and airflow in these individuals (i.e., reduced muscular efficacy).

In some cases, a negative dependence on the effort may occur when the airflow decreases, rather than increases due to a reduction in the size of the airways, within a single breath and between the breaths, in response to an increase in negative intrathoracic pressure. However, the potential contribution of activity of the upper airway muscles in mediating the negative effort dependence in OSA is not yet clear [6]. The lousy coordination of the neural drive to the various muscles of the upper airway during sleep, the direction of the mechanically inefficient muscle fibers (due to excess fat or muscle hypertrophy), or change in the type of muscle fiber, with higher propensity to fatigue, could all be factors that contribute to airflow reduction or apnea, resulting in specific morphologies of the respiratory flow wave [1].

Muscle effectiveness or dilator movement of the upper airway muscles can be assessed indirectly by assessing changes in the airflow by gradual reduction of CPAP pressure and by evaluating the morphology of the active inspiratory phase with the passive expiratory flow shape, or it can also be examined directly through direct visualization with a camera in the airway. Based on this knowledge, in the last 2 years, some studies have accurately evaluated the upper airway behavior during natural sleep conditions trying to find a direct relationship between the visual assessment of the collapsing anatomical structure and the morphology of the airflow shape. In addition to sleep staging, pharyngeal pressure was monitored with a 5-F catheter, while images were recorded with a 2.8 mm diameter pediatric bronchoscope inserted through the nostril. The subjects breathed through a nasal mask connected to a pneumotachograph and pressure transducer and a modified CPAP device capable of providing positive and negative pressures (including 0 cmH_2O). The subjects fell asleep in a supine position with the tip of the bronchoscope in the nasopharynx and CPAP set to eliminate airflow limitation. Once stable NREM sleep was obtained, CPAP was removed for 2- to 3-min intervals. After observing the airways at zero pressure for several falls, a CPAP pressure was set to induce a stable airflow restriction. The CPAP allowed keeping the airways open so that a particular structure involved in the collapse could be carefully observed throughout the respiratory cycle making a correlation between the site of collapse and the airflow shape. The bronchoscope was then moved to the oropharynx, and the procedure was repeated. Thus, many airflow restriction sequences were recorded at each level (nasopharynx and oropharynx) throughout the night. Since OSA results from the collapse of different pharyngeal structures (soft palate, tongue, lateral walls, and epiglottis), it has been assumed that this can generate different shapes of inspiratory flow between patients reflecting the underlying pharyngeal structure implicated in airway collapse [7–9].

The airflow wave analysis can be used as a noninvasive tool to determine the pharyngeal structure that causes collapse, thus being able to influence the success of specific OSA treatments for a given collapsing structure. Therefore, an inexpensive noninvasive technique to determine the structure that causes pharyngeal obstruction during natural sleep can improve the treatment of OSA allowing more individualized therapies. Inspiratory flow limitation is a primary feature of pharyngeal collapsibility, and several different airflow shapes have been recognized in patients with OSA [3]. A key feature of the airflow limitation is the dependence on negative inspiratory effort (NED), defined as the reduction of the airflow from the peak to the average inspiratory point with the increase of the effort in the respiratory system.

A particular morphology of the curve characterized by an airflow peak at the beginning and a smaller one at the end of the inspiration with a significant decrease in the airflow itself indicates that the airways initially open in response to the respiratory drive but then narrows to return to the basal conditions at the beginning of the next breath. The late peak is an expression of an improvement in the airway patency secondary to the downward traction caused by the increase in the volume of the lungs. Inspiratory effort can be assessed by the difference between airflow peak and mid-inspiration flow [10]. The NED is a

reflection of the dynamic compliance of the structure responsible for the collapse, with greater dependence on the effort that involves an airway or a more compliant structure and that can vary significantly among patients. It is probable that the variability of the NED results from the interaction between the oscillations of the intra-pharyngeal pressure and the consequent dynamic behavior of the pharyngeal structures involved in the collapse. It has been hypothesized that the pharyngeal structure implicated in the collapse in patients with OSA would determine the airflow shape [10]. Comparison of the video image with the recordings of respiratory effort and airflow confirmed that the tongue determined the collapse. It would cause a minimum dependence on the effort, while the collapse of the epiglottis or the isolated palate would have a greater dependence on the inspiratory effort.

In tongue-related obstruction (whether at atmospheric pressure or with low CPAP pressure), there is minimal phasic movement of the tongue and palate with breathing and a flattened airflow limitation pattern, which shows only a small amount of increased effort [7] (Fig. 20.1).

In the presence of an isolated palatal collapse, the subjects have a moderate dependence on the effort, consistent with the dynamic movement of the isolated palate observed by endoscopy. When the palate is the only or predominant collapsing structure, it has a phasic collapse and then reopens, which may be due to a free palate movement not mechanically coupled to the tongue located anteriorly [7] (Fig. 20.2).

The collapse of the lateral pharyngeal wall, a structure with high compliance and great dynamic wall movements, is similar to isolated palatal collapse associated with moderate NED [7] (Fig. 20.3).

Upper airway obstruction caused by the collapse of the epiglottis, either isolated or combined with the obstruction of other pharyngeal structures, has particular characteristics and above all is tightly dependent on respiratory effort. A key feature of epiglottis collapse is intermittence; it appears in groups of breaths and then disappears, only to be replaced by another site of the collapse. A group of authors specifically investigated epiglottis collapse, demonstrating that it occurs more often than previously described [8]. Indeed, some studies have reported that up to 30% of patients have a complete collapse of the epiglottis [11] and when present is difficult to treat with conventional therapies, such as intraoral devices and even with continuous positive airway pressure (CPAP). Therefore, recognizing whether and how often the upper airway collapses to the epiglottis could have important treatment implications. The authors also reported a link between the extent of inspiratory effort

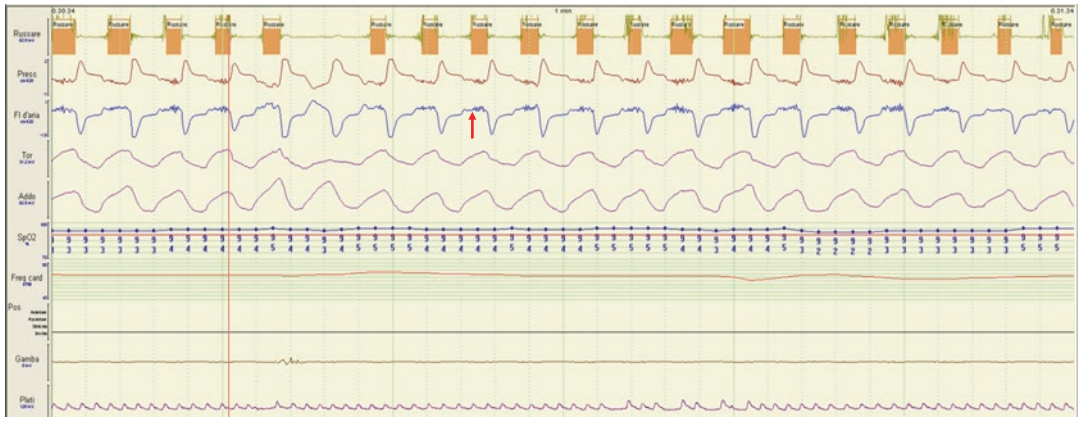

Fig. 20.1 From the top traces are snoring, nasal pressure, nasal cannula airflow, thoracic effort, abdominal effort, oxygen saturation, heart rate, body position, leg movements, and pulse wave. Red arrow highlights flattened airflow limitation pattern with a small amount of increased inspiratory effort

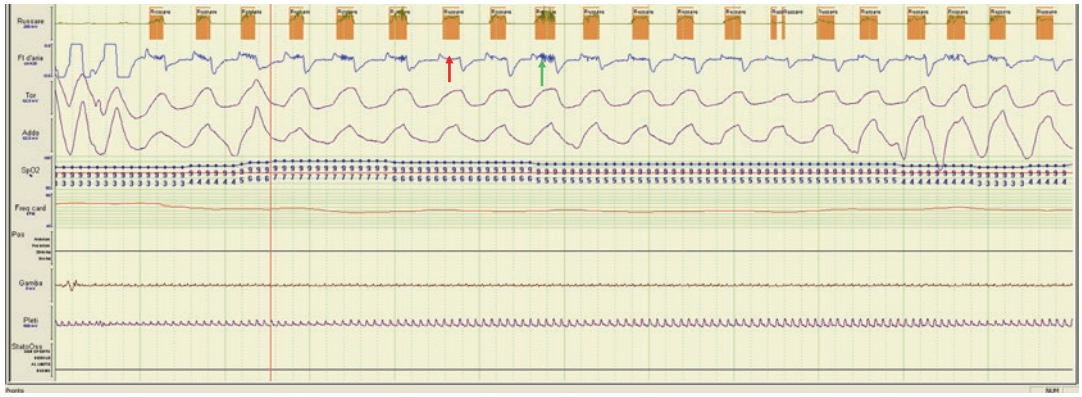

Fig. 20.2 From the top traces are snoring, nasal cannula airflow, thoracic effort, abdominal effort, oxygen saturation, heart rate, body position, leg movements, and pulse wave. The red arrow highlights a moderate peak followed by flattened airflow limitation. The green arrow highlights high-frequency snoring vibration on nasal cannula

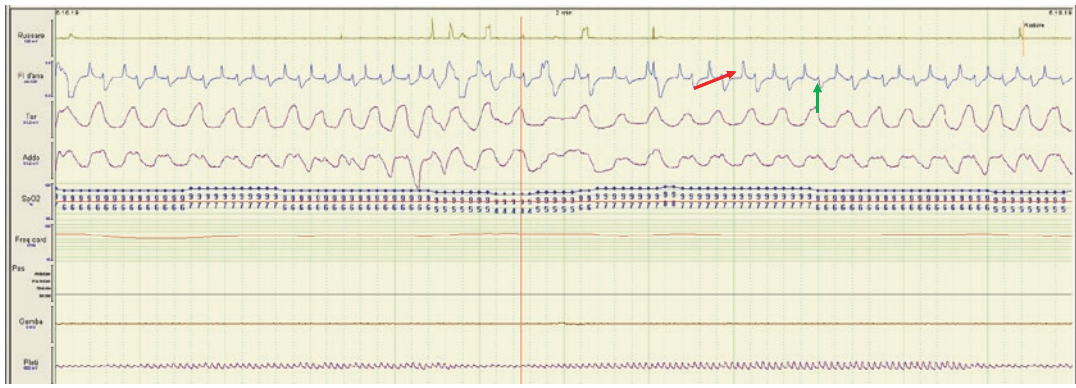

Fig. 20.3 From the top traces are snoring, nasal cannula airflow, thoracic effort, abdominal effort, oxygen saturation, heart rate, body position, leg movements, and pulse wave. The red arrow highlights a peak followed by dynamic pharyngeal wall movements. The green arrow highlights the second inspiratory peak due to the reopening of upper airways secondary to inspiratory lung dawn traction on the pharynx

dependence, reduced airflow in association with increased inspiratory effort, and the presence of epiglottis collapse in subjects with OSA. The results of the study have shown that the cardinal features of epiglottis collapse are the immediate changes in inspiratory flow within the single breath or discontinuity (drop of inspiratory flow) (Fig. 20.4a). Moreover, the visually evaluated inspiratory and expiratory jaggedness, i.e., the extent of the deviation of the airflow from the inspiratory and expiratory flattening (more unstable airflow results in a higher jaggedness index), is a recognizable hallmark of epiglottis collapse (Fig. 20.4b).

The authors' main conclusion is that epiglottis collapse produces airflow shapes that are different from the characteristics produced by non-epiglottis obstructions. They are easy to quantify and can be reliably estimated from nasal pressure signals collected during clinical sleep studies [8].

The soft palate, in addition to inspiratory collapse, has been observed to prolapse in the velopharynx during expiration causing a sudden reduction in the expiratory flow (EFL) observable on the airflow shape [9]. The palatal prolapse produces distinct and reproducible expiratory flow characteristics during sleep that can be identified by the drop of expiratory flow so the palatal pro-

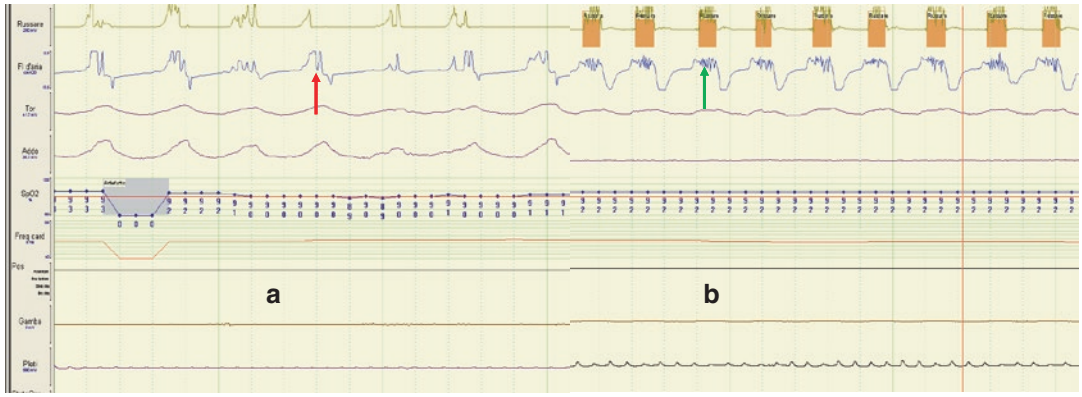

Fig. 20.4 From the top traces are snoring, nasal cannula airflow, thoracic effort, abdominal effort, oxygen saturation, heart rate, body position, leg movements, and pulse wave. (**a**) The red arrow highlights a discontinuity or sudden drop of inspiratory flow. (**b**) The green arrow highlights jaggedness

lapse can be diagnosed during polysomnography (PSG) or home polygraphy. The airflow shape is labeled as palatal prolapse if the free edge of the palate rotated posteriorly or swollen (with a narrowing higher than 50% of the velopharynx due to the posterior movement of the palate) in the nasopharynx during the expiration. Due to the anatomical relationship between the tongue and the palate, tongue-related obstruction was usually associated also with palatal obstruction [12]. The isolated palatal collapse, which probably must be large or elongated and mechanically separated from the base of the tongue without any involvement of other airway structures, is more frequent in the supine position. Therefore, prolapse/swelling of the soft palate in the nasopharynx during expiration is always associated with expiratory flow limitation (EFL).

Patients with OSA and palatal prolapse on exhalation are more likely to also have a palatal collapse (isolated) in inspiration; the characteristic airflow shape produced by the palatal expiratory prolapse can be detected with high sensitivity and specificity by the nasal pressure signal [9] (Fig. 20.5).

The pivotal feature of expiratory flow limitation is an increase in pharyngeal pressure (positive expiratory pressure developed at the epiglottis level without a concomitant increase in expiratory flow) and therefore high expiratory resistance (>20 cmH_2O/L/s) in the nasal airway.

Through direct observation of the soft palate and the uvula, it has been shown that the palate can show a valve-like behavior during expiration. Shunt airflow through the mouth could lead to a transition to oral breathing which, on its own, could increase the collapse of the upper airways and decrease adherence to CPAP therapy. The position of the palate in the nasopharynx, whether it is due to an elongated palate, an edematous uvula, or excess palatal tissue that moves more freely in the airways, can determine a condition for a compromised airway at the next inspiration because reduced inspiratory times and tidal volumes follow the palatal prolapse. The reason for this is that the airway pressure during inhalation falls (e.g., −5 cmH_2O) to remove the prolapsed palate and reopen the airways causing a decrease in the inspiratory tidal volume in subsequent breaths that could be classified as hypopneas.

Furthermore, the associated increase in EELV due to palatal prolapse may decrease inspiratory flow, because more negative inspiratory pressures are needed to produce inspiratory flow. Changes in EELV produced by palatal prolapse may also be clinically relevant. It was found that an average increase of 200–250 mL in EELV during EFL can have a stabilizing effect by improving airway patency and collapsibility and reducing sleep disordered breathing and the level of CPAP required to settle airflow limitation in patients with OSA [13]. From the clinical point of view,

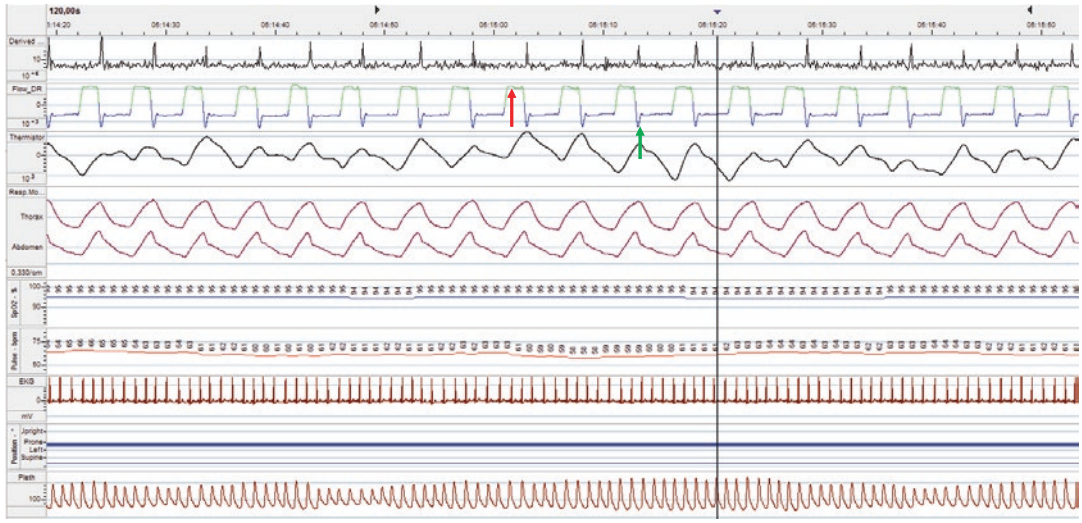

Fig. 20.5 From the top traces are snoring, nasal cannula airflow, thermistor, thoracic effort, abdominal effort, oxygen saturation, heart rate, ECG, body position, and pulse wave. The red arrow highlights a moderate peak followed by flattened airflow limitation suggestive for inspiratory palatal collapse. The green arrow highlights the abrupt reduction in expiratory flow suggestive for expiratory palatal prolapse

fluctuations and tissue movements related to palatal prolapse could independently contribute to the appearance of arousal. Therefore, in patients with a single predominant collapse mechanism, it may be possible to obtain informations on the pharyngeal structure that causes collapse. This study shows that when a single or predominant structure is the cause of pharyngeal airway collapse, it produces a recognizable effect on the airflow shape of inspiratory and expiratory flow. The relevance of these results is how the careful evaluation of the airflow shape is an inexpensive and noninvasive way to identify pharyngeal collapse site. NED is associated with the amount of phasic movement of the pharyngeal structure involved in obstruction and is associated with changes in upper airway resistance. Therefore, a smaller phasic movement of the pharyngeal structure (as observed in the tongue-related obstruction) is expected to lead to minor changes in upper airway resistance.

A posteriorly localized tongue can stabilize the soft palate through surface adhesion forces and prevent the phasic narrowing of the velopharynx in response to negative inspiratory pressure [11]. In contrast, without close contact with the tongue, the soft palate may exhibit more posterior movements in the lumen of the airway in response to negative inspiratory pressures (isolated palatal collapse with large NED) [7].

Therefore, the analysis of the airflow wave shapes can provide valuable information on the pharyngeal structure that causes collapse and improves personalized therapy of OSA avoiding failures. The concentric collapse has been shown to decrease the success of airway pacing [14]; palatal collapse is independently associated with a positive response to mandibular advancement therapy, while EFL patients may be less sensitive to mandibular advancement devices and upper airway stimulation [15]. The multilevel collapse was observed in all patients with severe OSA but only in 20% of patients with mild OSA. The most frequent combination is the collapse of the palate and base of the tongue followed by the palate and epiglottis [16].

The remarkable message of these studies is that using airflow wave shape analysis has a basis for noninvasive evaluation of the pharyngeal structure that causes collapse.

The identification of the site/structure of pharyngeal collapse in patients with OSA can improve the success of OSA therapy.

20.4 Conclusions

The OSA severity is conventionally defined on the apnea and hypopnea index. This approach leads to ignoring what happens before the event or in the absence of respiratory events. The articles published in recent years have provided a new way of analyzing the recordings by highlighting the information contained in the morphology of the airflow shapes that allow us to understand the possible site of the collapse of the upper airways. This model of approach associated with the phenotyping of the patient with sleep disordered breathing based not only on anatomical but above all functional characteristics is the key to personalized and successful therapy.

Few research papers have examined the validity and accuracy of the analysis of airflow shapes as a marker of the pharyngeal structure causing OSA. The available papers are difficult to compare and have some limitations: few patients involved due to the invasiveness of the methods, technical difficulties in comparing pneumotachograph airflow with nasal cannula airflow and video files, and difficulty in the storage of large high-definition video files during endoscopy. Further studies with a higher number of patients are needed to confirm the effectiveness of the interpretations.

The information that can be obtained from the sleep study and in particular from the airflow shapes recorded by nasal cannulas may allow us to identify the pharyngeal structure causing collapse.

References

1. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea—new pathways for targeted therapy. Sleep Med Rev. 2018;37:45–59.
2. Schwab RJ, Gefter WB, Hoffman EA, et al. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. Am Rev Respir Dis. 1993;148:1385–400.
3. Aittokallio T, Saaresranta T, Polo-Kantola P, et al. Analysis of inspiratory flow shapes in patients with partial upper-airway obstruction during sleep. Chest. 2001;119:37–44.
4. Saboisky JP, Butler JE, Fogel RB, et al. Tonic and phasic respiratory drives to human genioglossus motoneurons during breathing. J Neurophysiol. 2006;95:2213–21.
5. Nicholas CL, Jordan AS, Heckel L, et al. Discharge patterns of human tensor palatini motor units during sleep onset. Sleep. 2012;35:699–707.
6. Genta PR, Owens RL, Edwards BA, et al. Influence of pharyngeal muscle activity on inspiratory negative effort dependence in the human upper airway. Respir Physiol Neurobiol. 2014;201:55–9.
7. Genta PR, Sands SA, Butler JP, et al. Airflow shape is associated with the pharyngeal structure causing OSA. Chest. 2017;152:537–46.
8. Azarbarzin A, Marques M, Sands SA, et al. Predicting epiglottic collapse in patients with obstructive sleep apnoea. Eur Respir J. 2017;50(3):1700345.
9. Azarbarzin A, Sands SA, Marques M, et al. Palatal prolapse as a signature of expiratory flow limitation and inspiratory palatal collapse in patients with obstructive sleep apnea. Eur Respir J. 2018;51(2). pii: 1701419.
10. Owens RL, Edwards BA, Sands SA, et al. Upper airway collapsibility and patterns of flow limitation at constant end-expiratory lung volume. J Appl Physiol. 2012;113:691–9.
11. Lan MC, Liu SY, Lan MY, et al. Lateral pharyngeal wall collapse associated with hypoxemia in obstructive sleep apnea. Laryngoscope. 2015;125:2408–12.
12. Isono S, Tanaka A, Nishino T. Dynamic interaction between the tongue and soft palate during obstructive apnea in anesthetized patients with sleep-disordered breathing. J Appl Physiol. 2003;95:2257–64.
13. Heinzer RC, Stanchina ML, Malhotra A, et al. Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea. Am J Respir Crit Care Med. 2005;172:114–7.
14. Vanderveken OM, Maurer JT, Hohenhorst W, et al. Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. J Clin Sleep Med. 2013;9:433–8.
15. Vroegop AV, Vanderveken OM, Dieltjens M, et al. Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome. J Sleep Res. 2013;22:348–55.
16. Huon LK, Liu SY, Shih TT, et al. Dynamic upper airway collapse observed from sleep MRI: BMI-matched severe and mild OSA patients. Eur Arch Otorhinolaryngol. 2016;273:4021–6.

Obesity Hypoventilation Syndrome

21

Ahmet Cemal Pazarlı

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21.1 Introduction

Obesity is a complex, multifactorial, and largely preventable disease that affects more than a third of the world's population today [1]. If the secular trends continue, the predictions show that by the year 2030, 38% of the adult population in the world would be overweight and 20% obese. In the USA, the most frightful predictions based on previous trends indicate that by 2030 over 85% of adults would be overweight or obese [2].

The prevalence of overweight and obesity, together with accompanying health risks, causes especially a worldwide public health problem. Obesity brings along many medical condition risks that may cause morbidity and mortality. It is an important risk factor for obesity hypoventilation syndrome (OHS), known as important sleep-disordered breathing. Obesity is a defining characteristic of the disease, and there is a significant relationship between body mass index (BMI) and disease prevalence. The recognition of

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OHS is important due to the possibility of clinical exacerbation leading to respiratory failure and a high mortality rate in untreated patients. More than 90% of OHS cases are accompanied by OSA; although obesity is a significant risk factor in both, the presence of OSA is not necessary for the OHS diagnosis. Since 1999, the American Academy of Sleep Medicine has defined diagnostic criteria for OHS [3]. To date, many studies have been conducted on the epidemiology, clinical presentation, pathophysiology, and treatment of OHS.

21.2 Epidemiology

The actual prevalence of OHS in the general population is unknown. It has been reported that OHS is present in 10–20% of patients admitted to Sleep Disorders Laboratory and in approximately 50% of in-patients with BMI >50 kg/m^2. In a meta-analysis, the prevalence of OHS in OSA cases was determined as 19%, and the frequency of OHS was calculated to be between 1.5 and 3 in 1000, when compared to the whole population [4]. Mokhlesi et al. [5] have analyzed 180 patients retrospectively and 410 patients prospectively who applied to the sleep laboratory with suspicion of OSA in the USA. They have demonstrated that in retrospective and prospective samples, of patients diagnosed with OSA, 30% and 20% have met the OHS criteria, respectively, and these percentages increased as BMI increased. Akashiba et al. [6] have directed 611 patients in Japan to sleep centers for OSA, and they have got OHS diagnosis in 9% of these patients. In this study, patients with OHS were younger and fatter and have more severe OSA compared to those without OHS. Nowbar et al. [7], who attempted to determine the prevalence and inadequate diagnosis level of OHS, conducted a study that included obese patients who applied to internal medicine services for any reason. Of the 29 obese patients with BMI >50 kg/m^2, 14 (48%) were diagnosed with OHS, and in the same study, they have shown that 31% of 150 hospitalized obese patients, despite fulfilling the criteria for this diagnosis, did not have OHS diagnosis. Mokhlesi [8] has stated that in the event that approximately 3% of the general population in the USA is seriously obese (BMI >40 kg/m^2), half of these individuals may have OSA; and therefore, according to the prediction that 10–20% of the severely obese patients with OSA would have OHS, he has revealed the OHS prevalence as 0.15–0.30% in the general population of the USA as a conservative prediction.

Despite all the studies with the prevalence of OHS in the general population, the incidence of OHS in the world is expected to increase in parallel with the increasing epidemic of obesity.

21.3 Definition and Diagnosis

OHS is included under the heading "sleep-related hypoventilation disorders" in the International Classification of Sleep Disorders Version 3/ICSD-3, published by the American Academy of Sleep Medicine (AASM). According to this classification, the diagnostic criteria of OHS are;

1. Presence of hypoventilation in wakefulness (PCO_2 >45 mmHg)
2. Presence of obesity (body mass index (BMI) >30 kg/m^2)
3. Hypoventilation that cannot be explained with other reasons such as pulmonary parenchymal or obstructive diseases, chest wall diseases, and neuromuscular diseases

In addition to the above diagnostic criteria, the use of calculated serum bicarbonate levels greater than 27 mEq/L from arterial blood gas and/or calculated base excess greater than 2 mmol/L is also discussed [9]. The majority of OHS patients have symptoms of OSA such as snoring, night drowning, witnessed apneas, irregular sleep, excessive daytime sleepiness, and fatigue. In contrast to patients with only OSA, patients with OHS often have complaints of dyspnea and be hypoxic and have symptoms of cor pulmonale. Patients suspected of having OHS may be initially scanned by pulse oximetry and the determination of serum levels of venous bicarbonate. In OHS, in which borderline oximetry values are common findings and arterial blood gas analysis is done, PaO_2 values

are rarely >70 mmHg. As a result, the SpO_2 values in the pulse oximetry <93% suggest hypoventilation. However, the higher values are not eliminative; this explains why it is not a necessary criterion for diagnosis, although it may help in scanning. Demonstration of continuous hypoxia which is not associated with apnea in the night oximeter enhances hypoventilation suspicion. In addition, in the studies conducted, in the event that in OSA-diagnosed patients' blood gases, the serum bicarbonate level was above 27 mEq/L, it was determined to have a sensitivity of 92% and a specificity of 50% for OHS, and this justifies the use of scans [10]. Polysomnography is not required for the diagnosis of OHS. However, since individuals with OHS are observed to have obstructive events as well as lower oxygen saturation values in REM sleep, a polysomnography test is recommended to treat comorbid sleep apnea and to justify possible treatments [11].

21.4 Pathophysiology

The absence of hypoventilation in each obese patient suggests that the pathogenesis of OHS is mixed and multifactorial. The main pathophysiological mechanisms responsible for the development of OHS are therefore unknown. Various hypotheses have been suggested why some obese patients are accompanied by hypoventilation, while it is not observed in some patients. It is thought that it occurs as a result of complex interaction of impaired respiratory mechanics, impairment of central respiratory control, possible sleep-disordered breathing (SDB), and neurohormonal disorders [12]. Normally, obesity may adversely affect respiratory mechanics, respiratory muscle strength, pulmonary gas exchange, respiratory control, lung function tests, and exercise capacity and may cause undesirable changes. In obesity, there is superficial respiration with high frequency and low volume. With the effect of increased fat tissue, the thoracic expansion is decreased and chest wall compliance is significantly reduced. Obesity increases the workload of the lungs by increasing oxygen consumption and carbon dioxide production in the body. In simple obesity, it is seen that the work done for breathing is 70% more, and the amount of spent energy or oxygen is 4 times more than normal. In OHS, the work done is 280% more and the energy spent is 10 times more than normal [13]. Obesity has many negative effects on the respiratory system. In central (abdominal) obesity, chest wall compliance and respiratory muscle endurance decrease due to increased adipose tissue load on the chest wall. Adipose tissue in the anterior abdominal wall and intra-abdominal organs prevents the movement of the diaphragm. In addition, the diaphragm itself becomes infiltrated with fat tissue. As a result of these interactions, the expansion decreases in the basal regions of the lung in the inspirium, and collapse occurs in the small airways, leading to deterioration of the ventilation/perfusion (V/Q) balance and hypoxemia. Micro-atelectasis resulting from the collapse of airways causes alveolar surface tension to increase. As a result, lung compliance is reduced. In obese patients, loss of volume in basal lung areas causes a decrease in functional residual capacity (FRC) and expiratory reserve volume (ERV). The reduction in ERV and FRC leads to the limitation of airflow in the expiration and early closure of the airways in calm breathing. Airflow limitation leads to the development of positive pressure at the end of expiration, in other words, dynamic hyperinflation. This situation increases the feeling of dyspnea by increasing respiratory muscle load and respiratory work. In obese individuals, shortness of breath, wheezing, and breathing efforts at rest are more common than those with normal BMI. Oxygen consumption of respiratory muscles increases due to increased breathing work. Obese individuals spend 25% more oxygen at rest and 90% more oxygen in maximal exercise. Production of carbon dioxide per kilogram is 40% higher [14]. Respiratory muscle strength and endurance in obese patients are decreased. In the supine position, the excessively tensed diaphragm negatively affects the respiratory muscles mechanically and reduces the strength and effectiveness of the inspiratory muscles. In obese patients, lean muscle mass is reduced, and this leads to impairment in respiratory muscle function. Both inspiratory and expiratory muscle strengths are

affected. As a result, impairment in respiratory muscle function contributes to increased oxygen consumption to maintain ventilation and increased dyspnea feeling. Due to increased metabolic requirements, a rapid and surface breathing pattern is developed in obese individuals. Acapnic obese individuals are in an attempt to increase the central respiratory impulse to compensate for the mechanical restriction created by obesity, while OHS patients lack in this effort. In patients with OHS, central control of the respiration is impaired and the response to hypercapnia is decreased [15]. Leptin, produced from adipose tissue and suppressing appetite by binding to its receptors in the hypothalamus, also stimulates the respiratory center. Both obesity-related leptin resistance and leptin deficiency result in impaired neuromechanical control in the upper respiratory tract [16]. In fact, one of the hypotheses for the reason for not seeing hypoventilation in every individual with obesity is leptin resistance. The degree of obesity and the distribution of fat in the body are another important factor in the development of OHS. The central location of the fat in the body (abdominal obesity) makes the development of OHS easier [17]. The presence and degree of underlying OSA is another factor that is argued for contributing to the development of OHS. In 90% of the cases with OHS, sleep-disordered breathing is seen which is in the form of OSA, and 10% has isolated sleep-associated hypoventilation [8]. When apnea-hypopnea occurs in sleep, ventilation is reduced, intermittent carbon dioxide retention is seen, and the acapnic situation may be maintained by increasing ventilation between apnea periods. If a shorter interapneic period than apnea duration is performed, carbon dioxide increases since it is not sufficiently eliminated [18]. In conclusion, correcting daytime hypercapnia by effective treatment of the airway which is obstructed in sleep is an indicator that upper airway obstruction plays an important role in the development of OHS (Fig. 21.1) [19].

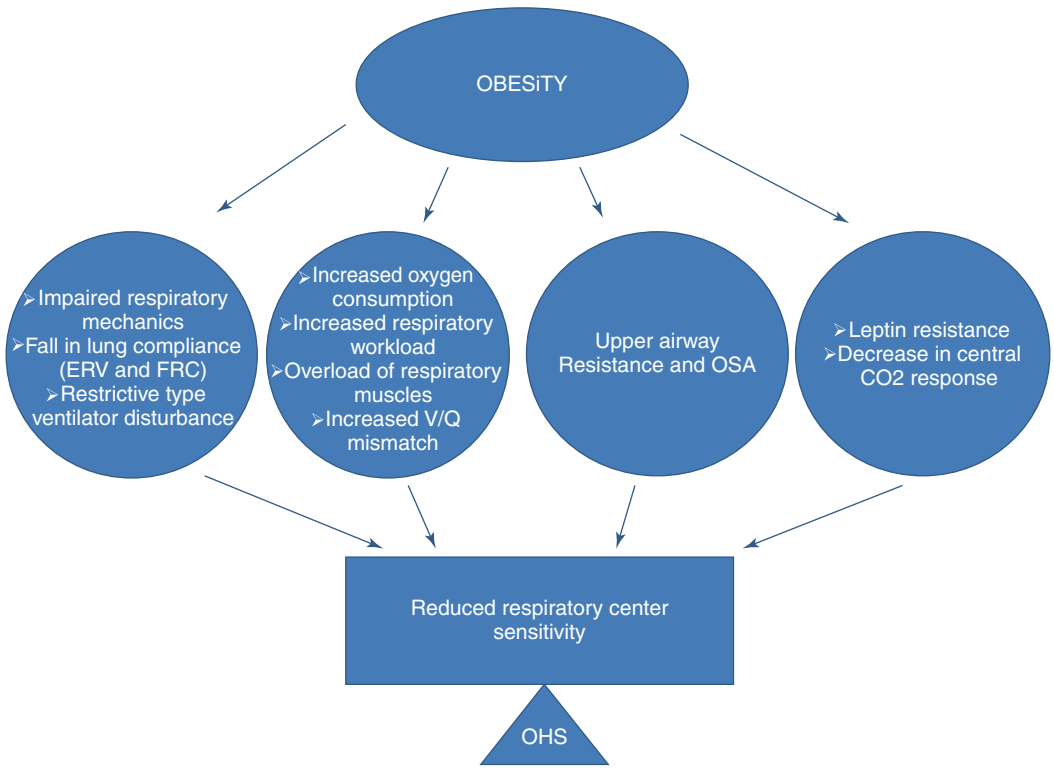

Fig. 21.1 Pathophysiology of obesity hypoventilation syndrome

21.5 Treatment

When OHS is not treated, acute, life-threatening cardiopulmonary risk and mortality rates increase. In addition, the risks of life quality deterioration, pulmonary hypertension, right heart failure, angina, and insulin resistance increase. Treatment goals in OHS can be summarized as the correction of hypercapnia in sleep and wakefulness, the prevention of hypoxemia, the prevention of erythrocytosis, pulmonary hypertension, and cor pulmonale development.

Generally, treatment can be examined under three main headings:

1. To restore $PaCO_2$ to normal in both wakefulness and sleep and to restore acid-base balance. For this, correcting the respiratory center control, reducing respiratory workload, and preventing respiratory muscle fatigue or resting muscles
2. To protect the level of oxyhemoglobin by correcting alveolar ventilation and *V*/*Q* ratio and by treating OSA if any, thus to prevent cor pulmonale formation
3. To improve the quality of life by correcting daytime sleep and to correct sleep structure Noninvasive ventilation (NIV) is the most effective treatment method, especially if respiratory failure developed in OHS in which respiratory workload increased and respiratory muscle fatigue is addressed. With NIV treatment, the patient is provided the necessary tidal volume, micro-atelectasic areas are open, thoracic flexibility is improved, lung volumes are increased, the workload of inspiratory breathing muscles is reduced, tired muscles are rested, and the respiratory center's response to CO_2 is improved.

At this point, positive airway pressure (PAP) treatment (various modes of CPAP or NIV) and weight reduction approaches are essential [20].

NIV in OHS is implemented in two different modes:

1. Continuous positive airway pressure (CPAP)
2. Noninvasive positive pressure ventilation (NPPV)
   (a) Pressure-supported modes (biphasic positive airway pressure)
      - BPAP spontaneous mode (S mode)
      - BPAP spontaneous time mode (ST mode)
      - BPAP time mode (T mode)
   (b) Volume-controlled positive airway pressure
      - AVAPS (average volume-assured pressure support) mode

21.6 Continuous Positive Airway Pressure (CPAP)

CPAP treatment is a very effective treatment for OSA. Most of the patients with OHS have comorbid severe OSA [4]. It would, therefore, be reasonable to expect that CPAP may help improve the gas exchange in a significant group of patients by stabilizing the upper airway. Application of CPAP treatment at night on a regular basis provides a decrease in wakefulness arterial CO_2 pressure ($PaCO_2$). Correction of hypercapnia in both wakefulness and sleep by CPAP is achieved by correction of respiratory muscle fatigue and central ventilatory stimulation [13].

In an observational study, as a result of 3 months of CPAP treatment in 29 patients with OHS and severe OSA who were admitted with mild-to-moderate basal nocturnal hypoventilation, daytime $PaCO_2$ was observed to be corrected [21]. In their Pickwick study, Masa et al. [22] have compared 2 months of CPAP treatment with lifestyle change and have provided a significant improvement with CPAP treatment, under the control of the polysomnographic measurements and sleep disturbance, compared to the control group, and have revealed an improvement in the daytime $PaCO_2$. In another study in which 20 patients with OHS were evaluated retrospectively, Berg et al. [23] have reported a reduction in hospitalization and resource use in 2 years after starting NIV or CPAP treatment, compared to 5 years prior to treatment.

21.7 Noninvasive Positive Pressure Ventilation (NPPV)

Several observational studies have demonstrated the medium- and long-term benefits of NIPV over different outcomes in OHS. Ventilator support provides an improvement in gas exchange; this results in a significant decrease in PCO_2 and an increase in arterial oxygen levels in daytime wakefulness. With NPPV treatment, symptoms such as the measurement of health-related quality of life (HRQoL) and sleepiness and dyspnea significantly improve. BPAP treatment is quite effective in OHS. It may also compensate for leaks from the mask edge; however, since it is pressure sensitive if the patient has upper airway obstruction or the respiratory system compliance of the patient is low, when the target pressure is reached, the formed tidal volume may be low and may result in hypoventilation. In cases of severe upper airway obstruction, both EPAP and IPAP should be increased together. In this case, tidal volume can be increased by pressure gradient while correcting upper airway obstruction. IPAP should be increased more when respiratory system compliance is reduced. In contrast to the long-term observational data of CPAP-treated OHS, few studies have been reported on OHS treated with NPPV (BPAP) for more than 3 months. In a randomized controlled trial of 35 patients with mild OHS, 1-month NPPV treatment was associated with a significant decrease in daytime $PaCO_2$ and improvement in sleep disturbance, depending on lifestyle modification [24]. In another branch of the Pickwick study, this time they have compared the effectiveness of NIV with the lifestyle intervention as a control group, and it was observed that after 2 months, NIV, polysomnography, HRQoL, sleep parameters, and daytime $PaCO_2$ were significantly improved in 221 patients with severe OSA. NIV also provided a significant improvement in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and respiratory function in a 6-min walk [22]. In a subsequent multicenter randomized study comparing CPAP with constant level BPAP-ST for 3 months, in each group, although there was a faster downward trend in $PaCO_2$ at first month with BPAP-ST, there was no difference in the proportion of participants with a 3-month course of treatment failure [25]. In the same study, similar developments after 1 and 3 months of treatment in $PaCO_2$ and bicarbonate occurred in each group; however, $PaCO_2$ showed a faster downward trend in the first month with BPAP-ST. There were no differences between groups in other secondary outcomes such as sleepiness, HRQoL, cardiovascular risk markers, and physical activity.

However, the high rates of prevalence of pulmonary hypertension and right ventricular dysfunction are reported in patients with OHS, and some studies have shown that NIV has potential benefits over heart results. In an observational study involving 30 patients, NPPV treatment has been shown to provide a decrease in pulmonary systolic arterial pressure and an improvement in 6-min walk distance in patients with OHS with echocardiographic right ventricular overloading [26].

21.8 Volume-Controlled Positive Airway Pressure (AVAPS)

Currently, the initiation of CPAP treatment for OHS usually consists of CPAP or NIV given at constant pressures set during a titration study in a sleep laboratory or hospital environment. Dynamic respiratory support with different levels of PAP in different stages of sleep or body positions suggests that it leads to better control of sleep disturbance in OHS. As home-type ventilator technology improved, the devices are able to estimate the pre-set volume, which led to the development of algorithms for adjusting the inspiratory pressure support provided to reach a predetermined target tidal volume. Although studies have demonstrated the feasibility of volume-targeted pressure support methods to effectively control irregular breathing during sleep in patients with OHS, it is important to carefully consider the setup settings used at the start of therapy when evaluating the advantages compared to fixed two-level PAP therapy. For example, if very high target volumes are deter-

mined in the treatment, the pressure support given will result in better control of night hypoventilation. However, then it may cause a detrimental effect on sleep quality. In a randomized controlled study evaluating the physiological and clinical benefits of AVAPS and BPAP-ST in patients with OHS, ten cases in which CPAP therapy was unsuccessful were randomized to one of two devices, and after 6 weeks of treatment, no difference was observed between the two devices in terms of sleep quality, health-related quality of life parameters, and daytime gas exchange [27]. In a randomized controlled trial of 50 cases with morbid obesity, after 3 months of AVAPS and BPAP treatment, it was found that the efficiency of the two devices was similar in terms of sleep architecture, sleep efficiency, daytime sleepiness level, health-related quality of life, gas exchange, lung volumes, night oxygenation, and transcutaneous PCO_2 [28]. As a result, AVAPS can exhibit better treatment compliance since it provides better patient-ventilator synchronization and lower median pressure support. However, in the measurements such as daytime hypercapnia, nocturnal gas exchange, sleep architecture, and quality of life, it is not superior to BPAP. Further research is needed to examine the long-term outcomes and cost-effectiveness of this strategy.

Recommended initial settings in the treatment of volume-targeted pressure-supported ventilation (AVAPS) with stable chronic OHS [29] are the following.

- EPAP = 4 cmH_2O
- $IPAP_{min}$ = EPAP = 4 cmH_2O
- $IPAP_{max}$ = 25–30 cmH_2O
- Initial tidal volume setting 8 mL/kg (according to ideal body weight)

The standard PAP titration strategy proposed in the light of all this information is shown in Fig. 21.2 [22].

NPPV in acute decompensated OHS: OHS patients admitted with acute decompensation should be hospitalized or taken into intensive care, NPPV treatment should be initiated immediately, and the patient should be followed up

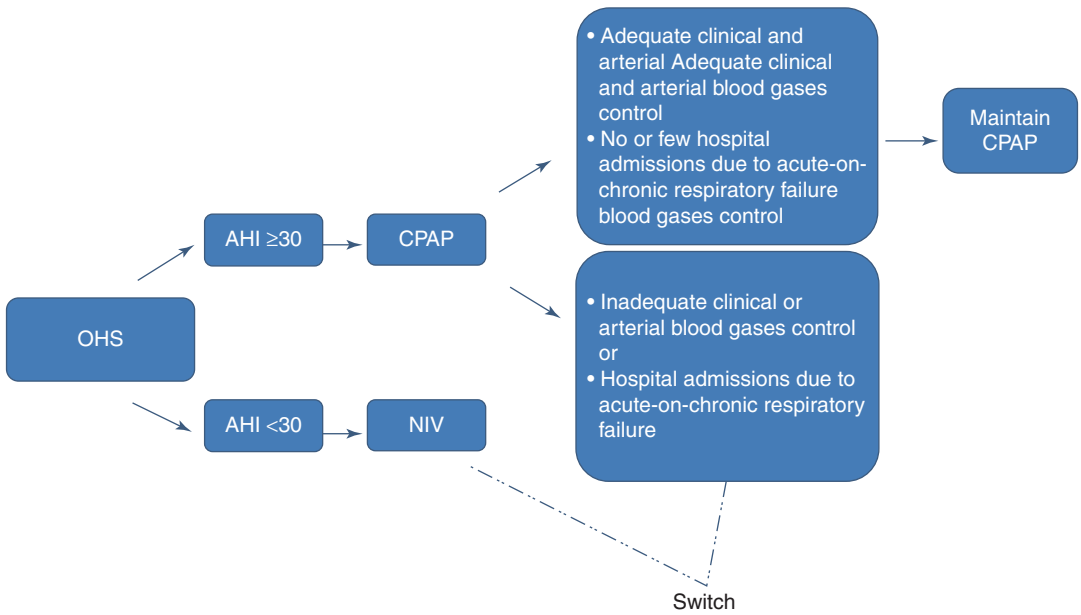

Fig. 21.2 OHS management strategy: continuous positive airway pressure (CPAP) may be the first-line treatment for OHS patients with obstructive sleep apnea (OSA). NIPV should be considered as the first-line treatment for OHS patients without OSA or with mild OSA. If patients treated initially with CPAP did not positively respond to treatment, NIPV therapy should be initiated. *AHI* apnea-hypopnea index

closely. NPPV is suitable for patients who can be cooperative and can maintain the airway and with pH >7.20. If patients are not under these conditions or NPPV fails, invasive mechanical ventilation should be administered by performing endotracheal intubation. First of all, BIPAP mode should be initiated, and if enough alveolar ventilation could not be provided with BIPAP, then it should be switched to AVAPS mode. Solely CPAP should not be used in acute decompensated patients. There is no recommended international strategy for initial settings; however, an initial approach in this manner can be used for initial settings. For BIPAP, it should be started with 4 cmH_2O IPAP pressure and 4 cmH_2O EPAP pressure, and IPAP pressure should be increased by 2 cmH_2O with a few minutes interval until patient comfort, tachypnea, tachycardia, oxygen saturation, and pH (respiratory rate <30/min, oxygen saturation >90%, heart rate <100/min, pH >7.30) are corrected. If oxygenation is impaired, EPAP should be increased. It should be kept in mind that increasing IPAP simultaneously with EPAP is important for providing the pressure difference and reducing the respiratory workload. The patient should be monitored with frequent blood gas follow-up. For AVAPS, ventilator mode should be selected, and respiratory rate, tidal volume, FiO_2, and PEEP values should be set. The number of breaths should be adjusted to minute ventilation of 6–10 L/min. High interface pressure can cause sleep interruption, intolerance, and leakage. In this case, the tidal volume should be reduced and the respiratory rate should be increased.

Studies have shown that the second most common indication for the treatment of NPPV in patients hospitalized with acute decompensated OHS is OHS, after COPD (chronic obstructive pulmonary disease). In a prospective study on an acute decompensated OHS patient who was administered NPPV treatment, late NPPV failure, PCO_2 at discharge, taking back into intensive care, and intensive care hospital mortality were significantly lower in the OHS group than in the COPD group. Again, the 1-year survival rate was found to be higher in the OHS group [30]. It was reported that NIV failure was 0–40% in patients with acute decompensated OHS in different series in obese patients, higher PEEP values are required in obese patients compared to nonobese patients for NIV treatment in acute hypercapnic respiratory failure, and more time is needed to achieve PCO_2 <50 mmHg [31].

NPPV in chronic compensated OHS: Patients who have chronic compensated OHS or whose acute decompensation is stabilized should undergo night polysomnography (PSG). If the presence of the accompanying OSA is detected with the PSG, the NPPV devices to be used can also be adjusted simultaneously. The aim of treatment in patients with OSA is to treat OSA, to improve sleep structure and quality, to rest respiratory muscles and to reduce respiratory workload at night, and to correct arterial blood gas values.

- In patients with OSA and OHS, it should be started with CPAP at 4 cmH_2O pressure, and the pressure should be increased by 2 cmH_2O until the obstructive event is corrected. If persistent alveolar hypoventilation is present, it should be switched to BIPAP treatment. Initial IPAP and EPAP values should be similar to CPAP pressure. The IPAP pressure should be increased by 1–2 cmH_2O every 5 min until the alveolar hypoventilation is corrected, and an appropriate setting should be found [29].
- In patients with only OHS, the initial IPAP and EPAP values can be set to 8 and 4 cmH_2O, respectively. By increasing IPAP by 1–2 cmH_2O in every 5 min, the appropriate setting is determined. The maximum IPAP for adults is 30 cmH_2O. The aim of treatment is to correct alveolar hypoventilation.

After the initiation of NIV therapy at night, patients should be checked periodically to determine whether the alveolar hypoventilation and the arterial blood gas has corrected. Modification of the treatment modality may be appropriate if alveolar hypoventilation in patients is persistent (night dyspnea, morning headache, and lack of improvement in blood gas values). PSG should be repeated in these patients. If patients' blood gas values are corrected, PSG can be repeated in

order to readjust patient NIV pressures. In the study of Berger et al. [18] on the evaluation of NPPV activity in OHS, it was determined that 14 cmH_2O EPAP and 25 cmH_2O IPAP are required in patients, and IPAP and EPAP mean pressures were 18 and 8 cmH_2O (respectively). In some cases, NPPV treatment may be insufficient in 1–3 weeks of follow-up, and after 3 months of treatment, it is recommended to evaluate in terms of the transition to CPAP.

21.9 Results

21.9.1 Learning Points

NPPV treatment should be applied to all OHS patients, and weight loss, lifestyle modification, and rehabilitation should be considered as part of the treatment. OSA-associated patients should first be treated with CPAP, and if alveolar hypoventilation continues despite treatment, BPAP should be switched in the treatment. In patients who do not respond to BPAP therapy, AVAPS mode should be tried. If hypoxemia continues despite NPPV treatment, oxygen therapy should be added to the treatment.

21.9.2 Critical Points

If OHS is not treated, concomitant morbidity and mortality increase, and the quality of life of patients decreases. Selecting appropriate NIV therapy is important for patient compliance and treatment response. To ensure the use of PAP devices, usage should be monitored objectively, and the problems encountered during the treatment, the management of side effects, and the methods of increasing compliance should be part of the close follow-up.

21.9.3 Key Summary

OHS is a clinical entity that is often nondiagnostic and sometimes misdiagnosed. In general, the increase in the prevalence of OHS is normal, given the increased epidemic of obesity. These patients have a poor quality of life, often prolonged hospital stays, and worsening comorbidities and are at high risk of mortality. The high sensitivity of clinicians to this condition is important because early diagnosis of such patients and the application of adequate forms of management by referring them to sleep clinics can help to change the course of comorbidities.

References

1. American Medical Association. AMA adopts new policies on second day of voting at Annual Meeting; 2013.
2. Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. Obesity (Silver Spring). 2008;16(10):2323–30.
3. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien: American Academy of Sleep Medicine; 2014.
4. Verin E, Tardif C, Pasquis P. Prevalence of daytime hypercapnia or hypoxia in patients with OUAS and normal lung function. Respir Med. 2001;95:693–6.
5. Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans AT. Obesity hypoventilation syndrome: prevalence and predictors inpatients with obstructive sleep apnea. Sleep Breath. 2007;11(2):117–24.
6. Akashiba T, Akahoshi T, Kawahara S, Uematsu A, Katsura K, Sakurai S, et al. Clinical characteristics of obesity-hypoventilation syndrome in Japan: a multicenter study. Intern Med. 2006;45(20):1121–5.
7. Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, et al. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. Am J Med. 2004;116(1):1–7.
8. Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care. 2010;55(10):1347–65.
9. Hart N, Mandal S, Manuel A, et al. Rebuttal: 'Obesity hypoventilation syndrome (OHS):does the current definition need revisiting?'. Thorax. 2014;69(10):955.
10. Harada Y, Chihara Y, Azuma M, Murase K, Toyama Y, Yoshimura C, et al. Obesity hypoventilation syndrome in Japan and independent determinants of arterial carbon dioxide levels. Respirology. 2014;19(8):1233–40.
11. Castro-Añón O, Pérez de Llano LA, De la Fuente Sánchez S, Golpe R, Méndez Marote L, Castro-Castro J, et al. Obesity-hypoventilation: increased risk of death over sleep apnea syndrome. PLoS One. 2015;10(2):e0117808.
12. Koenig S. Pulmonary complications of obesity. Am J Med Sci. 2001;321(4):249–79.

13. Kaw R, Hernandez AV, Walker E, Aboussouan L. Determinants of hypercapnia in obese patients with obstructive sleep apnea. Chest. 2009;136:787–96.
14. Kress JP, Pohlman AS, Alverdy J, Hall JB. The impact of morbid obesity on oxygen cost of breathing at rest. Am J Respir Crit Care Med. 1999;160(3):883–6.
15. Emigril C, Sobol B. The effects of weight reduction on pulmonary function and the sensitivity. Am Rev Respir Dis. 1973;108(4):831–42.
16. Polotsky M, Elsayed-Ahmed AS, Pichard L, Harris CC, Smith PL, Schneider H, et al. Effects of leptin and obesity on the upper airway function. J Appl Physiol (1985). 2012;112(10):1637–43.
17. Zavorsky GS, Wilson B. Sex, girth, waists andhips (what matters for gas exchange in extreme obesity?). Respir Physiol Neurobiol. 2010;170(1):120–2.
18. Berger KI, Ayappa I, Sorkin IB, Norman RG, Rapoport DM, Goldring RM. Postevent ventilation as a function of CO(2) load during respiratory events in obstructive sleep apnea. J Appl Physiol (1985). 2002;93(3):917–24.
19. Özol D, Köktürk O. Obesity hypoventilation syndrome. Eurasian J Pulmonol. 2013;15(3):137–43.
20. Shetty S, Parthasarathy S. Obesity hypoventilation syndrome. Curr Pulmonol Rep. 2015;4(1):42–55.
21. Salord N, Mayos M, Miralda RM, et al. Continuous positive airway pressure in clinically stable patients with mild-to-moderate obesity hypoventilation syndrome and obstructive sleep apnoea. Respirology. 2013;18:1135–42.
22. Masa JF, Corral J, Alonso ML, et al. Efficacy of different treatment alternatives for obesity hypoventilation syndrome. Pickwick Study. Am J Respir Crit Care Med. 2015;192:86–95.
23. Berg G, Delaive K, Manfreda J, et al. The use of health-care resources in obesity-hypoventilation syndrome. Chest. 2001;120:377–83.
24. Borel JC, Tamisier R, Gonzalez-Bermejo J, et al. Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. Chest. 2012;141:692–702.
25. Howard M, Piper A, Stevens B, et al. A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax. 2017;72(5):437–44.
26. Castro-Añón O, Golpe R, Pérez-de-Llano LA, et al. Haemodynamic effects of non-invasive ventilation in patients with obesity-hypoventilations syndrome. Respirology. 2012;17:1269–74.
27. Storre JH, Seuthe B, Fiechter R, Milioglou S, Dreher M, Sorichter S, et al. Average volume-assured: a randomized crossover trial. Chest. 2006;130(3):815–21.
28. Murphy PB, Davidson C, Hind MD, Simonds A, Williams AJ, Hopkinson NS, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax. 2012;67(8):727–34.
29. Berry RB, Chediak A, Brown LK, et al. Best clinical practices for the sleep center adjustment of noninvasive positive pressure ventilation (NİV) in stable chronic alveolar hypoventilation syndromes. J Clin Sleep Med. 2010;6:491.
30. Carrello A, Ferrer M, Gonzalez-Deaz G, Lopez-Martinez A. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186(12):1279–85.
31. Gursel G, Aydogdu M, Gulbas G, Ozkaya S. The influence of severe obesity on non-invasive ventilation (NIV) strategies and responses in patients with acute hypercapnic respiratory failure attacks in the ICU. Minerva Anestesiol. 2011;77(1):17–25.

Congenital Diseases Predisposing to Sleep Apnea

22

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Abbreviations

AAP	American Academy of Pediatrics
AT	Adenotonsillectomy
CF	Cystic fibrosis
CM	Chiari malformation
CPAP	Continuous positive airway pressure
CSA	Central sleep apnea
DMD	Duchenne muscular dystrophy
DS	Down syndrome
EDS	Ehlers-Danlos syndrome
GAG	Glycosaminoglycan
GH	Growth hormone
MPS	Mucopolysaccharidoses
NIV	Noninvasive ventilation
OSA	Obstructive sleep apnea
PRS	Pierre-Robin syndrome
PSG	Polysomnography
PWS	Prader-Willi syndrome
SCD	Sickle cell disease
SDB	Sleep disordered breathing
SNC	Central nervous system

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22.1 Introduction

Congenital diseases are a large and heterogeneous group of developmental alterations that occur during pregnancy. Congenital diseases have very different causes that can be classified as follows: genetic defects; exposure to infectious

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agents, chemicals, and drugs with teratogenic action; and a combination of genetic and environmental factors [1]. Congenital disease causes structural, functional, or metabolic abnormalities [2]. Congenital disorders are associated with a higher risk of sleep-related respiratory disorders (SDB) that occur from the first months of life [1]. The various pathophysiological factors involve a variable presence of breathing disturbed in sleep with obstructive and central manifestations. The upper airway (UA) is a collapsible tube and their collapsibility increases during sleep. Intrinsic factors and extrinsic factors influence this risk of collapsibility.

Three external factors have been firmly established, craniofacial features, UA fat deposits, and hypertrophy of UA tissues in which chronic inflammation is a contributor [3], all elements that, in different proportions, are found in most congenital disorders. Primary care providers should have an increased index of suspicion for SDB when there is a history of snoring, gasping, and pauses in breathing that may result in sudden arousals during sleep. However, the children with congenital disease, at high risk for SDB, may not present with these symptoms and deserve special attention as well as a low threshold for a sleep study referral [1]. Untreated SDB can lead to a worsening of neurocognitive or behavioral manifestations, as well as metabolic, cardiovascular manifestations, which make the treatment of patients with congenital disorders very demanding. Identifying, diagnosing, and treating SDB can significantly improve the patient's quality of life, prevent the development of sequelae or comorbidities, and prolong survival [2].

22.2 Search Methodology

A PubMed search from 2017 to March 2019 was performed on the publications on sleep apnea in congenital disorders. The combination of keywords "congenital disease" and "sleep apnea" was used to improve the sensitivity of the search. Abstracts and full-text publications were screened to fit the search criteria. We have manually analyzed all the publications and described, for each congenital disorder, its relationships with SDB. This review critically evaluates the current literature on SDB in congenital diseases and also explores the impact of these on their evolution and treatment. Articles were summarized to answer clinically relevant questions on the conditions that predispose to the SDB (Table 22.1). It is estimated that at least one-third of genetic disorders are mainly neurological or that it has an extensive neurological involvement [2].

Table 22.1 Congenital disorders included in this chapter

Congenital malformations and deformations of the musculoskeletal system	• Craniosynostosis • Achondroplasia • Pycnodysostosis • Treacher Collins syndrome • Ehlers-Danlos syndrome • Pierre Robin syndrome
Chromosomal abnormalities	• Down syndrome • Prader-Willi syndrome
Congenital malformations of the nervous system	• Chiari malformation
Inborn errors of metabolism	• Mucopolysaccharidoses • Cystic fibrosis • Congenital hypothyroidism
Neuromuscular disease	• Duchenne muscular dystrophy • Charcot-Marie-Tooth disease • Becker • Myotonic dystrophy • Limb dystrophy • Amyotrophic lateral sclerosis • Myasthenia gravis • Poliomyelitis • Muscle-spinal atrophy
Other	• Sickle cell disease

22.3 Findings

22.3.1 Congenital Malformations and Deformations of the Musculoskeletal System

22.3.1.1 Craniosynostosis

Craniosynostosis is the premature fusion of cranial sutures with secondary anomalies of the

shape of the head and is observed in 1 of 2000 births. This condition can be classified as non-syndromic or syndromic craniosynostosis, mainly caused by mutations in genes for fibroblast growth factor receptors. The most common syndromic craniosynostosis includes Apert, Crouzon, Pfeiffer (characterized by mandibular hypoplasia), Muenke, and Saethre-Chotzen, without mandibular hypoplasia. Studies show that 40–70% of these children have SDB, particularly obstructive sleep apnea (OSA), caused by a combination of anatomical abnormalities of the upper airway, as well as a decrease in pharyngeal muscle tone during sleep. Airway anomalies include choanal stenosis, macroglossia, adenotonsillar hypertrophy, laryngomalacia, tracheomalacia, subglottic stenosis, bronchomalacia, and laryngeal cleft [4]. Central sleep apnea is uncommon, secondary to limited brain growth, increased intracranial pressure, and Chiari malformation, reported in more than 70% of patients with syndromic craniosynostosis. Sleep apnea can lead to neurocognitive impairment, behavioral difficulties, growth failure, pulmonary hypertension, congestive heart failure, and sudden death. The different treatment options concern adeno-tonsillectomy (AT), support of positive nasal pressure, palatal devices, maxillofacial surgery such as the advancement of the median face, and tracheostomy [5].

22.3.1.2 Achondroplasia

Achondroplasia is the most common inherited skeletal dysplasia with a birth incidence of 1/10,000–30,000 [2]. SDB is a common feature in children with achondroplasia. The factors that predispose predominantly obstructive respiratory disorders are hypoplasia of the median face, micrognathia and choanal stenosis, adenotonsillar hypertrophy, macroglossia, ogival palate, decreased mobility of the temporomandibular joint, and hypotonia of the airway muscles. The observation of reduced prevalence of OSA after AT is in favor of this type of surgery when possible. However, OSA correction should be controlled by a PSG after each therapeutic intervention [6]; the residual OSA is, in fact, common after the surgery [2], also due to obesity, challenging to manage because of the low stature of the patients [7]. Cervical cord compression at the cervical medullary junction may cause central sleep apneas (CSA) and may require surgical decompression in infancy or early childhood. CSA may increase the risk of sudden unexpected death in infants, and as children with achondroplasia are still at a much higher risk of death compared with the general population, CSA detection should be one of the criteria to be taken into account in favor of the neurosurgical intervention [6]. The American Academy of Pediatrics (AAP) recommends performing polysomnographic investigations at the time of diagnosis and as a systematic evaluation at least until the age of 8 years.

22.3.1.3 Pycnodysostosis

Pycnodysostosis is a rare autosomal, recessive, skeletal dysplasia caused by a mutation in the cathepsin k gene. Pycnodysostosis is characterized by short stature, characteristic facial appearance (delayed closure of fontanelles and cranial sutures, mandibular hypoplasia and angle disorder, blue sclera), and acro-osteolysis of the distal phalanges. Follow-up of these patients and appropriate treatment of upper airway problems are essential to achieve an acceptable quality of life. AT and positive pressure ventilation, used as conservative approaches in treating upper airway collapsibility, are effective and could be used instead of an aggressive surgery such as tracheostomy or maxillomandibular advancement [8].

22.3.1.4 Treacher Collins Syndrome

Treacher Collins xyndrome is a rare disorder (1/50,000 live births) with features that include hypoplastic orbitozygomatic complex with downward slanting eyes and maxillary/mandibular retrusion. Obstructive sleep apnea and tracheostomy dependence are common [9, 10].

22.3.1.5 Ehlers-Danlos Syndrome

Patients with connective tissue disorder Ehlers-Danlos syndrome (EDS) often suffer from fatigue, excessive daytime sleepiness, and

impaired quality of life. Obstructive sleep apnea may be an underlying cause for these symptoms, but its prevalence in this population is unclear. The prevalence of OSA is higher in patients with EDS than in a matched control group. This is of clinical relevance as it is associated with fatigue, excessive daytime sleepiness, and impaired quality of life. Further studies are needed to assess the clinical benefit of OSA treatment in patients with EDS [11].

22.3.1.6 Pierre Robin Syndrome

Pierre Robin sequence (or syndrome) (PRS) is characterized by the triad of micrognathia, glossoptosis, and upper airway obstruction. It is commonly associated with the secondary cleft palate, but other phenotypes have also been described that are usually secondary to failure of fusion of palate due to mandibular hypoplasia and glossoptosis during embryogenesis. It is estimated that the PRS affects 1/8500 births. The sequence can be isolated or associated with other syndromes [12]. High rates of obstructive sleep apnea are described (47–80%), compared to the general pediatric population, due to the craniofacial anomalies of these patients (choanal atresia, a small epiglottis that allows the tongue to obstruct the laryngeal opening, laryngomalacia, tracheal stenosis) [13]. CSA and nocturnal hypoventilation are less common than OSA. Clinical symptoms do not correlate clinically with the severity of OSA [12]. The severity of the obstruction varies from mild to life-threatening requiring immediate intubation or tracheostomy (up to 13.4% of cases). Airway obstructions can improve with growth in the first year of life [14]. There are many treatment options for these patients including surgical and nonsurgical therapies, but to date, there is no consensus in the literature to the best therapeutic approach. However, many institutions have adopted personalized algorithms to manage their patients with PRS. Treatment options include prone positioning [nasopharyngeal tube insertion, palatal reconstruction, tongue-lip adhesion, and mandibular distraction osteogenesis, which were used to avoid tracheostomy [12].

22.3.2 Chromosomal Abnormalities

22.3.2.1 Down Syndrome

Down syndrome (DS) is due to the presence of an additional full or partial copy of chromosome 21 and affects 1/1000 live births [2]. There is a high prevalence of SDB in DS children, of which OSA is the most frequent (50–75%) [15]. These patients appear to have more central apneas when they are infants and young children while the obstructive features appear more frequently as the children age and with the body mass index. Patients with comorbidities such as hypothyroidism or cardiac anomalies may be more likely to have severe OSA [2]. The AAP guidelines recommend that symptoms of OSA such as heavy breathing, snoring, restless sleep, uncommon sleep positions, night awakenings, and daytime sleepiness should be sought at each DS clinic evaluation, and obesity should be discussed as a risk factor. Because there is a weak correlation between parental report and polysomnography (PSG) results, referral for a sleep study for all children with DS by 4 years of age is recommended, regardless of the presence of symptom [15, 16] surveillance for SDB throughout the life span of subjects with DS [17]. Upper airway obstruction in children with DS is multifactorial. The high prevalence of anatomical abnormalities of the upper airways, including midfacial and mandibular hypoplasia, narrow nasopharynx, macroglossia, ogival palate, lingual hypertrophy, adenotonsillar hypertrophy (in 42% of cases), laryngomalacia, subglottic stenosis, and tracheal stenosis, aggravated by generalized hypotonia and an immature immune system, with the risk of frequent respiratory tract infections, predispose these children to upper airway obstruction during sleep. The causes of upper airway obstruction in DS are age-related. Laryngomalacia is the most common cause of upper airway obstruction in children with DS under the age of 2 years and is eclipsed by other causes such as adenotonsillar hypertrophy as the children grow older [18]. Since upper airway obstruction (UAO) in children with DS is often multifactorial, residual upper airway obstruction is common after AT. When present, positive airway pressure ther-

apy is generally the next line of treatment for OSA in children with DS [19]. A postoperative sleep study should be obtained to assess improvement in severity and assessment of any residual disease despite intervention [2]. In such children, continuous positive airway pressure (CPAP) or noninvasive two-level ventilation (NIV) is often the next step [15], although poor compliance is described; consequently, additional surgical treatment options were used including tonsillectomy, supraglottoplasty, and maxillomandibular advancement [19].

22.3.2.2 Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a genetic disease that involves chromosome 15, characterized by hypothalamic-pituitary abnormalities associated with severe hypotonia in the neonatal period and in the first 2 years of life and the onset of hyperphagia which results in the risk of pathological obesity in childhood and adulthood, as well as severe behavioral/psychiatric disorders. The disease affects 1/25,000 births. Other related endocrine abnormalities contribute to a clinical picture characterized by short stature and growth hormone deficiency. Early diagnosis and growth hormone (GH) therapy significantly improved the quality of life of these patients. High prevalence of SDB is reported among children with PWS, including OSA, CSA, and hypoventilation syndromes [20]. Factors impacting SDB in infants and young children with PWS include facial dysmorphism, small nasopharynx, small oropharynx, and adenotonsillar hypertrophy; furthermore, due to hypotonia, children with PWS have a lower residual functional capacity at rest than healthy children, putting them at risk of sleep-related hypoventilation, particularly during REM sleep. Hypothalamic dysfunction and blunted chemoreceptor sensitivity likely contribute to altered central respiratory control in response to hypoxemia and hypercapnia with an increase in CSA, particularly in very young children PWS [2, 20]. These patients require continuous surveillance with sleep monitoring at different ages because [21] central apnea, more typical in the newborn, tends to improve with age, while obstructive sleep apnea and hypoventilation related to sleep can develop with growth [2]. The benefits of GH therapy on improving lean muscle mass and its likely positive impact on hypotonia have led to the increased therapeutic use of GH in children with PWS [20]. There has been some evidence suggesting a worsening of upper airway obstruction due to the increase in adenotonsillar hypertrophy in patients receiving growth hormone therapy. This therapy is however recommended, with an indication for close monitoring of SDB. AT may be helpful in the reduction of upper airway obstruction and obstructive apnea-hypopnea index in patients with PWS, but, in many patients, particularly those with a severe OSA, it may not be sufficient, because of tonsillar hypertrophy, tongue base obstruction, airway hypotonia, laryngomalacia, pharyngomalacia, and obesity. Approximately 17–40% of PWS patients require positive airway pressure (PAP) initiation or other surgical procedures to treat residual OSA, and this rate appears to increase with age [2, 22].

22.3.3 Congenital Malformations of the Nervous System

22.3.3.1 Chiari Malformation

The Chiari malformation (CM) is a structural anomaly of the posterior cranial fossa that is characterized by the herniation of the cerebellar tonsils through the foramen magnum. This malformation condition can produce symptoms of dysfunction affecting some parts of the central nervous system, in particular, the cerebellum, brainstem, cranial nerves, and spinal cord. There may also be an alteration in the circulation of the cerebral spinal fluid until the appearance of hydrocephalus. Three variants are recognized (CM type I, II, III). CM type I (CM-I) has been associated with sleep SDB, with a variable prevalence in the pediatric population (24–70%) [23]. An increased frequency of moderate to severe SDB was found to be associated with male sex, older age, excess weight, and the presence of hydrocephalus [24]. Screening for SDB is suggested in this population as SDB can be an etiological factor for potentially fatal complications

and sudden death [23]. SDB in patients with CM may be caused by several mechanisms that involve direct compression of the central respiratory centers and compression of the lower cranial nerves (VII, VIII, IX, X, XI, and XII), producing central and obstructive respiratory events, respectively. Obstructive respiratory events could be related to lesions in the efferent cranial nerves (IX, X, XI, and XII), possibly leading to pharyngeal collapse due to muscular hypotonia or atrophy. Retrognathia, increased neck circumference, and macroglossia have been associated with small oral cavity and may be involved in the pathophysiology of SDB in patients with CM. Central respiratory events could be related to dysfunction of the central respiratory centers due to compression of the brainstem, which compromises the ascending reticular activating system. Another explanation for the central respiratory events in these patients could be the potential dysfunction of the afferent inputs from the carotid bodies to the brainstem. Hydrocephalus was associated with the presence and severity of SDB. Several mechanisms may explain the relationship between hydrocephalus and SDB in patients with CM. It has been postulated that increased intracranial pressure, secondary to nocturnal hypercapnia and vasodilatation during apnea-hypopnea episodes, could be one such mechanism. At the same time, hydrocephalus may impair certain brain hemisphere functions essential to the maintenance of upper airway patency during sleep. Nocturnal PSG should be regularly conducted on all patients diagnosed with CM-1, especially if they present hydrocephalus [24]. In symptomatic patients the therapy is neurosurgical.

22.3.4 Inborn Errors of Metabolism

22.3.4.1 Mucopolysaccharidoses

The mucopolysaccharidoses (MPS) represent a heterogeneous group of lysosomal storage disorders, each one associated with a deficiency in one of the enzymes involved in glycosaminoglycan (GAG) degradation. There are 1/20,000 live births. Sleep disorders are a common manifestation of all types of MPS [25]. It has been suggested that there is little correlation between the symptoms of sleep apnea and the presence of OSA on PSG. Therefore, patients with MPS should undergo PSG in the early stages of life [14]. The underlying causes are different: they include abnormalities of the central nervous system (CNS) (hydrocephalus, spinal cord compression) and, more frequently, obstruction of the upper airway and alterations in the respiratory mechanics that cause a restrictive pulmonary disease [25]. The obstruction is often multifactorial as the GAG accumulation may affect each level of the respiratory tract. Abnormalities frequently seen include enlargement of the tongue, adenoids, and tonsils and infiltration of the pharyngolaryngeal walls secondary to GAG deposition. Bony manifestations such as depressed nasal bridge, high epiglottis, and mandibular abnormalities limiting jaw opening can increase upper airway resistance and contribute to SDB. Other skeletal manifestations common in MPS disorders, including kyphosis, kyphoscoliosis, pectus carinatum, short stature, or short trunk, cause a restrictive pattern to pulmonary function [25]. Furthermore, a diaphragmatic weakness secondary to spinal cord compression may be present. Restrictive abnormalities and diaphragmatic weakness can lead to hypoventilation even in the absence of obstructive events of the upper respiratory tract, which appears for the first time during REM sleep, later during sleep, and eventually in wakefulness. When evaluating SDB, it is essential to distinguish between OSA and sustained hypoventilation, as these require different treatment approaches. OSA can be managed by alleviating upper airway obstruction by surgical removal of tonsils and/or adenoids if these are enlarged, although the recurrence rate in MPS patients is high [25]. In patients undergoing AT, an increased risk of postoperative bleeding was reported. A postoperative sleep study should be obtained to assess the need to continue treatment of OSA with the application of CPAP or ventilatory support systems, up to the tracheostomy. New treatment options have been used that include enzyme replacement therapy or hematopoietic stem cell transplantation; however, the effects of these treatments on sleep-related problems are not known [14, 25].

22.3.4.2 Cystic Fibrosis

Cystic fibrosis (CF) is a chronic, inherited, and systemic disorder affecting the function of chloride channels. In the respiratory system, CF is characterized by inefficient airway mucous clearance leading to recurrent pulmonary infections and chronic inflammation. The natural history of CF is progressive bronchiectasis and deterioration in lung function. Children with CF present with a spectrum of pulmonary manifestations. The prevalence of OSA is higher in children with CF, as upper airway obstruction is complicated by chronic infections and sino-nasal polyposis. Furthermore, children with moderate or severe lung disease may present with sleep hypoxemia. The main proposed mechanism for this finding is atelectasis of the distal airways leading to a ventilation-perfusion mismatch. Sleep hypoxemia in CF may also coexist with OSA; the etiology of hypoxemia may represent a combination of lung disease and upper airway obstruction [26]. PSG in children with CF between 6 months and 11 years of age reveals moderate OSA (apnea-hypopnea index (AHI) ≥5) in approximately 46%. Patients with CF who have SDB, as compared to those who do not, have more infective pulmonary exacerbations [27].

22.3.4.3 Congenital Hypothyroidism

The thyroid hormone (TH) plays a prominent role in brain development. Congenital hypothyroidism facilitates the presence of central sleep apnea, predominantly in the neonatal era, with decreasing age. It seems that the respiratory alterations of sleep in congenital hypothyroidism are linked to the processes of brain maturation in which the thyroid hormones play an essential role [28].

22.3.5 Neuromuscular Disease

SDB in neuromuscular disorders is a widely developed topic that led to several reviews. SDB is a frequent event in neuromuscular pathologies with a prevalence exceeding 40%. Noninvasive ventilation (NIV) may be the winning weapon for resolving SDB, but can, in turn, be a trigger event to trigger ventilation-related events (device-related sleep disordered breathing events) and in some cases may be related to an unfavorable outcome. There are several pathophysiological conditions during sleep that favor peculiar respiratory events of neuromuscular pathologies [29, 30]. **Duchenne muscular dystrophy** (DMD) is the most common and severe form of myopathy in children affecting 1/3600–6000 male births. Respiratory failure is the leading cause of death in DMD. Its evolution typically evolves into four phases: (1) SDB without hypercapnia, (2) hypercapnia and hypoxemia only during the REM phase, (3) hypercapnia and hypoxemia also during NREM, and finally (4) daytime chronic respiratory failure [31]. SDB in neuromuscular disorders is a widely developed topic that led to several reviews. Mechanisms of respiratory events are as follows:

- *Diaphragmatic weakness*: episodes of diaphragmatic weakness occur during REM sleep with consequent partial falls of the flow or hypopneas and sawtooth desaturation; the complete fall of the flow resulting from a significant diaphragm dysfunction with the loss of abdominal and thoracic movements leads to pseudo-central events. Diaphragmatic events may represent the most common SDB in neuromuscular patients and are often misunderstood.
- *Nocturnal hypoventilation*: this condition may initially occur with greater ease in the REM phases of sleep, and following a further progression of the disease when the vital capacity will be <40%, there will be persistent hypoventilation during REM and NREM sleep.
- *OSA*: the combination of OSA with the other events mentioned above occurs in neuromuscular patients due to hypotonia of the upper airway muscles that may predispose to develop obstructive events during sleep with a "bimodal" time pattern: a higher susceptibility to present obstructive events in the initial phase of the disease combined or replaced by hypoventilation in the late phase of the disease.
- *Pharyngeal neuropathy*: typical of patients with hereditary sensorimotor neuropathy (**Charcot-Marie-Tooth disease**) resulting

from a significant reduction in the median nerve conduction velocity. Pharyngeal neuropathy can increase the risk of collapse of the upper airway.

– *Chemo-reflexed mediated events, central apnea, periodic breathing, and Cheyne-Stokes breathing*: dilated cardiomyopathy can be present in many muscular dystrophies (**Duchenne, Becker, myotonic dystrophy, limb dystrophy**). In this condition it is, therefore, possible to highlight central-type events associated with Cheyne-Stokes's periodic breathing following an instability of breath control with a high gain loop; the Cheyne-Stokes breathing in neuromuscular diseases with cardiomyopathies is related to an increase in mortality.
– *Bulbar dysfunction*: typical of **amyotrophic lateral sclerosis**, **myasthenia gravis, poliomyelitis, and muscle-spinal atrophy**; in such diseases, the obstructive events seem to be rare and very often mistaken for diaphragmatic or pseudo-central events due to the inability to generate sufficient negative pressure.
– *Respiratory events resulting from noninvasive ventilation*: it is interesting to note that while NIV has been shown to prolong survival in neuromuscular patients, it is the reason of the onset of events closely related to ventilation: asynchronisms, central events resulting in over-assistance, and central events with associated closure of the glottis.

22.3.5.1 Sickle Cell Disease

Sickle cell disease (SCD) is one of the most common hereditary hemoglobinopathies. A growing body of evidence has shown that sleep disordered breathing, and in particular, obstructive sleep apnea, occurs at high frequency in the sickle cell population and that there is significant overlap in the underlying pathophysiology of these two conditions. Through a variety of mechanisms including nocturnal hypoxemia and increased oxidative stress, production of proinflammatory cytokines and endothelial dysfunction, sickle cell anemia, and SDB potentiate each other's clinical effects and end-organ complications [32]. There is sound scientific rationale to assume that SCD with SDB will have more severe complications since SDB will contribute to the already compromised pathologic states induced by the hypoxia due to microvascular occlusion from vaso-occlusive disease [32]. Acute and chronic pulmonary complications are among the most common causes of morbidity and mortality [33]. SDB is more common in children with SCD compared to the general population. They have higher frequencies of both adenoidal and tonsillar hypertrophy compared to the general pediatric population. The pathophysiologic mechanisms underlying SCD include HbS polymerization in the presence of hypoxemia, red cell-endothelial cell interactions, hypercoagulability, neutrophil activation, and vasoactive factor release. These result in hemolysis and vaso-occlusive episodes leading to oxidative stress, ischemia, and inflammation. Accordingly, local inflammation secondary to oxidative stress and ischemia-reperfusion injury has been hypothesized as the primary mechanism leading to adenotonsillar hypertrophy in SCD patients. Of note, compensatory lymphoid tissue growth has also been suggested. Clinically, adenotonsillitis occurs more frequently in patients with SCD and has been associated with increased vaso-occlusive crises. The established treatment for OSA in these patients is AT; however, as with any surgical procedure in SCD, it is associated with significant morbidity [34].

22.4 Conclusions

Congenital diseases are commonly encountered in general pediatric practice and are associated with a higher risk of SDB that may occur from the first months of life. The different pathophysiological factors of congenital diseases involve a variable recurrence of SDB with obstructive and central respiratory events. The underlying causes include dysfunction of some portions of the central nervous system with a predisposition to central events, deficiency of respiratory mechanics, diaphragmatic weakness, hypoventilation, and craniofacial malformations with anatomical

abnormalities of the upper airway predisposing to obstructive events during sleep (Fig. 22.1). The upper airways are a collapsible tube and their collapse increases during sleep. Among the factors affecting the lumen, there are craniofacial features, fat deposits in the upper airways, and hypertrophy of the upper airway tissues in which chronic inflammation is a contributory factor [3], elements that, in different proportions, are found in most congenital disorders.

From the analysis of every congenital disorder with its own structural, pathophysiological, and clinical characteristics, common key conclusive points emerge (Table 22.2). In children with congenital disorders at high risk for SDB, clinical symptoms often do not correlate with the severity of the disease during sleep and therefore deserve special attention and a lower threshold than the general population for the sleep study. Screening for SDB is helpful in this population as SDB may be an etiological factor for potentially fatal complications and sudden death. A gradual approach to treatment is recommended in subjects with SDB. Given the multifactorial nature and complexity of SDB in children with congenital disease, monotherapy is often insufficient. After any treatment, a sleep study should be performed to assess the efficacy. Within the same congenital disorder, during development, different manifestations of SDB can be found, with central and obstructive components different in different periods of life. This chapter included the congenital diseases most frequently associated

Table 22.2 Key points common to congenital disorders

Children with a congenital disorder, at high risk for OSA even without symptoms, deserve special attention as well as a low threshold for a sleep study referral
Screening for SDB is cautious in this population as SDB may be an etiological factor for potentially fatal complications and sudden death
Identification and treatment of SDB can improve quality of life, avoid the development of symptoms and comorbidities, and improve survival
Within the same congenital disorder, during development, different manifestations of SDB with a central or obstructive component can be found in different periods of life
A postoperative sleep study should be obtained following any interventions to assess for improvement in severity or for residual disease

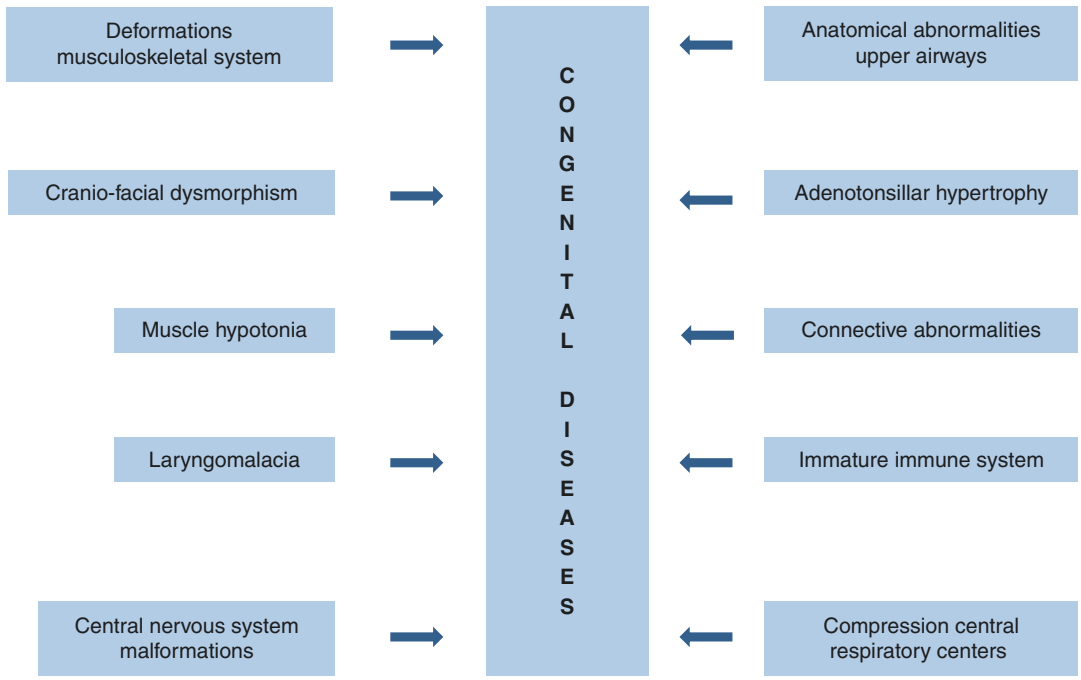

Fig. 22.1 Factors predisposing the SDB in congenital diseases

with the risk of SDB. Patients with a congenital disease are often at risk of other sleep disorders, such as altered intrinsic sleep structure, interrupted circadian rhythm, lack of melatonin, and other sleep disorders that were not included. Untreated sleep disruptions may lead to worsening of neurocognitive or behavioral manifestations that make the treatment of patients with neurogenetic disorders very challenging. It is important to screen congenital disease patients for SDB during routine health follow-up examinations. Identifying, diagnosing, and treating SDB can significantly improve the quality of life of these patients, prevent the development of symptoms and comorbidities, and extend survival. Treatment of SDB in patients with these complex and often multisystemic diseases is often best managed by a multidisciplinary setting.

References

1. ElMallah M, Bailey E, Trivedi M, et al. Pediatric obstructive sleep apnea in high-risk populations: clinical implications. Pediatr Ann. 2017;46(9):e336–9.
2. Dosier LBM, Vaughn BV, Fan Z. Sleep disorders in childhood neurogenetic disorders. Children. 2017;4(9):82.
3. Guilleminault C, Huang YS. From oral facial dysfunction to dysmorphism and the onset of pediatric OSA. Sleep Med Rev. 2018;40:203–14.
4. Mathews F, Shaffer AD, Georg MW, et al. Airway anomalies in patients with craniosynostosis. Laryngoscope. 2019;129(11):2594–602.
5. Müller-Hagedorn S, Wiechers C, Arand J, et al. Less invasive treatment of sleep-disordered breathing in children with syndromic craniosynostosis. Orphanet J Rare Dis. 2018;13(1):63.
6. Tenconi R, Khirani S, Amaddeo A, et al. Sleep-disordered breathing and its management in children with achondroplasia. Am J Med Genet A. 2017;173:868–78.
7. Ceroni JRM, Soares DCQ, Testai LC, et al. Natural history of 39 patients with Achondroplasia. Clinics (Sao Paulo). 2018;73:e324.
8. Baglam T, Binnetoglu A, Fatih Topuz M, et al. Pycnodysostosis at otorhinolaryngology. Int J Pediatr Otorhinolaryngol. 2017;95:91–6.
9. Biskup NI, Pan BS, Elhadi-Babiker H, et al. Decannulation and airway outcomes with maxillomandibular distraction in treacher collins and nager syndrome. J Craniofac Surg. 2018;29:692–7.
10. Esenlik E, Plana NM, Grayson BH, Flores RL. Cephalometric predictors of clinical severity in Treacher Collins syndrome. Plast Reconstr Surg. 2017;140:1240–9.
11. Gaisl T, Giunta C, Bratton DJ, et al. Obstructive sleep apnoea and quality of life in Ehlers-Danlos syndrome: a parallel cohort study. Thorax. 2017;72:729–35.
12. Khayat A, Bin-Hassan S, Al-Saleh S. Polysomnographic findings in infants with Pierre Robin sequence. Ann Thorac Med. 2017;12:25–9.
13. Aaronson NL, Jabbour N. Can telemetry data obviate the need for sleep studies in Pierre Robin Sequence? Int J Pediatr Otorhinolaryngol. 2017;100:238–41.
14. Kaditis AG, Alonso Alvarez ML, Boudewyns A, et al. ERS statement on obstructive sleep disordered breathing in 1- to 23-month-old children. Eur Respir J. 2017;50(6)
15. Trucco F, Chatwin M, Semple T, et al. Sleep disordered breathing and ventilatory support in children with Down syndrome. Pediatr Pulmonol. 2018;53:1414–21.
16. Friedman NR, Ruiz AG, Gao D, et al. Accuracy of parental perception of nighttime breathing in children with Down syndrome. Otolaryngol Head Neck Surg. 2018;158:364–7.
17. Nehme J, LaBerge R, Pothos M, et al. Predicting the presence of sleep-disordered breathing in children with Down syndrome. Sleep Med. 2017;36:104–8.
18. Alsubie HS, Rosen D. The evaluation and management of respiratory disease in children with Down syndrome (DS). Paediatr Respir Rev. 2018;26:49–54.
19. Ong AA, Atwood CM, Nguyen SA, et al. Down syndrome and pediatric obstructive sleep apnea surgery: a national cohort. Laryngoscope. 2018;128:1963–9.
20. Canora A, Franzese A, Mozzillo E, et al. Severe obstructive sleep disorders in Prader-Willi syndrome patients in southern Italy. Eur J Pediatr. 2018;177:1367–70.
21. Khayat A, Narang I, Bin-Hasan S, et al. Longitudinal evaluation of sleep disordered breathing in infants with Prader-Willi syndrome. Arch Dis Child. 2017;102:634–8.
22. Padia R, Muntz H, Pfeffer K, Meier J. Effectiveness of adenotonsillectomy and risk of velopharyngeal insufficiency in children with Prader-Willi syndrome. Ann Otol Rhinol Laryngol. 2017;126:733–8.
23. El-Kersh K, Cavallazzi R, Fernandez A, et al. sleep disordered breathing and magnetic resonance imaging findings in children with Chiari malformation type I. Pediatr Neurol. 2017;76:95–6.
24. Ferré Á, Poca MA, de la Calzada MD, et al. Sleep-related breathing disorders in Chiari malformation type 1: a prospective study of 90 patients. Sleep. 2017;40(6)
25. Rapoport DM, Mitchell JJ. Pathophysiology, evaluation, and management of sleep disorders in the mucopolysaccharidoses. Mol Genet Metab. 2017;122S:49–54.

26. Isaiah A, Daher A, Sharma PB, Naqvi K, Mitchell RB. Predictors of sleep hypoxemia in children with cystic fibrosis. Pediatr Pulmonol. 2019;54:273–9.
27. Shakkottai A, O'Brien LM, Nasr SZ, Chervin RD. Sleep disturbances and their impact in pediatric cystic fibrosis. Sleep Med Rev. 2018;42:100–10.
28. Santana-Miranda R, Murata C, Bruni O, et al. Cyclic alternating pattern in infants with congenital hypothyroidism. Brain Dev. 2019;41:66–71.
29. Aboussouan LS, Mireles-Cabodevila E. Sleep-disordered breathing in neuromuscular disease: diagnostic and therapeutic challenges. Chest. 2017;152:880–92.
30. Albdewi MA, Liistro G, El Tahry R. Sleep-disordered breathing in patients with neuromuscular disease. Sleep Breath. 2018;22:277–86.
31. Lo Mauro A, D'Angelo MG, Aliverti A. Sleep disordered breathing in duchenne muscular dystrophy. Curr Neurol Neurosci Rep. 2017;17(5):44.
32. Raghunathan VM, Whitesell PL, Lim SH. Sleep-disordered breathing in patients with sickle cell disease. Ann Hematol. 2018;97:755–62.
33. Worsham CM, Martin ST, Nouraie SM, et al. Clinical and laboratory findings associated with sleep disordered breathing in sickle cell disease. Am J Hematol. 2017;92(12):e649–51.
34. Grady AJ, Hankins JS, Haberman B, et al. Hydroxyurea treatment effect on children with sickle cell disease and obstructive sleep apnea. Sleep Breath. 2017;21:697–701.

23 Sleep Tracker and Smartphone: Strengths and Limits to Estimate Sleep and Sleep-Disordered Breathing

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Abbreviations

AHI	Apnea hypopnea index
ECG	Electrocardiogram
HR	Heart rate
HRV	Heart rate variability
OSA	Obstructive sleep apnea
PPG	Photoplethysmography
PSG	Polysomnography
SDB	Sleep-disordered breathing
SE	Sleep efficiency
TST	Total sleep time

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23.1 Search Methodology

A PubMed search was performed with the following keywords: "sleep trackers" OR "smartphone applications" AND "sleep" OR "sleep-disordered breathing" OR "snoring." Full-text publications were screened to fit the search criteria. For each selected research paper,

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the methods and the results obtained were reported. This critical review of literature explores the experimental validity of the accuracy of sleep trackers and smartphone applications to assess sleep quality, snoring, or SDR.

23.2 Introduction

The influence of sleep on general health is an essential aspect of well-being. Many hours of sleep are not necessarily associated with a good rest condition, when sleep is disturbed, making it not restorative. When night rest is not satisfactory, a wide range of disorders is a common experience, which influences our organism. The feeling of drowsiness during the day, fatigue, and nervousness resulting from an inadequate rest is frequently reported. While sleeping, a series of physical processes occur, slowing all body and brain activity and allowing the whole organism to rest. The chronic lack of rest, as well as interference with the growth and the immune system weakness, produces adverse effects on concentration, decision-making ability, and efficiency.

To sleep is essential for our body as eating or drinking, and its lack produces damage to our body at a physiological and psychological level. It is therefore essential to understand what is sleep, how it develops during the night, and what are the conditions that disturb it, such as problems that make rest unsatisfactory or even insufficient for the organism. The knowledge of sleep disorders, from snoring to insomnia, gives us the possibility of facing and solving them. A sleep diary, in which the subject reports what happened during the night, is a tool for the subjective evaluation of sleep. Interviews and questionnaires are other examples of subjective evaluation used to obtain information on sleep behaviors. The most commonly used method for the objective assessment of sleep is the nocturnal polysomnography (PSG). This method usually takes place in a sleep laboratory with EEGs recording. However, PSG is expensive and has a high resource consumption, so other measurement methods are desirable.

An increasing number of consumers are using wearable devices (trackers) or smartphones to monitor and measure a variety of body functions. The trackers usually are worn as a wrist strap. They were initially designed to measure movement and physical activity (activity trackers). Manufacturers now claim that trackers can also measure sleep (sleep trackers). Nearly 1 out of 10 of American adults over 18 years own an activity tracker, and in 2018 a 50-billion-dollar industry revenue was estimated [1]. Besides, almost 69% of Americans own a smartphone, and more than half of them use it as an alarm clock [2].

23.3 Findings

23.3.1 Sleep Trackers

Most trackers have exclusive apps that transmit and display data graphically on smartphones to provide information on sleep quality. In most cases, trackers provide sleeping and waking times; others also claim to detect light sleep, number and duration of awakenings, and even sleep stages.

Most seem to rely on three-axis accelerometers, i.e., electromechanical devices that measure the movements from front to back, side to side, and up and down motion and convert that data into an activity count. Activity counts are acquired in 30- or 60-s intervals and, as actigraphy, are used to identify whether the subject is awake or asleep. However, most of the actigraphy used in medicine are provided with validated algorithms and provide clinicians with the option to choose the optimal algorithm for classifying the type of activity in periods of sleep or wake. None of the sleep trackers currently available on the market provide the characteristics of the algorithm used to detect sleep and wakefulness.

23.3.2 Smartphone Apps

The smartphone alone is used to approach sleep monitoring. Smartphones have become part of today's society, including the field of medicine.

Beyond mobile communication, smartphones allow customers to download third-party applications. There has been a growing interest to use the apps for health and fitness improvements. As a result, the number of apps focused on these problems has grown exponentially. There are over 100,000 health apps combined in the Apple mobile App Store and Google Play [3].

A goal for health and fitness app developers is sleep hygiene. These apps provide a wealthy range of features, including smart alarm, sleep aids, sound recording during sleep, and sleep quality assessment. Others are developing smartphone programs to help healthcare professionals in selecting snoring patients or who may have obstructive sleep apnea (OSA) [4]. Despite the growing use of health apps by the population, the medical profession still has limited experience with these apps in clinical practice. More and more consumers are adopting apps to assess the quality of their sleep. Therefore, physicians should be aware of the available apps and be able to counsel patients appropriately on which app to use. The apps used by smartphones to assess sleep quality are based on movement detection, audio recordings, or questionnaires. Through the presence of integrated accelerometers, the smartphone can act as an actigraph to detect movements and assess the wake or sleep state. Other smartphone apps calculate their sleep ratings based on sound and noise analysis in the sleeping room. Furthermore, apps for sleep assessment can consist of a digital implementation of specific questionnaires such as Epworth sleepiness scale [5], the Berlin Questionnaire [6], the STOP-BANG Questionnaire [7], etc. Other apps are based on multiple modes (sensors plus questionnaires) and signal processing from a combination of external and internal smartphones sensors that provide a wider range of physiological signal recordings. Such applications can produce more complex sleep analysis, including sleep phases. The smartphone could represent a radically innovative product, widely accessible, and a low-cost sleep monitoring device with the possibility of long-term use and large-scale sleep assessment [8]. Since the collection of sleep data relies on a smartphone placed on the mattress (use of accelerometer and smartphone microphone) or the bedside table (use of smartphone microphone), the movements and the sounds generated by the bed partner may interfere with the results. In most cases, apps display results in a format similar to sleep trackers. Some apps are advertised as systems to identify the sleep phase and to identify the optimal time to awaken the user. However, the scientific validity of the sleep analysis produced by these apps remains an open question. The companies that provide these apps, to date, do not provide information on the specific algorithms they use to detect if the patient is awake or asleep or sleep stage.

Given the interest and potential clinical significance, smartphone apps proposed for OSA screening and diagnosis came into the market. Only recently have studies been performed to examine the clinical validity of these devices.

23.4 Studies on the Assessment of Sleep Trackers

Few studies have examined the validity and accuracy of sleep trackers to assess sleep quality. Available studies are difficult to compare; most include small samples and use actigraphy or PSG as a reference device. Some studies include healthy volunteers, while other subjects with diagnosed or suspected sleep disorders.

Two sleep tracker devices "Fitbit" (Fitbit Inc., San Francisco, CA, USA) [9], "Fitbit Ultra" (Fitbit Inc., San Francisco, CA, USA) [10], and "Jawbone UP" (Jawbone, San Francisco CA, USA) [11–13] were compared with PSG and actigraphy in several studies on children and adults (Table 1). These devices tended to overestimate sleep time, sleep efficiency (SE), and the latency to fall asleep. Some studies have noted that the differences were more pronounced in subjects with sleep disorders. In general, sleep trackers effectively detect sleep but are inaccurate in identifying wakefulness. It is recurrent to spend time in bed, firm but still awake: sleep trackers cannot distinguish such moments from when instead we are actually sleeping, ending up to indicate both as "sleep" and therefore overesti-

Table 1 Sleep trackers

Sleep tracker	Reference	Comparison methods	Population	Results
Fitbit	9	PSG and actigraphy	24 Healthy adult Mean age 26.1 years	Overestimate sleep time, sleep efficiency, and the latency to fall asleep
Fitbit Ultra	10	PSG and actigraphy	63 Children and adolescent Mean age 9.7 years	Overestimate sleep time, sleep efficiency, and the latency to fall asleep
Jawbone UP	11	PSG	65 Healthy adolescents Mean age 15.8 years	Overestimate sleep time, sleep efficiency, and the latency to fall asleep
Jawbone UP	12	PSG	28 Midlife women Mean age 50.1 years	Sensitivity in detecting sleep (0.97) and low specificity in detecting wake (0.37). Overestimate sleep time and sleep efficiency
Jawbone UP 3 Fitbit Charge	15	Sleep diary for three full nights	78 Adults Mean age 27.6 years	Equivalence with the sleep diary total sleep time for the two apps Effect size = 0.09 and 0.23, respectively
Fitbit Charge 2	16	Three-lead electrocardiography in determining HR during sleep	35 (17 female) Healthy adults Mean age 25.1 years	There was no significant difference in the mean HR (0.09 beats per minute, $P = 0.426$) between "Fitbit Charge 2" and ECG

mating the hours of bedtime effectively slept. They are inaccurate in determining sleep parameters (total sleep time (TST), SE, waking time after falling asleep, and sleep latency) and do not distinguish the different sleep stages compared to PSG (Table 2).

Almost no validations for these devices are available, and questions about their sleep architecture accuracy remain unanswered [14]. Despite the lack of evidence for the effectiveness of these devices that are also based on the reflection photoplethysmography in detecting sleep architecture, the physiological link between cardiac activity and sleep is known. These sensors have been shown to measure heart rate (HR) accurately. However, there is a second group of more advanced sleep trackers that include, in addition to accelerometers, heart rate monitors based on reflection photoplethysmography (PPG). Devices such as "Jawbone UP 3" (Jawbone, San Francisco CA, USA) and "Fitbit Charge HR" (Fitbit Inc., San Francisco, CA, USA) claim, in addition to detecting sleep and wakefulness, the ability to describe sleep architecture. These two trackers showed a good equivalence with the sleep diary TST (effect size = 0.09 and 0.23, respectively). [15]

The accuracy of "Fitbit Charge 2" was evaluated in 18 men and 17 healthy women aged 25.11 ± 10.6 years. PurePulse® photoplethysmography with reference to three-lead electrocardiography (ECG) was used to determine heart rate (HR) during sleep. The HRs obtained from the "Fitbit" and the electrocardiograph were recorded continuously during a single night of sleep. The results showed that during sleep, there was no significant difference in the mean HR (0.09 beats per minute, $P = 0.426$) between "Fitbit Charge 2" and ECG. The authors concluded that "Fitbit Charge" adequately evaluates HR during sleep in healthy young adults [16].

These sensors can also offer the possibility of measuring heart rate variability (HRV) throughout the night. The relationships between HRV, autonomic nervous system, and sleep stages have been widely described in the literature [17, 18]. Machine learning techniques have successfully exploited the relationships between HRV and

Table 2 Smartphone applications

App	Reference	Comparison methods	Population	Results
Sleep Time for iPhone	24	PSG	20 Volunteers with no previously diagnosed sleep disorders (40% women, ages ranging from age 22 to 57 yrs.)	No correlation between PSG and app • Sleep efficiency • Light sleep • Deep sleep • Sleep latency
Smartphone app + EarlySense contact-free sleep monitoring system	25	PSG	63 Subjects: 43 patients with indication for nocturnal PSG (mean age 45.9 years) 7 Healthy women subjects (mean age 31.2 years) 13 Healthy men (mean age 40.0 years) studied at home with a portable PSG system	Total sleep time estimates with the contact-free sleep-monitoring system were closely correlated with PSG
Sleep on Cue for iPhone	26	PSG	12 Young adult university students (10 females) Mean age 25.1 years.	High correspondence between the onset of sleep detected by the app and by the PSG
SnoreMonitorSleepLab Quit Snoring Snore Spectrum	27	ApneaLink Plus	1 Healthy subject	The tested apps are not accurate enough to replace the common diagnostic standard to detect snoring
MotionX 24/7	28	PSG and actigraphy	78 Children and adolescents with suspected OSA Mean age 28.4 years	Overestimate sleep time and sleep efficiency Underestimated sleep onset latency
Sleep Cycle	29	PSG	25 Children ages 2–14 years	There was no correlation between total sleep time and sleep latency between the app and PSG

sleep stages. Several algorithms have been shown to automatically identify sleep stages based on HRV, typically measured by ECG, often in combination with respiratory effort [19–22]. The ability to monitor the HR of these new devices, and HRV analysis in combination with body movements evaluated by the accelerometers, ordinarily available in these devices, may increase the ability to detect wakefulness and sleep and provide more detailed pieces of information on sleep architecture.

Recently, a new approach has been used as artificial intelligence to increase the diagnostic capabilities of wearable devices that use HR and body movements. When we talk in medicine about artificial intelligence, we want to realize systems that, using large data sets and modern computational tools such as deep learning, can recognize models like a human being. A new deep neural network was presented to predict cardiovascular risk factors, using wearable devices with an HR sensor, a PPG, and an accelerometer. The variability of longitudinal HR and patterns of activity have been previously associated with hypertension, diabetes, and the underdiagnosed conditions of OSA. For the construction of the neuronal network of the Cardiogram app for "Apple Watch," 6.115 active users were enrolled. HR and step counting were collected for a period from 1 to 53 weeks. Data from 70% of participants were used to train the neural network to predict hypertension, sleep apnea, or diabetes.

The performance characteristics of the test were estimated using the remaining 30% of the participants whose diagnosis was known. The neural network created by Cardiogram data, "DeepHeart," recognized hypertension and OSA from wearable HR sensors with an accuracy of 82% and 90%, respectively. This new approach has just begun, and further clinical research undergoing peer review is necessary to confirm that screening for the leading health conditions is possible with wearable devices [23].

23.5 Assessment of Smartphone Apps for the Evaluation of Sleep Quality and SDB

23.5.1 Reliability of Detection of the Sleep–Wake Cycle in Healthy Subjects

The app named "Sleep Time" (Azumio Inc., Palo Alto, CA, USA) for sleep–wake detection was evaluated in 20 healthy subjects, to evaluate its reliability. The volunteers without previously diagnosed sleep disorders underwent laboratory nocturnal PSG with simultaneous use of the app. The parameters reported were compared with those obtained from the PSG. The "Sleep Time" was designed to provide information on the sleep pattern, placing the smartphone in the bed and monitoring movements throughout the night. There was no correlation between the parameters of SE, the percentage of light sleep, the percentage of deep sleep, and sleep latency provided by the app and those obtained by PSG. The app had high sensitivity but little specificity in sleep detection (89.9% and 50%, respectively).

This study shows that the absolute parameters and the sleep structure reported by the "Sleep Time" app for iPhones are poorly correlated with those obtained by PSG [24].

Another study [25] evaluated a sleep-monitoring system (EarlySense, Ltd., Israel) including a piezoelectric sensor placed under the mattress and a smartphone application. HR, respiratory rate, body movement, and sleep-related parameters calculated by the sensor of "EarlySense" were compared to data recorded simultaneously by PSG. The study evaluated 20 healthy subjects studied at home with a portable PSG system (7 were recorded sleeping alone, while 13 were sleeping with the bed partner). Compared to PSG, this noncontact system showed similar values for average TST and the percentage of awakenings. A linear correlation of 0.98 ($R = 0.87$) between the TST measured by the sensor and the TST determined by the PSG was reported. This system showed good ability to detect sleep with improved performance compared to apps with smartphone accelerometer alone.

Scott et al. [26] studied the accuracy of the iPhone application "Sleep On Cue" (SOC, by MicroSleep, LLC), which uses behavioral responses to auditory stimuli to estimate sleep onset. The app generates a 1-s low-intensity sound stimulus (100 Hz) every 30 s, by earbud headphones connected to the iPhone, to which the user responds by gently moving the phone within 2 s after the beginning of the sound stimulus. When an individual does not respond for two consecutive tones, the app judges that the user has fallen asleep. Twelve subjects underwent PSG recording simultaneously with the use of the app. The results showed a high correspondence between the onset of sleep detected by the app and by the PSG ($r = 0.79$, $P < 0.001$).

Overall, the results of studies of healthy populations show that the sleep–wake discrimination of sleep apps is similar to that provided by PSG and better than those reported by the sleep wrist trackers.

23.5.2 Reliability of Snoring Detection

The capabilities of three apps (SnoreMonitorSleepLab, Quit Snoring, and Snore Spectrum) were assessed in distinguishing, by smartphone microphone, between snoring events and other environmental noises, such as road noise, chatter in the bedroom, or even just the rustle of sheets and blankets. The study compared the three apps with the ApneaLink Plus

(ResMed Germany Inc., Martinsried, Deutschland). The results showed a mismatch with the ApneaLink Plus screening device, leading the authors to conclude that their reliability and accuracy are insufficient to replace standard monitoring tools [27].

23.5.3 Reliability of Sleep–Wake Cycle Detection in Subjects with Sleep Disorders

In a sample of 78 children and adolescents, with suspected sleep disorders, 2 sleep-monitoring devices were tested, an accelerometer was worn as a bracelet (Jawbone's UP), and a smartphone sleep application "MotionX 24/7" was used. The children, during nocturnal PSG and actigraphy recording (Actiwatch2), wore the bracelet "Jawbone UP" simultaneously and a smartphone with the application "MotionX 24/7" activated near their right shoulder. Sleep latency time, TST, and SE, obtained by PSG and actigraphy, were compared with data obtained by the "Jawbone UP" bracelet and the application "MotionX 24/7." The authors concluded that "Jawbone UP" was comparable to "Actiwatch2" and may have some clinical utility in children with sleep disorders. Instead, "MotionX 24/7" does not accurately reflect sleep or wake and should be used with caution [28].

The "Sleep Cycle" smartphone app was evaluated in 25 subjects aged 2–14 years undergoing night PSG. The phone was placed on the mattress, next to the pillow, and data were recorded simultaneously to the PSG. TST, sleep latency, and sleep stages were compared between the app and the PSG, and no correlation was found. The authors conclude that the "Sleep Cycle" app can be valuable in increasing user awareness of sleep problems, but it is not accurate enough to be used as a clinical tool [29].

The monitoring system "EarlySense" was evaluated in 43 patients with PSG indication for nocturnal PSG in a sleep laboratory. Sleep stages obtained by both systems were compared showing an 83.4% sensitivity for wakefulness and an 89.7% sensitivity for sleep detection. The detailed sensitivities for each sleep state were 40.0% for REM sleep, 63.3% for light sleep, and 53.6% for slow-wave sleep [25].

From these papers, it can be seen that the "Sleep Cycle" and "MotionX 24/7" applications for sleep analysis do not significantly detect sleep stages with respect to PSG, which may be due to the movement algorithms that are not sensitive enough to identify sleep stages. On the other hand, "EarlySense" showed a good performance in discriminating sleep stages by the integration of data from multiple signals (HR, respiratory rate, and motion detection).

23.5.4 Reliability of the Evaluation of Snoring and SDB

A snoring monitoring system has been developed consisting of a smartphone to quantify snoring and the severity of the OSA. For the development of the analysis software, 50 patients underwent diagnostic PSG, 10 patients for the development of the software, and 40 patients for evaluation. A smartphone was attached to the anterior chest wall over the sternum. The smartphone acquired environmental sounds from the built-in microphone and processed it in real time in an audio signal. The results showed a high correlation of snoring time measured by the smartphone with the snoring time determined by the PSG ($r = 0.93$). The smartphone-estimated respiratory disorder index was highly correlated with the apnea–hypopnea index (AHI) obtained from PSG ($r = 0.94$). The diagnostic sensitivity and specificity of this system for the diagnosis of OSA (AHI $\geq$ 15) were 0.70 and 0.94, respectively. The authors conclude that it is possible to use a smartphone to detect snoring and OSA in a controlled laboratory environment effectively. The use of this technology in a noisy home environment has not been proven, and further investigation is needed [4].

For SDB screening and monitoring, the "SleepAp" app was developed. "SleepAp" uses internal phone sensors to record audio, movements, and body position, an external pulse oximeter for oxygen saturation recording, and

data from the clinically validated STOP-BANG questionnaire. The app classifies subjects as non-OSA (healthy or snorer) or OSA (mild, moderate, and severe). For the realization of the algorithm, used by this app, 856 patients underwent home polygraphy, and a database was obtained. The data obtained were used as input of a support vector machine (SVM) classifier. The SVM was trained on 735 patients and tested on 121 patients. The algorithm had an accuracy of 92.2% when classifying subjects for moderate or severe OSA compared to healthy or snoring subjects. The signal processing and machine learning algorithms have been integrated into the "SleepAp." The authors concluded that "SleepAp" is the first step toward a clinically validated automatic sleep screening system, which could provide a new, easy-to-use, low-cost, and widely available method for OSA screening. So far, no appraisal of this app has been reported [8].

23.6 Conclusions

Sleep trackers and smartphone apps based only on accelerometers overestimated TST and SE and underestimated wake time after sleep onset. However, they could be used to check a short sleep time, while sleep data from tracking devices in patients with sleep disorders are less reliable. About sleep staging, smartphone apps with external sensor devices showed a good performance by the integration of data from multiple signals. The technology applied to wearable systems is continuously evolving. It began with the use of accelerometers alone, for the detection of the movement. Later, these devices were integrated with photoplethysmography and sensors to measure HR. Finally, the research is being addressed to use these devices together with algorithms derived from techniques of artificial intelligence, improving the app's ability to provide accurate sleep–wake and SDB detection.

Few research papers have examined the validity and accuracy of current sleep trackers and smartphone apps for measuring sleep, snoring, or SDB. The available papers are difficult to compare; they applied different methods to validate (actigraphy, sleep diary, or PSG). Most studies have a small sample that included healthy volunteers, sleep-disordered subjects, and confirmed OSA.

An increasing number of consumers are using wearable devices (trackers) or smartphone apps to monitor and measure a variety of body functions. Many people now report sleep quality data from these devices to their doctor. The purpose of this review was to verify the evidence of reliability and validity of these devices. A PubMed review of the literature was performed to explore the experimental validity and accuracy of sleep trackers and smartphone applications to assess sleep quality, snoring, or SDB. The review has shown that these devices, when applied in non-healthy subjects, have serious shortcomings and limited usefulness. In healthy subjects, instead, they can be a useful tool to improve sleep. Multi-signal systems have shown better performance for detection of sleep–wake state or SDB.

The use of multi-signal systems together with algorithms derived from artificial intelligence techniques, based on large databases, can offer best performances. So far, no assessment of this approach has been reported.

References

1. Rock Health. The future of biosensing wearables. http://rockhealth.com/reports/the-future-of-biosensing-wearables/. Accessed 16 Mar 2019.
2. Time, Inc. Your wireless life: results of Time's mobility poll. http://content.time.com/time/interactive/0,31813,2122187,00.html. Accessed 16 Mar 2019.
3. Research 2 Guidance. mHealth App Developer Economics. 2014. https://research2guidance.com/product/mhealth-app-developer-economics-2014
4. Nakano H, Hirayama K, Sadamitsu Y, et al. Monitoring sound to quantify snoring and sleep apnea severity using a smartphone: proof of concept. J Clin Sleep Med. 2014;10:73–8.
5. Johns M. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540–5.
6. Netzer N, Stoohs R, Netzer C, et al. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome Ann. Intern Med. 1999;131:485–91.

7. Chung F, Yegneswaran B, Liao P, et al. Stop questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology. 2008;108:812–21.
8. Behar J, Roebuck A, Shahid M, et al. SleepAp: an automated obstructive sleep apnoea screening application for smartphones. IEEE J Biomed Health Inform. 2015;19:325–31.
9. Montgomery-Downs HE, Insana SP, et al. Movement toward a novel activity monitoring device. Sleep Breath. 2012;16:913–7.
10. Meltzer LJ, Hiruma LS, Avis K, et al. Comparison of a commercial accelerometer with polysomnography and actigraphy in children and adolescents. Sleep. 2015;38:1323–30.
11. de Zambotti M, Baker FC, Colrain IM. Validation of sleep-tracking technology compared with polysomnography in adolescents. Sleep. 2015;38:1461–8.
12. de Zambotti M, Claudatos S, Inkelis S, et al. Evaluation of a consumer fitness-tracking device to assess sleep in adults. Chronobiol Int. 2015;32:1024–8.
13. Lee J, Finkelstein J. Consumer sleep tracking devices: a critical review. Stud Health Technol Inform. 2015;210:458–60.
14. Ko PR, Kientz JA, Choe EK, et al. Consumer sleep technologies: a review of the landscape. J Clin Sleep Med. 2015;11:1455–61.
15. Lee JM, Keill A, Dinkel D, et al. Comparison of wearable trackers' ability to estimate sleep. Int J Environ Res Public Health. 2018;15(6)
16. Haghayegh S, Khoshnevis S, Smolensky MH, et al. Accuracy of pure pulse photoplethysmography technology of Fitbit Charge 2 for assessment of heart rate during sleep. Chronobiol Int. 2019;36(7):927–33.
17. Trinder J, Kleiman J, Carrington M, et al. Autonomic activity during human sleep as a function of time and sleep stage. J Sleep Res. 2001;10:253–64.
18. Lanfranchi PA, Pépin J-L, Somers VK. Cardiovascular physiology: autonomic control in health and in sleep disorders. In: Kryger M, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 6th ed. Philadelphia: Elsevier; 2016. p. 142–54.
19. Redmond SJ, de Chazal P, O'Brien C, et al. Sleep staging using cardiorespiratory signals. Somnologie-Schlafforschung und Schlafmedizin. 2007;11:245–56.
20. Domingues A, Paiva T, Sanches JM. Hypnogram and sleep parameter computation from activity and cardiovascular data. IEEE Trans Biomed Eng. 2014;61:1711–9.
21. Willemen T, Van Deun D, Verhaert V, et al. An evaluation of cardiorespiratory and movement features with respect to sleep-stage classification. IEEE J Biomed Health Inform. 2014;18:661–9.
22. Fonseca P, Long X, Radha M, et al. Sleep stage classification with ECG and respiratory effort. Physiol Meas. 2015;36:2027–40.
23. Tison G, Singh A, Ohashi D, et al. Cardiovascular risk stratification using off-the-shelf wearables and a multi-task deep learning algorithm. Circulation. 2018;136:A21042.
24. Bhat S, Ferraris A, Gupta D, et al. Is there a clinical role for smartphone sleep apps? Comparison of sleep cycle detection by a smartphone application to polysomnography. J Clin Sleep Med. 2015;11:709–15.
25. Tal A, Shinar Z, Shaki D, et al. Validation of contact-free sleep monitoring device with comparison to polysomnography. J Clin Sleep Med. 2017;13:517–22.
26. Scott H, Lack L, Lovato N. A pilot study of a novel smartphone application for the estimation of sleep onset. J Sleep Res. 2018;27:90–7.
27. Stippig A, Hübers U, Emerich M. Apps in sleep medicine. Sleep Breath. 2015;19:411–7.
28. Toon E, Davey MJ, Hollis SL, et al. Comparison of commercial wrist-based and smartphone accelerometers, actigraphy, and PSG in a clinical cohort of children and adolescents. J Clin Sleep Med. 2016;12:343–50.
29. Patel P, Kim JY, Brooks LJ. Accuracy of a smartphone application in estimating sleep in children. Sleep Breath. 2017;21:505–11.

Obstructive Sleep Apnea and Cardiovascular Disease

24

Jun Shitara and Takatoshi Kasai

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Abbreviations

ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHI	Apnea hypoxia index
BP	Blood pressure
CAD	Coronary artery disease
CI	Confidence interval
CPAP	Continuous positive airway pressure
CSA	Central sleep apnea
CVD	Cardiovascular disease
DRH	Drug-resistant hypertension
ESS	Epworth Sleepiness Scale
HF	Heart failure
HR	Heart rate

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IH	Intermittent hypoxia
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
OSA	Obstructive sleep apnea
PCI	Percutaneous coronary intervention
PVI	Pulmonary vein isolation
QOL	Quality of life
RCT	Randomized controlled trial
SDB	Sleep-disordered breathing
SNA	Sympathetic nerve activity
UA	Upper airway

24.1 Introduction

Sleep is regarded as a restorative period for the human body and an important resting phase, especially for the cardiovascular system that has to work persistently. Therefore, sleep plays an important role in the development and progression of cardiovascular disease (CVD). Furthermore, patients with CVD generally sleep less than the general population and frequently have sleep disorders, such as insomnia or sleep-disordered breathing (SDB), which have adverse prognostic effects. There are two types of SDB: one caused by obstructive sleep apnea (OSA) by sleep-related upper airway (UA) collapse or obstruction and the other one is due to central sleep apnea (CSA) by instability of the respiratory control system. OSA is characterized by repeated pharyngeal collapse during sleep leading to intermittent hypoxia (IH). OSA is a common chronic condition, which is observed in 5–10% of the general population, although it is more prevalent in patients with CVD (up to 50%) [1].

Relationships between OSA and CVD, such as hypertension, coronary artery disease (CAD), heart failure (HF), and cardiac arrythmias, have been reported. Epidemiological studies suggested that patients with OSA have high risks of CVD development and progression. Thus, OSA is a significant factor in cardiovascular morbidity and mortality. Moreover, in the relationship between OSA and CVD, obesity may act as a confounder. However, because OSA has been reported to have adverse effects on the cardiovascular system, such as enhanced intrathoracic negative pressure, sympathetic nerve overactivity, and increased oxidative stress and inflammatory response, direct relationships between OSA and CVD, independent of obesity, is possible. In this chapter, we describe the pathophysiological mechanisms linking OSA and CVD and the clinical importance of OSA in CVD.

24.2 Cardiovascular Effects of OSA (Fig. 24.1)

24.2.1 Negative Intrathoracic Pressure

Enhanced negative intrathoracic pressure during futile inspiratory efforts against the occluded pharynx that is associated with OSA has direct effects on hemodynamics. Enhanced negative intrathoracic pressure increases venous return, thereby augmenting right ventricular preload, and OSA-induced hypoxic pulmonary vasoconstriction increases right ventricular afterload, consequent right ventricular distension, and leftward septal displacement during diastole impair left ventricular (LV) filling. In addition, enhanced negative intrathoracic pressure increases LV transmural pressure, which is a key element of LV afterload. The combination of increased LV afterload and diminished LV preload during obstructive apneas causes a progressive reduction in stroke volume. Stroke volume reduction is more pronounced in patients with LV systolic dysfunction than in those with normal LV function [2].

24.2.2 Sympathetic Nerve Activity

The sympathetic nervous system is activated simultaneously by cycles of apnea-induced hypoxia and CO_2 retention, which stimulate both central and peripheral chemoreceptors and result in apnea-induced cessation of pulmonary stretch receptor-mediated inhibition of central sympa-

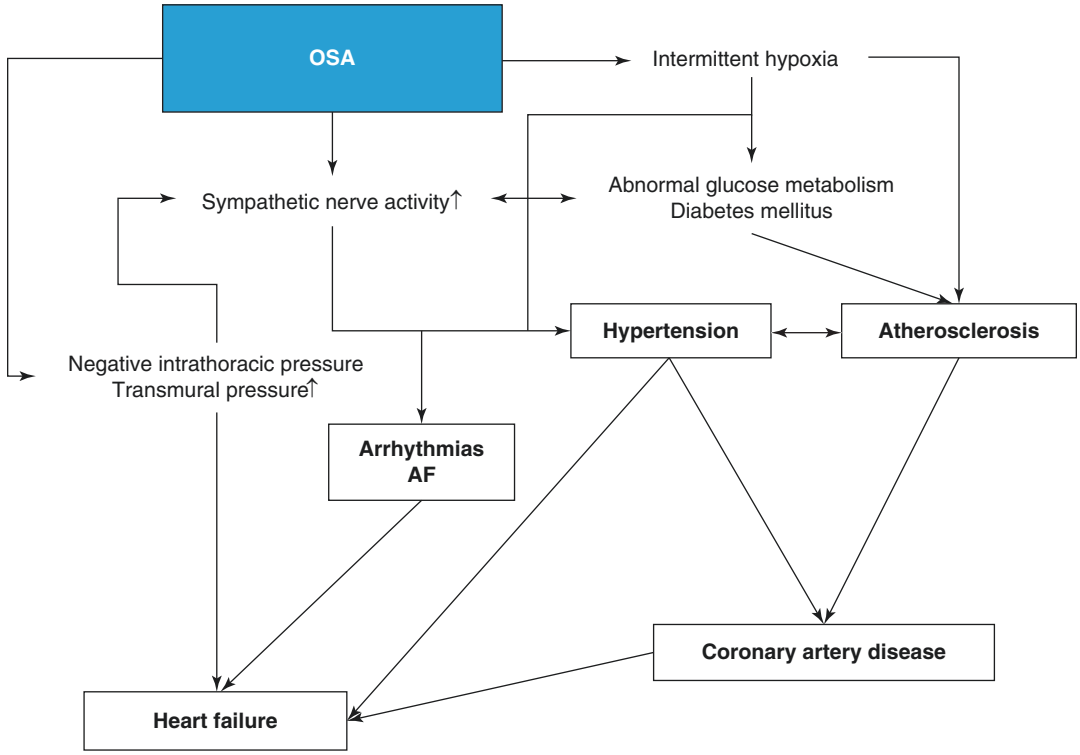

Fig. 24.1 Relationship between OSA and CVD. *AF* atrial fibrillation

thetic outflow and silencing of sympathoinhibitory input from carotid sinus baroreceptors by reductions in stroke volume during obstructive apneas, as mentioned previously. When apnea is interrupted by arousal from sleep, the latter process simultaneously augments sympathetic nerve activity (SNA) and reduces cardiac vagal activity, thereby resulting in a postapneic surge in both blood pressure (BP) and heart rate (HR). Cardiac vagal withdrawal increases HR and reduces HR variability at high frequencies; the latter is a marker of adverse outcomes, such as malignant arrhythmias. Hence, sympathetic overactivation could increase HR, which is itself an adverse effect, albeit a nonspecific prognostic signal, and could worsen the prognosis of patients with CVD specifically by causing cardiac β-adrenoreceptor desensitization, arrhythmias, myocyte injury and necrosis, and peripheral vasoconstriction and consequently increased afterload and BP.

These acute adverse effects of OSA on the autonomic nervous system are not limited during sleep. In dogs exposed chronically to experimental OSA, BP elevation during sleep was sustained into wakefulness. Patients with OSA and HF have elevated SNA and depressed cardiac vagal activity when awake. Mechanisms for such daytime carryover effects remain unclear, although it could be related to the adaptation of chemoreceptor reflexes or central processes governing autonomic outflow. Furthermore, OSA suppression by continuous positive airway pressure (CPAP) lowers SNA and increases cardiac vagal modulation of high-frequency HR variability not only at night but also during wakefulness.

24.2.3 Oxidative Stress

OSA induces IH and reoxygenation, and frequent episodes of hypoxia/reoxygenation could result in oxidative stress that produces reactive oxygen species that could impair vascular endothelial function and promote atherogenesis [3]. IH could

also activate nuclear transcriptional factors, including nuclear factor κ-B, which stimulates the production of inflammatory mediators and intracellular and vascular cell adhesion molecules, thereby facilitating endothelial damage and promoting atherogenesis. In addition, accompanying high cholesterol levels in the bloodstream may further facilitate atherosclerotic process [4].

Moreover, patients with OSA show more signs of early atherosclerosis, including increased carotid intima–media thickness and increased arterial stiffness, compared with control subjects [5]. In a randomized controlled trial (RCT) involving patients with OSA, CPAP reduced both carotid intima–media thickness and arterial stiffness, thereby supporting a causal relationship between OSA and atherosclerosis [6]. However, several other RCTs failed to show the beneficial effects of CPAP on signs of early atherosclerosis [7, 8]. Thus, effects of CPAP therapy on signs of early atherosclerosis remain controversial.

24.3 Diabetes and OSA

Recently, the relationship between OSA and diabetes has been reported. Several prospective cross-sectional studies have suggested an independent association between OSA severity and insulin resistance in individuals without type 2 diabetes [9, 10]. The features of OSA, such as sleep restriction, sleep fragmentation, and IH, could lead to glucose metabolism dysregulation. Thus, chronic IH could result in several metabolic alterations, including higher fasting glucose and insulin levels, insulin resistance, glucose intolerance, and possibly β-cell dysfunction. However, the pathophysiological and causal links between OSA and glucose metabolism dysregulation are not fully elucidated. Nevertheless, sympathetic hyperactivity is considered a significant factor because most endocrine organs are inhibited by sympathetic tone elevations and incretin hormone secretion, such as glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, is linked to autonomic nervous system activity [11]. Furthermore, recent studies have demonstrated β-cell dysfunction or β-cell death after exposure to IH [12].

Hence, OSA treatment may help prevent the severe consequences of diabetes. However, the effect of CPAP treatment on metabolic outcomes remains uncertain. Although several RCTs including mainly morbidly obese patients have been performed, discrepancies in treatment duration or challenges with CPAP compliance were noted; thus, the results vary [13–15]. Moreover, treatment seems to be more beneficial to glycemic health in nonobese subjects, and improvement in insulin resistance with CPAP in obese subjects is unlikely to be expected without concomitant weight loss. Therefore, OSA may worsen metabolic abnormalities, and OSA treatment with sufficient adherence to CPAP therapy could play a protective role, especially when concomitant lifestyle interventions and weight loss are implemented.

24.4 Hypertension and OSA

Approximately 50% of patients with OSA have hypertension, which is a common comorbidity. A population-based study has shown that the likelihood of developing hypertension is 2.89 greater in subjects with moderate to severe OSA, which is defined as apnea hypoxia index (AHI) >15, than in those with an AHI of 0 [16]. However, other studies showed that the relationship between OSA and incident hypertension attenuated when the effects of body mass index were taken into account [1]. In patients who have already developed hypertension, the OSA prevalence is about 35% [17], and in patients with drug-resistant hypertension (DRH), the OSA prevalence is 65–80% [18, 19].

One mechanism linking OSA and hypertension is sympathetic nerve activation. As previously mentioned, the sympathetic nervous system is activated simultaneously by cycles of respiratory events. Investigations using dogs exposed chronically to experimental OSA revealed that elevations in sleep BP are sustained into wakefulness [20]; moreover, in 12 healthy subjects exposed to periods of IH, BP and muscle

sympathetic nerve activity were significantly increased after the exposure, and such elevation in BP was sustained throughout the waking hours [21]. In addition, patients with OSA have a high muscle sympathetic nerve activity when awake compared with controls, which corresponds to increased BP while awake.

Another important mechanism linking OSA and hypertension, particularly DRH, is the activation of renin-angiotensin-aldosterone system. A recent meta-analysis showed that blood levels of angiotensin II are increased in OSA patients compared with those of controls and that OSA patients with hypertension have increased blood levels of aldosterone compared with those without hypertension [22]. Moreover, a recent experimental study clearly showed that in rats, renal sympathetic nerve activation due to chronic IH could cause RAS activation, oxidative stress, endothelial dysfunction, and BP elevation, which were all reversible by renal sympathetic nerve denervation; this suggests that renal sympathetic nerve activation, possibly with RAS activation, may contribute to the development of hypertension [23]. Furthermore, frequent episodes of IH and reoxygenation also play a role in the development of hypertension and drug resistance. As previously mentioned, hypoxia/reoxygenation could induce free oxygen radical generation and increase oxidative stress and activation of inflammatory mediators [3]. Reactive oxygen species and inflammation reduce nitric oxide levels and impair endothelium-dependent vasodilatation, which may contribute to increased BP independent of sympathetic activation.

OSA suppression by CPAP acutely reduces nocturnal SNA and BP [1]. The effects of chronic CPAP treatment have been assessed in several small-scale RCTs, and most meta-analyses found that CPAP significantly reduces BP but in a modest effect size [1]. In trials in which most subjects had uncontrolled hypertension, OSA treatment by CPAP reduced BP particularly in patients with high BP levels at baseline and more severe OSA accompanied by hypersomnolence [1]. In patients with DRH, two RCTs suggested that CPAP could significantly reduce BP in a relatively short term (3–6 months) [24, 25]. In the Sleep Apnea Cardiovascular Endpoints (SAVE) study, which is a large-scale RCT, the effects of CPAP on cardiovascular morbidity and mortality in OSA patients with coronary artery disease and/or cerebrovascular disease were investigated; approximately 80% of the participants had hypertension, and patients receiving CPAP tended to have reduced diastolic BP [26]. Another RCT evaluated the effects of CPAP on BP in non-sleepy, hypertensive patients with OSA (defined as an Epworth Sleepiness Scale (ESS) score <11); a significant diastolic BP reduction was observed in the CPAP group. When the analysis was subdivided according to CPAP compliance, BP reduction was only observed in the CPAP-compliant group (>5.6 h per night) [27]. In a multicenter RCT, the effects of CPAP on cardiovascular mortality and morbidity, including incident hypertension, in non-sleepy patients with OSA (defined as an ESS score <11) were investigated; although changes in BP during the study period were not specifically mentioned, more hypertensive patients were compliant to CPAP, and patients compliant to CPAP (i.e., nightly usage ≥4 h) had better outcomes than less-compliant patients [28]. Thus, CPAP compliance could be associated with BP changes, and improved cardiovascular outcomes may be derived from BP reduction associated with CPAP compliance.

24.5 Coronary Artery Disease and OSA

A prospective observational study involving a sleep clinic patient population showed that patients with untreated severe OSA have a significantly increased risk of fatal and nonfatal cardiovascular events (odds ratio 2.87 and 3.17, respectively) compared with those without OSA [29]. Several US community-based cohort studies demonstrated significant relationships between OSA and cardiovascular morbidity and mortality, suggesting that OSA is a risk factor for CAD and is important in the aspect of primary prevention of CAD [1]. Moreover, the prevalence of sleep-disordered breathing (SDB), mainly OSA, in patients who already have CAD is

reported to be 30–57%, which is much greater than that in the general population (i.e., 5–10%) [30]. A recent meta-analysis revealed that SDB appears to increase the risk of cardiovascular events, including cardiac death, myocardial infarction (MI), and coronary revascularization, in patients with CAD even following percutaneous coronary intervention (PCI) [31]. In addition, our group recently reported that of 539 patients who underwent PCI, 296 (54.9%) had SDB which was assessed by frequency of IH and were at a significantly higher risk of adverse cardiac and/or cerebrovascular event (hazard ratio 2.26; 95% confidence interval (CI) 1.05–5.4, $p = 0.036$) compared to patients without SDB [32]. These findings suggest that SDB, especially OSA, plays significant roles in the secondary prevention of CAD and SDB could be determined using simple screening tools such as pulse oximetry.

OSA could cause or worsen CAD. As previously mentioned, SDB causes hypertension and could indirectly develop CAD through systemic atherosclerosis. OSA possibly has direct influence on coronary atherosclerosis through increased oxidative stress, inflammation, and sympathetic nerve activity. Using intravascular ultrasound in 289 patients with CAD who underwent PCI, Wada et al. showed that patients with SDB have a larger total atheroma plaque volume of the culprit lesion in the coronary artery than those without SDB [33]. Other studies showed that moderate to severe OSA increases the risk of acute coronary syndrome and repeated PCI due to progression of coronary atherosclerotic lesions [34].

Determining whether treatment by CPAP could improve the clinical outcome in patients with OSA (i.e., primary prevention) or in OSA patients with CAD (i.e., secondary prevention) remains a major challenge. Barbe et al. performed a multicenter RCT in which the effects of CPAP (i.e., primary prevention) on cardiovascular mortality and morbidity, including incident hypertension, in non-sleepy patients with OSA (defined as an ESS score <11) were investigated. In their study, although the primary endpoints showed no statistically significant difference, patients with CPAP seemed to have better outcomes. In the subgroup analysis, patients compliant to CPAP (nightly usage ≥4 h) had significantly better outcomes than controls [28]. Moreover, Casser et al. conducted an observational study and reported that OSA patients with CAD treated with CPAP (i.e., secondary prevention) following PCI have significantly less cardiovascular death ($p = 0.027$) and insignificant tendency to have less all-cause mortality ($p = 0.058$) compared with untreated OSA patients with CAD [35].

Recently, Huang et al. performed a RCT in a sleep clinic cohort and investigated non-sleepy or mildly sleepy patients (i.e., ESS <15) with moderate to severe OSA and concomitant hypertension and CAD at baseline. They randomly assigned patients to either the CPAP ($n = 42$) or no-CPAP ($n = 41$) group and followed them for a median of 36 months. The CPAP group showed no significant reduction in the incidence of the primary composite outcome (i.e., a composite of new-onset acute MI, hospitalization for HF, coronary revascularization, stroke, and death associated with cardiovascular and cerebrovascular disease); one event was noted in the CPAP group and five events in the no-CPAP group [36]. Possible explanations for the neutral results include the small sample size and limited number of the composite endpoints. In a recent large-scale RCT (the SAVE study), the effects of CPAP on cardiovascular morbidity and mortality among OSA patients with CAD and/or cerebrovascular disease were investigated; CPAP failed to show beneficial effects on cardiovascular outcome although it improved sleepiness and quality of life (QOL) [26]. Moreover, in the SAVE study, subjects with sleepiness and severe hypoxia, who could receive maximum benefits from CPAP treatment, were excluded, and as less symptomatic patients were enrolled and a number of patients enrolled were from China where CPAP is not in clinical use, compliance to CPAP was poor (mean nightly usage was 3.5 h). Matched comparisons between compliant patients and controls suggested that CPAP reduces incident cerebrovascular disease [26]. Furthermore, in the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea study, non-sleepy (ESS <10) OSA (AHI ≥15) patients following PCI were randomized to

auto-titrating CPAP (n = 122) or no-CPAP (n = 122) group and were followed for a median of 57 months. The incidence of the primary composite cardiovascular endpoint (new revascularization, MI, stroke, or cardiovascular mortality) did not differ between the two groups. However, adjusted on-treatment analysis demonstrated a significant risk reduction in those who used CPAP for at least 4 h/night (adjusted hazard ratio 0.29; 95% CI 0.10–0.86) [37]. Hence, no RCTs showed that CPAP improves cardiovascular outcome in OSA patients with and without CAD. Nonetheless, physicians should keep in mind that CPAP may be effective in improving cardiovascular outcomes if patients are compliant with CPAP therapy.

24.6 Heart Failure and OSA

A community-based cohort study in the USA demonstrated significant relationships between OSA and incident HF, suggesting that OSA is a risk factor for HF [1]. Cross-sectional data from the Sleep Heart Health Study (SHHS) showed that OSA with AHI ≥11 is associated with a 2.38 relative increase in the likelihood of having HF, independent of confounding factors [38]. OSA prevalence in patients with HF has been reported to range from 12% to 53%, which is greater than that in the general population [39, 40]. This high OSA prevalence in patients with HF may be explained by fluid retention and fluid shift. Distension of neck veins or edema of the peripharyngeal soft tissue could increase tissue pressure around the upper airway, thereby predisposing an individual to OSA. Moreover, a Canadian group demonstrated that in response to a 5-min application of lower-body positive pressure, the neck circumference increased, pharyngeal cross-sectional area decreased, and pharyngeal resistance and collapsibility increased simultaneously with a reduction in leg fluid volume in healthy subjects. Such rapid changes in neck circumference and upper airway properties could only be caused by a change in fluid volume within the peripharyngeal area [1]. Redolfi et al. identified direct relationships between the volume of fluid displaced gravitationally from the legs overnight, and both the overnight increase in neck circumference and OSA severity, as assessed by AHI, in 23 otherwise healthy nonobese men [41]. These findings were replicated in men with HF.

A unique feature of SDB in patients with HF is the coexistence of CSA with OSA. While OSA and CSA interrupt breathing by different mechanisms, they may result in qualitatively similar autonomic, chemical, and inflammatory burdens on the heart and circulation. However, the mechanical burden may be different between OSA and CSA; OSA may have adverse mechanical effects on the heart and circulation through enhanced negative intrathoracic pressure, which is not observed in CSA. In patients who are diagnosed as having HF, OSA has an influence on the underlying HF. In the observational study by Wang et al., untreated OSA with AHI ≥15 in HF patients was associated with increased mortality compared with that with an AHI <15, even after adjustment for confounding risk factors [42]. In terms of pathophysiology, negative intrathoracic pressure during futile inspiratory efforts against the occluded pharynx directly affects hemodynamics even in patients with HF; acutely raises arterial, ventricular, and aortic wall tension; and draws venous blood into the right heart. This abrupt generation of negative intrathoracic pressure is a cardiac afterload and remodeling force. The consequent septal shift could compromise the stroke volume by reducing left ventricular diastolic filling. All these mechanisms in patients with HF could in turn cause decompensated HF, poor left ventricular dysfunction, and poor prognosis. Additional mechanisms by which OSA may worsen outcomes in patients with HF include systemic hypertension exacerbation, increased risk of arrhythmias including sudden cardiac death, and elevated risk of coronary events.

As fluid retention and overnight rostral fluid shift contribute to the pathogenesis of OSA [43], medical therapy should be optimized in patients with HF. Data from a nonrandomized trial in which the administration of furosemide and spironolactone resulted in an increase in upper airway caliber and a modest reduction in AHI among patients with diastolic HF and severe OSA support this approach [44]. In addition,

when patients with HF and OSA are treated with CPAP, negative intrathoracic pressure swings are attenuated, and left ventricular afterload, BP, and HR are all reduced [45]. Several short-term RCTs of CPAP involving HF patients with OSA have evaluated the effects of OSA treatment with CPAP on cardiovascular variables. Particularly, Kaneko et al. showed that after 1 month of CPAP treatment, daytime systolic BP and HR decreased, and left ventricular ejection fraction (LVEF) increased by 9% [46]. Expansion of their trial demonstrated that such reduction in systolic BP was accompanied by a reduction in sympathetic vasoconstrictor nerve discharge [47], suggesting that the sympathoexcitation of OSA is superimposed on the background sympathoexcitation of HF [48]. In another randomized trial with a duration of 3 months involving patients with less severe HF and milder OSA, Mansfield et al. showed that LVEF increased by 5% [49] and that urinary norepinephrine excretion decreased significantly despite no reduction in daytime BP. Egea et al. reported that in 50 HF patients, CPAP improved LVEF after 3 months [50] but did not improve ESS scores and QOL. By contrast, Smith et al. [51] found no improvement in LVEF in HF patients with OSA by CPAP; unlike the other three RCTs, they used auto-titrating CPAP but did not confirm whether it eliminated OSA. Hence, fixed-pressure CPAP could increase LVEF and decrease SNA, and increases in LVEF and reductions in BP were more obvious in RCTs involving patients with lower LVEF and higher AHIs. Although no RCTs have identified the effects of CPAP on morbidity and mortality in OSA patients with HF, observational studies comparing patients with and those without CPAP treatment have been conducted. In a study from Canada, Wang et al. reported a trend toward a lower mortality rate in CPAP-treated patients over a mean follow-up period of 2.9 years ($p = 0.07$). In a study from Japan, Kasai et al. found that CPAP-treated patients have significantly greater hospitalization-free survival after a mean follow-up of 2.1 years. No studies suggested potential harmfulness of CPAP in OSA patients with HF. Nevertheless, large-scale RCTs remain warranted.

24.7 Arrhythmias and OSA

In patients with OSA, the prevalence of atrial fibrillation (AF) is up to 5%, and notably, the OSA prevalence in patients was diagnosed as having AF is 32–39%. A significant independent association between the two disorders exists even after controlling for confounding conditions, such as systemic hypertension, obesity, and HF [52]. In the cross-sectional analysis of the Sleep Heart Health Study, the subjects with OSA were five times as likely to have AF as those without OSA [53]. Furthermore, observational studies showed that OSA could predict a greater risk of new-onset AF or AF recurrence following cardioversion to sinus rhythm or catheter ablation [1]. Recent meta-analyses showed that patients with OSA have a 25% greater risk of AF recurrence after catheter ablation than those without OSA [54], and the prevalence of non-sustained ventricular tachycardia was also significantly higher in patients with severe OSA than in controls (5.3% versus 1.2%, respectively; $p = 0.004$) [53]. In a study involving 283 patients who were followed for 54 months after implantation of an implantable cardioverter defibrillator in conjunction with biventricular pacing, the discharge risk doubled, and the time to first appropriate discharge was 17 months earlier in patients with OSA compared with those who did not have SDB [55]. Another observational study showed that the risk of sudden cardiac death was increased in patients with severe OSA [56]. Several mechanisms elicited by OSA could initiate atrial or ventricular arrythmias: wall stretch in the atrium and ventricle secondary to abrupt decreases in intrathoracic pressure, with attenuation over time of normal cell-to-cell communication through remodeling, and myocardial ischemia secondary to apnea-induced cardiac inflammatory pathways. In dogs, pacing of the right atrium with upper airway occlusion increased the autonomic activity of the right pulmonary arterial ganglionated plexi and could more readily induce AF compared with that without upper airway occlusion [57]. After blockade of the ganglionated plexi, either pharmacologically or by neural ablation, AF induction during upper airway occlusion was inhibited, sug-

gesting a causative link between OSA and AF mediated by autonomic neural factors.

Although cross-sectional studies have not demonstrated an increased prevalence of bradyarrhythmias in OSA [53], apnea-induced hypoxia could provoke parasympathetically mediated atrioventricular block that is reversible with CPAP [58]. Thus, bradyarrhythmias especially during sleep may be a consequence of OSA. Moreover, OSA is highly prevalent (>80%) in patients with AF recurrence following pulmonary vein isolation (PVI) [59]. Thus, OSA may play a role in AF recurrence following AF treatment. An observational study showed that the recurrence rate of AF 1 year after cardioversion is significantly lower in patients with CPAP-treated OSA than in those with untreated OSA (42% versus 82%, respectively) [60]. In addition, recent meta-analyses showed that patients with OSA have a 25% greater risk of AF recurrence after PVI compared with those without OSA [1]. The effects of OSA treatment with CPAP on ventricular arrhythmia have also been investigated. In a small, 1-month randomized trial involving HF patients with OSA and frequent ventricular ectopy during sleep, a significant reduction in ectopic frequency in those treated with CPAP was observed [61]. In terms of bradyarrhythmias, several observational studies and case series suggested that sinus pause and atrioventricular block are reversible with CPAP [58]. Data suggesting the influence of CPAP therapy on the improvement of arrhythmias in patients with OSA are limited. Thus, further studies are necessary given the small size and the predominantly observational nature of the existing trials.

24.8 Conclusion

Mechanistic investigations showed that OSA contributes to the incidence and progression of CVD by stimulating the sympathetic nerve system and RAS, by altering hemodynamics and increasing cardiac load that is associated with increased intrathoracic negative pressure, and by increasing oxidative stress and inflammation and impairing endothelial function.

Population-based studies and short-term RCTs strongly suggest that OSA is a common and treatable risk factor for hypertension and CVD. Observational studies report an association between OSA and CVD, such as CAD, HF, or cardiac arrhythmias. In addition, observational studies suggest that among patients with preexisting CAD, HF, or cardiac arrhythmias, OSA treatment with CPAP is associated with a lower risk of cardiovascular events.

However, the following two important questions regarding the clinical significance of OSA for CVD remain unresolved: (1) Does OSA cause CVD independent of coexisting cardiovascular risk factors? (2) Does treating OSA reduce the risk of developing and/or worsening CVD? The most important approach to answer one or both of these questions is to conduct a large-scale, long-term randomized trial to assess the effects of OSA treatment on cardiovascular morbidity and mortality, taking compliance with CPAP therapy and enrollment of subjects who have a greater potential to receive benefits from CPAP into consideration. Several important clinical trials that involve OSA patients with CVD and include cardiovascular morbidity and mortality evaluation are presently underway.

References

1. Kasai T, Floras JS, Bradley TD. Sleep apnea and cardiovascular disease: a bidirectional relationship. Circulation. 2012;126:1495–510.
2. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet (London, England). 2009;373:82–93.
3. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol. 2010;7:677–85.
4. Savransky V, Nanayakkara A, Li J, et al. Chronic intermittent hypoxia induces atherosclerosis. Am J Respir Crit Care Med. 2007;175:1290–7.
5. Drager LF, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: an emerging risk factor for atherosclerosis. Chest. 2011;140:534–42.
6. Drager LF, Bortolotto LA, Figueiredo AC, et al. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med. 2007;176:706–12.
7. Paz YMHL, Hazen SL, Tracy RP, et al. Effect of continuous positive airway pressure on cardiovascular

biomarkers: the sleep apnea stress randomized controlled trial. Chest. 2016;150:80–90.
8. Sivam S, Witting PK, Hoyos CM, et al. Effects of 8 weeks of CPAP on lipid-based oxidative markers in obstructive sleep apnea: a randomized trial. J Sleep Res. 2015;24:339–45.
9. Ip MS, Lam B, Ng MM, et al. Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med. 2002;165:670–6.
10. Punjabi NM, Sorkin JD, Katzel LI, et al. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med. 2002;165:677–82.
11. Hansen L, Lampert S, Mineo H, et al. Neural regulation of glucagon-like peptide-1 secretion in pigs. Am J Physiol Endocrinol Metab. 2004;287:E939–47.
12. Wang N, Khan SA, Prabhakar NR, et al. Impairment of pancreatic beta-cell function by chronic intermittent hypoxia. Exp Physiol. 2013;98:1376–85.
13. Hoyos CM, Killick R, Yee BJ, et al. Cardiometabolic changes after continuous positive airway pressure for obstructive sleep apnoea: a randomised sham-controlled study. Thorax. 2012;67:1081–9.
14. Lam JC, Lam B, Yao TJ, et al. A randomised controlled trial of nasal continuous positive airway pressure on insulin sensitivity in obstructive sleep apnoea. Eur Respir J. 2010;35:138–45.
15. West SD, Nicoll DJ, Wallace TM, et al. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. Thorax. 2007;62:969–74.
16. Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342:1378–84.
17. Sjostrom C, Lindberg E, Elmasry A, et al. Prevalence of sleep apnoea and snoring in hypertensive men: a population based study. Thorax. 2002;57:602–7.
18. Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension. 2011;58:811–7.
19. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens. 2001;19:2271–7.
20. Brooks D, Horner RL, Kozar LF, et al. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest. 1997;99:106–9.
21. Tamisier R, Pepin JL, Remy J, et al. 14 nights of intermittent hypoxia elevate daytime blood pressure and sympathetic activity in healthy humans. Eur Respir J. 2011;37:119–28.
22. Jin ZN, Wei YX. Meta-analysis of effects of obstructive sleep apnea on the renin-angiotensin-aldosterone system. J Geriatr Cardiol. 2016;13:333–43.
23. Takahashi K, Ueda S, Kobayashi T, et al. Chronic intermittent hypoxia-mediated renal sympathetic nerve activation in hypertension and cardiovascular disease. Sci Rep. 2018;8:17926.
24. Martinez-Garcia MA, Capote F, Campos-Rodriguez F, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA. 2013;310:2407–15.
25. Pedrosa RP, Drager LF, de Paula LKG, et al. Effects of OSA treatment on BP in patients with resistant hypertension: a randomized trial. Chest. 2013;144:1487–94.
26. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016;375:919–31.
27. Barbe F, Duran-Cantolla J, Capote F, et al. Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. Am J Respir Crit Care Med. 2010;181:718–26.
28. Barbe F, Duran-Cantolla J, Sanchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA. 2012;307:2161–8.
29. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365:1046–53.
30. Lee CH, Sethi R, Li R, et al. Obstructive sleep apnea and cardiovascular events after percutaneous coronary intervention. Circulation. 2016;133:2008–17.
31. Qu H, Guo M, Zhang Y, et al. Obstructive sleep apnea increases the risk of cardiac events after percutaneous coronary intervention: a meta-analysis of prospective cohort studies. Sleep Breath. 2018;22:33–40.
32. Yatsu S, Naito R, Kasai T, et al. Influence of sleep-disordered breathing assessed by pulse oximetry on long-term clinical outcomes in patients who underwent percutaneous coronary intervention. Clin Res Cardiol. 2018;107:711–8.
33. Wada H, Dohi T, Kasai T, et al. Culprit plaque characteristics in patients with sleep-disordered breathing undergoing percutaneous coronary intervention: an intravascular ultrasound study. J Am Heart Assoc. 2018;7:e009826.
34. Nakashima H, Kurobe M, Minami K, et al. Effects of moderate-to-severe obstructive sleep apnea on the clinical manifestations of plaque vulnerability and the progression of coronary atherosclerosis in patients with acute coronary syndrome. Eur Heart J Acute Cardiovasc Care. 2015;4:75–84.
35. Cassar A, Morgenthaler TI, Lennon RJ, et al. Treatment of obstructive sleep apnea is associated with decreased cardiac death after percutaneous coronary intervention. J Am Coll Cardiol. 2007;50:1310–4.
36. Huang Z, Liu Z, Luo Q, et al. Long-term effects of continuous positive airway pressure on blood pressure and prognosis in hypertensive patients with coronary heart disease and obstructive sleep apnea: a randomized controlled trial. Am J Hypertens. 2015;28:300–6.
37. Peker Y, Glantz H, Eulenburg C, et al. Effect of positive airway pressure on cardiovascular outcomes

in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. Am J Respir Crit Care Med. 2016;194:613–20.
38. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med. 2001;163:19–25.
39. Vazir A, Hastings PC, Dayer M, et al. A high prevalence of sleep disordered breathing in men with mild symptomatic chronic heart failure due to left ventricular systolic dysfunction. Eur J Heart Fail. 2007;9:243–50.
40. Ferrier K, Campbell A, Yee B, et al. Sleep-disordered breathing occurs frequently in stable outpatients with congestive heart failure. Chest. 2005;128:2116–22.
41. Redolfi S, Yumino D, Ruttanaumpawan P, et al. Relationship between overnight rostral fluid shift and obstructive sleep apnea in nonobese men. Am J Respir Crit Care Med. 2009;179:241–6.
42. Wang H, Parker JD, Newton GE, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. J Am Coll Cardiol. 2007;49:1625–31.
43. Alahdab F, Arwani R, Pasha AK, et al. A systematic review and meta-analysis of endovascular versus open surgical revascularization for chronic mesenteric ischemia. J Vasc Surg. 2018;67:1598–605.
44. Bucca CB, Brussino L, Battisti A, et al. Diuretics in obstructive sleep apnea with diastolic heart failure. Chest. 2007;132:440–6.
45. Tkacova R, Rankin F, Fitzgerald FS, et al. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. Circulation. 1998;98:2269–75.
46. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med. 2003;348:1233–41.
47. Usui K, Bradley TD, Spaak J, et al. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. J Am Coll Cardiol. 2005;45:2008–11.
48. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am Coll Cardiol. 2009;54:375–85.
49. Mansfield DR, Gollogly NC, Kaye DM, et al. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. Am J Respir Crit Care Med. 2004;169:361–6.
50. Egea CJ, Aizpuru F, Pinto JA, et al. Cardiac function after CPAP therapy in patients with chronic heart failure and sleep apnea: a multicenter study. Sleep Med. 2008;9:660–6.
51. Smith LA, Vennelle M, Gardner RS, et al. Autotitrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnoea: a randomized placebo-controlled trial. Eur Heart J. 2007;28:1221–7.
52. Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation. 2004;110:364–7.
53. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the Sleep Heart Health Study. Am J Respir Crit Care Med. 2006;173:910–6.
54. Ng CY, Liu T, Shehata M, et al. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. Am J Cardiol. 2011;108:47–51.
55. Bitter T, Westerheide N, Prinz C, et al. Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. Eur Heart J. 2011;32:61–74.
56. Patel N, Donahue C, Shenoy A, et al. Obstructive sleep apnea and arrhythmia: a systemic review. Int J Cardiol. 2017;228:967–70.
57. Ghias M, Scherlag BJ, Lu Z, et al. The role of ganglionated plexi in apnea-related atrial fibrillation. J Am Coll Cardiol. 2009;54:2075–83.
58. Becker H, Brandenburg U, Peter JH, et al. Reversal of sinus arrest and atrioventricular conduction block in patients with sleep apnea during nasal continuous positive airway pressure. Am J Respir Crit Care Med. 1995;151:215–8.
59. Hoyer FF, Lickfett LM, Mittmann-Braun E, et al. High prevalence of obstructive sleep apnea in patients with resistant paroxysmal atrial fibrillation after pulmonary vein isolation. J Interv Card Electrophysiol. 2010;29:37–41.
60. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation. 2003;107:2589–94.
61. Ryan CM, Usui K, Floras JS, et al. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. Thorax. 2005;60:781–5.

Effect of CPAP on Cognition and Brain Function

25

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Abbreviations

AD	Alzheimer's disease
ADNI	Alzheimer's disease neuroimaging initiative
AHI	Apnea–hypopnea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
DTI	Diffusion tensor imaging
EC	Entorhinal cortex
EDS	Excessive daytime sleepiness
FA	Fractional anisotropy
GM	Gray matter
IH	Intermittent hypoxia
MD	Mean diffusivity
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
OCST	Out-of-center sleep testing
OSA	Obstructive sleep apnea
PSG	Polysomnography
RERA	Respiratory effort-related arousal
SVD	Small vassal disease
WM	White matter

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25.1 Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repeated episodes of upper airway obstruction during sleep, consequent chronic intermittent hypoxia, and sleep fragmentation. These episodes last from 10 to 30 s but may also persist for more than 1 min and cause a reduction in blood oxygen desaturation and brief arousal from sleep [1]. OSA diagnosis comprises both a clinical assessment and an objective demonstration of impaired breathing during sleep. Typical features of this disorder are nonrestorative sleep and sleep disruption caused by the occurrence of upper airway obstruction. These nocturnal deficits can result in daytime impairments, in particular, OSA patients frequently report daytime sleepiness, tiredness, insomnia, anxiety, stress-related disorder, and mood swings [2]. OSA prevalence is strictly associated with the gravity of the disorder. Accordingly, at ≥5 events/h apnea–hypopnea index (AHI), it ranges from 9% to 38% in the general population. At AHI ≥15, the overall prevalence is lower, ranging from 6% to 17%, with higher rates in men and increasing with age [3].

OSA has detrimental effect on the structure and function of blood vessels, culminating in increased mortality and morbidity, and a strong association with vascular diseases. Negative effects are observed also in cognitive domains, brain structures, and functioning. These impairments may lead to deleterious daytime consequences in occupational and educational functioning as well as road safety. Furthermore, a link between OSA and neurodegenerative disease has been proposed [4].

The mainstay for the treatment of this disorder is continuous positive airway pressure (CPAP). CPAP is usually delivered throughout a nasal mask that provides continuous air pressure to the upper airways. This therapy reduces the frequency of respiratory events during sleep, sleep fragmentation, and sleepiness and improves daytime functioning. Of note, it is reported that several studies showed beneficial effects on neuropsychological impairment and brain functioning [5].

In this chapter, we will discuss the effect of CPAP treatment in OSA patients on neurocognitive domains and on the structure and functionality of the brain.

25.2 Effect of CPAP on Cognition

OSA patients exhibit several neuropsychological impairments mainly caused by decreased level of vigilance, with body mass index (BMI), age, and disrupted sleep that predict the decrement in performances. A recent meta-analysis reported that psychomotor speed and executive function are strongly impaired, whereas memory functions, motor control, attention, and speed of processing abilities are affected to a lesser degree [6]. The causal relationship between OSA and cognitive impairment is not yet understood; however, it has been hypothesized that structural brain damages resulting from the intermittent hypoxia observed during sleep act as a stressor affecting the blood–brain barrier [7]. Another, important factor is represented by excessive daytime sleepiness (EDS). EDS is a common symptom in OSA patients that may severely affect quality of life and diurnal functionality. Despite being frequently reported, some patients with severe OSA do not exhibit EDS. Several studies reported that EDS in these patients could be related to AHI index, sleep fragmentation, nocturnal oxygenation, and hypoxemia, but some other factors such as age, sex, obesity, and depression may play a role, indicating that its pathogenesis is multifactorial [8]. Sleepiness is frequently associated to sleep deprivation and fragmentation, which specifically contribute to impairment in attention and memory. Furthermore, hypoxia affects both hippocampal and cortical region. In particular, the prefrontal cortex is specifically sensitive to sleep deprivation and blood gas anomalies that, in turn, may disrupt the restorative process accountable to this region that is of particular importance for executive functioning.

The presence of cognitive impairments in OSA patients can lead to dramatic consequences; however, it is of utmost importance to investigate whether standard treatment technique, as CPAP

therapy, is able to improve these deficits. This treatment decreases arousals and sleep fragmentation, limits nocturnal hypoxia, and improves sleep architecture leading to clinical improvement of symptoms commonly attributed to OSA. In particular, a significant improvement in subjective EDS is reported in OSA patients even after short-term treatment. Of note, improvement in EDS is associated with CPAP therapy adherence.

Several studies evaluated the effect of CPAP on cognitive function in OSA patients. Canessa and coworkers [9] aimed to investigate cognitive deficts and corresponding brain morphological changes after a 3-month CPAP treatment in 17 never treated severe OSA patients using combined comprehensive neuropsychological evaluation and magnetic resonance imaging (MRI). At the baseline, patients exhibited decreased performances in all the investigated cognitive areas (executive functions, short and long-term memory), as well as impaired mood and the presence of daytime sleepiness in comparison to a group of healthy controls. Furthermore, neuropsychological impairments were associated with reductions of gray matter volume in the left hippocampus (entorhinal cortex), left posterior parietal cortex, and right superior frontal gyrus. After treatment, significant improvement was found in all cognitive domains that were related to increase in gray matter volume in the hippocampus, the medial orbitofrontal cortex, and the rostral portion of the right superior frontal gyrus, indicating that negative effects observed before therapy are consistently recovered throughout treatment [9]. However, a meta-analysis conducted on 13 studies comprising 554 OSA patients in order to quantify the effect of CPAP treatment on a large number of cognitive domains reported different results [10]. Despite a significant effect on both subjective and objective sleepiness as well as on mood, the authors found that CPAP showed only a small improvement in cognitive functioning, therefore challenging the optimistic idea that this treatment is effective in restoring cognition in OSA. In particular, significant improvement was found only in the domain of executive function but with some specific consideration. Of note, only attention domain showed significant improvement, whereas verbal fluency and working memory did not increase with the treatment. In line with these results, a recent randomized controlled trial specifically evaluated the effect of CPAP therapy on memory processes in OSA patients. A total of 36 patients were randomly divided into groups that received CPAP or sham CPAP for 6 weeks. Despite a significant amelioration of sleep apnea, no improvement in mnestic functioning was found. It is plausible that this lack of effect may be ascribable to irreversible brain damages resulting from hypoxia [11].

Jackson and coworker [12] evaluated the neuropsychological functioning of more than 100 OSA patients in comparison to a community dwelling group asymptomatic for OSA. Results showed that patients have more EDS, both objectively and subjectively, and have impaired quality of life, mood, working memory, and psychomotor function but were not impaired in verbal fluency, verbal memory, set shifting, or information processing speed. After adequate CPAP treatment for 3 months, patients showed significant ameliorations in subjective sleepiness, mood, and most neuropsychological domains in comparison to baseline. Despite some neurocognitive function return to the level of the healthy participants, some neurocognitive functions did not normalize after therapy, such as vigilance and working memory. This difference in the improvement between different cognitive domains may be explained by several factors, for example, the temporal difference in restoration of cognitive function with treatment or improvements in the structure or functionality of brain regions associated with performance on these tasks or that a 3-month therapy is not sufficient to resolve cognitive impairment. Another important issue for the evaluation of the cognitive improvement after treatment is represented by EDS. Although reported among diurnal symptoms, it is not universally present in all OSA patients. However, it has been reported as a reliable predictor for CPAP compliance. Furthermore, CPAP therapy is effective in significantly reducing EDS and can partially reverse neuropsychological functions in OSA patients with sleepiness but fails to improve

cognitive dysfunctions in patients without EDS [13]. Patients' age is another important issue, since deficits that remain, despite sufficient CPAP therapy, may be secondary to irreversible, long-term hypoxic neural effects (which could be more evident in elderly patients).

An increasing number of evidences reported an association between OSA and cognitive decline in the elderly. A study by Yaffe and coworkers in 2011 [14] assessed the relationship between sleep-disordered breathing and cognitive impairment. In this prospective study, 298 women without dementia were recruited and underwent a sleep and cognitive evaluation. The 105 women with sleep-disordered breathing had an increased risk to develop mild cognitive impairment or dementia in comparison to 193 women without sleep-disordered breathing. Specifically, elevated oxygen desaturation index and high percentage of total sleep time in apnea or hypopnea were associated with cognitive decline, whereas sleep fragmentation or duration had no significant association. Accordingly, a study with the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort [15] found that patients with sleep-disordered breathing had mild cognitive impairment or Alzheimer's dementia onset at a younger age in comparison to those without breathing disorders. Therefore, the evaluation of CPAP effectiveness in reducing or slowing the onset of dementia and cognitive impairment might be crucial. Osorio and coworkers [15] found that CPAP treatment is able to delay the onset of mild cognitive impairment. More recently, Richards and coworkers [16] tried to determine if CPAP treatment adherence (defined as the use of CPAP for 4 h or more per night over 1 year) was able to predict cognitive function in older adults with mild cognitive impairment. The authors found that 1 year of CPAP adherence in OSA patients significantly improved cognition and slowed the trajectory of cognitive decline in comparison to nonadherent patients. Moreover, it has also been reported that the usage of CPAP intervention in the early stage of dementia may slow down the progression of the disease, underlying the importance of a timely assessment and intervention in demented patients [17].

In conclusion, OSA patients reported a variety of cognitive impairments that range from basic functions, such as vigilance, to higher domains, such as executive function, with some inconsistencies across studies. These deficits might be caused by sleep fragmentation, hypoxia, and their negative effects on hippocampal and cortical regions. However, several other factors, such as EDS and age, contribute to the presence and the type of impairment. CPAP therapy is effective in decreasing arousals and sleep fragmentation, limits nocturnal hypoxia, and improves sleep architecture, but its efficacy on cognitive function is not universally reported in all studies and is particularly limited in those patients without EDS or with severe brain damages. However, usage of CPAP in the early stage of dementia seems to slow down the progression of the cognitive deterioration.

25.3 OSA Brain Before and After CPAP Treatment: The Contribution of Neuroimaging

There are at least three important reasons for questioning how obstructive sleep apnea (OSA) affects the human brain. First, from a pathogenetic point of view, it is necessary to assess the neurobiological correlate underlying brain abnormalities to better characterize OSA brain pathology. Second, from a clinical point of view, it is important to investigate if and what brain alterations are strictly associated with neurocognitive impairment including alterations of domains of attention/vigilance, verbal and visual delayed long-term memory, visuospatial/constructional abilities, and executive dysfunction. Third, from a therapeutic point of view, it is crucial to know whether brain alterations occurring in OSA may revert after the treatment.

In the past three decades, the contribution of neuroimaging in OSA is become increasingly emerging and relevant for the possibility to answer to these questions. Indeed, sophisticated techniques have allowed to investigate not only to the brain regions involved in OSA but also the

mechanisms underlying the pathogenesis of the brain damage -related to OSA. Of importance, imaging has proved to be also crucial to demonstrate the reversible nature of the brain damage after CPAP treatment. Focusing on neuroimaging studies, in this section we will describe the impact of OSA on human brain keeping in mind (1) brain damage occurring in OSA, (2) relationship between specific damaged brain regions and cognition, (3) reversibility of brain damage after CPAP-treatment.

In this prospective, neuroimaging represents a great opportunity since it opens a new interesting horizon on the importance of the CPAP treatment and its adherence.

25.4 Brain Damage in OSA

A consistent number of neuroimaging studies have well-documented that human OSA brain may be characterized by several tissue damages including alterations of white matter (WM) integrity, free water content, brain metabolites, and regional gray matter (GM) volume changes. Indeed, structural and functional alterations have been widely reported in cortical and subcortical structures such as frontal regions and hippocampus. Frontal lobes are a primary site of neurocognitive dysfunctions in patients with OSA, and hippocampus plays a crucial role in the cognitive and autonomic control [18]. Of great interest, however, is not only to identify the location of the brain abnormalities occurring in OSA patients but specially to define the nature of these OSA-related alterations. Neuroimaging studies had tried to approach these goals to move closer to these goals.

Cerebral small vassal disease (SVD) including white matter lesions and lacunar infarcts plays a crucial role in the pathogenesis of vascular diseases including vascular parkinsonism and dementia. This condition usually is associated with the presence of one or more vascular risk factors such as hypertension, smoking, diabetes mellitus, obesity, hyperlipidemia, and heart disease (coronary artery disease, atrial fibrillation, arrhythmias). Interestingly, the risk factors for developing cerebral SVD are the same for OSA. Moreover, OSA may be considered itself a nontraditional vascular risk factor suggesting a strict relationship between these two diseases. Thus, it not surprising that brain damage occurring in OSA patients is a vasculopathy involving cerebral SDV through two main mechanisms triggered by the recurrent episodes of intermittent hypoxia (IH): first, an increase in endothelin, a potent vasoconstrictor with sustained hypertensive effects, second, endothelial dysfunction with consequent lack of repair's vassal mechanisms [19]. The involvement of cerebral SVD commonly results in changes in subcortical WM and deep GM nuclei appearing as areas of increase signal intensity (hyperintensities) on MRI scan.

Several diffusion tensor imaging (DTI) studies, a tool able to assess the integrity of WM architecture, have contributed to detect the WM microstructural subcortical damage in OSA patients also demonstrating a relationship between severity of hyperintensities and level of hypoxemia [20]. In addition, Del Brutto et al. recently found that individuals with moderate-to-severe OSA are almost four times more likely to have diffuse subcortical damage of vascular origin than those with none-to-mild OSA, independent of demographics and cardiovascular risk factors, thus suggesting a relationship between severity of vascular damage and severity of OSA.

It remains, however, until debated whether OSA is the cause or the consequence of subcortical vascular damage. In this prospective, disruption of periventricular fibers which are part of the breathing control pathways might be the mediator of the apneic episodes [21]. Further studies in a large cohort of OSA patients are need to answer to this complex question.

25.5 Brain Damage and Cognition

The cognitive abilities that are especially susceptible to OSA brain damage are memory and attention associated to mood symptoms. Indeed, OSA patients commonly exhibit impaired memory and depressive symptoms. Interestingly, both these functions are strictly related with the

hippocampus. Animal models have well-demonstrated that intermittent hypoxia (IH), one OSA characteristic, may cause different patterns of low-grade neuroinflammation in the hippocampus of mice, including early but transient cytokine elevations, delayed but long-term microglial changes, and cytokine response alterations to lipopolysaccharide inflammatory challenge. These changes may contribute to IH-induced cognitive impairment and pathological brain aging making it essential to detect and treat [22]. This is not surprising, considering that animal hippocampal neurons show an increased sensitivity to low-O_2 conditions and repetitive IH reduces neuronal excitability in specific hippocampal subfield as CA1 [23]. In addition, recent neuropathological investigations performed on human OSA brain tissue have demonstrated that the thickness and myelination of the hippocampus and entorhinal cortex (EC) are compromised and vary as a function of OSA severity [24].

The emerging theory as OSA damages the hippocampus is actually supported by substantial neuroimaging studies allowing the direct examination of structure and function of the hippocampus. A recent meta-analysis [25] of structural and functional MRI studies has reported that hippocampal functional alterations may be the key reason of memory deficits and that structural changes could just be a result or inducement in OSA patients. Structural hippocampal damage, however, may be dual. Indeed, neuronal death may result in volume loss, whereas glial responses to IH-related OSA may increases tissue volume as a model of hippocampal neurogenesis strictly related to the age. On this basis, MRI volumetric studies have reported both increases and decreases in hippocampal volume in patients with OSA. By contrast, the relationship between hippocampal damage and impaired cognitive function, especially verbal memory, is unique. Autotypic data demonstrated that the regions of hippocampus involved in the decreased thickness and demyelination are locations of memory pathways, thus explaining the impairments observed in episodic, semantic, and spatial memory in people with OSA [23]. Patterns of altered activity within the structures as hippocampus and basal ganglia have been seen by functional neuroimaging studies. Hippocampal–cortical functional connectivity is compromised in OSA and might underlie depression and anxious mood levels in these patients, whereas the impairment of caudate–cortical functional connectivity might indicate deficits in reward processing and cognition [26]. These functional imaging findings provide insights into the neural mechanisms underlying the comorbidity of mood and cognitive deficits in OSA [26]. Finally, a combined neuropsychological and brain imaging study performed in OSA patients showed metabolic right-lateralized changes in several structures including hippocampus [27] despite the presence of minor memory deficits. These findings also suggest that in OSA patients without notable cognitive impairments, brain pathology probably starts many years before the onset of neuropsychological symptoms. On this basis, imaging may be more sensitive when it comes to detecting the impact of subclinical OSA on brain morphology and function [27].

On the other hand, hippocampal degeneration and consequent memory deficit are two hallmark features of Alzheimer's disease (AD). It is well-documented that AD patients show mainly a reduced volume of subfield CA1 when compared to healthy elderly controls. Interestingly, hippocampal CA1 is the most susceptible subfield to IH OSA damage in animal and human models [23, 24], thus suggesting something more than a simple link between these two pathologies.

25.6 Reversible Brain Damage After CPAP Treatment

The most interesting prospective of this section concerns the reversibility of OSA-related brain after CPAP treatment. There is convergence that, in addition to clinical resolution, CPAP treatment may exhibit multiple effects on OSA brain with restoration to the initial brain configuration.

A clear neuroimaging picture is emerging and demonstrates that not only that the tissue brain damage may be reversible but also that the neuro-

cognitive impairment related to brain alterations may revert after CPAP treatment. More in detail, several imaging evidences have demonstrated that GM structural alterations, such as focal volume reductions in the basal ganglia, thalamus, basal ganglia, and hippocampus, may be reversible after treatment.

Of note, a GM volume increase related to improvement of cognitive functions has been also reported in OSA after CPAP treatment. Additionally, metabolite changes in crucial structures such as hippocampus of OSA patients have been also detected in OSA as partially reversal after treatment. Below are some main neuroimaging applications in post-CPAP treatment study in patients with OSA.

Among the wide range of neuroimaging tools, it should be mentioned DTI since it was proven useful in detecting both brain damage and long-term CPAP treatment-induced changes in patients with OSA. Pioneers were Castronovo et al. [28] from which subsequently some neuroimaging studies started. In the pretreatment, OSA patients showed reduced DTI parameters such as fractional anisotropy (FA) and mean diffusivity (MD) reflecting a diffuse reduction of white matter (WM) fiber integrity in multiple brain areas. Limited changes of WM were found after 3-month CPAP treatment. In addition, significant improvements involving multiple cognitive domains as memory, attention, and executive functioning-paralleled WM changes after 12-month treatment were also found in OSA patients. These findings were consistent with the presence of a reversible structural neural injury in OSA patients [28]. After about 10 years, similar reductions of FA suggestive of decreased axonal degeneration and decreased demyelination have been reported in a prospective OSA study [29] after CPAP treatment, thus supporting the hypothesis of a reversibility of the brain damage.

To investigate the relationship between severity of OSA and effects of long-term CPAP treatment was a further turning point. This was possible using MRI morphometry, a tool able to measure local volume brain changes. Analysis of MRI scans before and after clearly showed brain volume increase in the areas including hippocampal dentate gyrus and the cerebellar dentate nucleus and prefrontal initially seen atrophic. Moreover, higher impairment of working memory in patients prior to treatment correlated with prefrontal volume increase after treatment in OSA, thus providing additional neuroimaging evidences on the positive effects of long-term CPAP [30]. A promising tool able to investigate tissue brain changes in OSA patients has been the proton magnetic resonance spectroscopy (MRS). MRS measures tissue concentrations of brain metabolites considered as a neural density marker, a membrane marker, and an intracellular neurotransmitter marker. Cerebral metabolite changes in frontal lobe white matter and in the hippocampus of untreated severe OSA patients have been reported in OSA patients, whereas frontal, but not hippocampal, changes persisted after 6 months of treatment with CPAP.

Moreover, metabolite concentrations were significantly correlated with the severity of OSA [31]. Overall, these evidences obtained with different MRI techniques demonstrate a cessation on the brain damage occurrence after CPAP treatment in patients with OSA.

The theory of the reversibility of brain damage has been recently supported by neuropathological investigations on brain tissue of CPAP-treated OSA patients. Indeed, OSA patients known to have used CPAP treatment showed no significant reductions in thickness of hippocampus of the hippocampus and EC when compared with controls, thus suggesting that CPAP had a protective effect [24]. The reversibility of OSA brain tissue damage after CPAP treatment, however, raises important questions on the nature of injury itself. Whether the OSA pathology was responsible for a permanent structural or functional brain damage, CPAP treatment would not be able to partially return the brain structures to the initial configuration. Thus, it is possible to speculate that structural changes observed in OSA may be not all permanent, but there is a combination of irreversible changes leading to neuronal death mixed to adaptive and/or reactive changes related to the brain's repair mechanisms. These last alterations could explain the increase of hippocampal

and prefrontal volume after treatment and could represent the therapeutic target of the CPAP treatment.

25.7 Conclusion

OSA is a sleep-related breathing disorder characterized by repeated episodes of upper airway obstruction during sleep, consequent chronic intermittent hypoxia, and sleep fragmentation. OSA diagnosis comprises a clinical assessment and an objective demonstration of impaired breathing during sleep throughout a polysomnography assessment. These nocturnal deficits result in daytime impairments such as EDS, tiredness, insomnia, anxiety, stress-related disorder, and mood swings. CPAP is the first-choice treatment for these patients since it reduces the frequency of respiratory events during sleep, sleep fragmentation, and sleepiness and improves daytime functioning.

Negative effects of this disorder are observed at different levels in cognitive domains, brain structures, and functioning. OSA patients frequently reported impaired psychomotor speed and executive function, whereas memory functions, motor control, attention, and speed of processing abilities are affected to a lesser degree. Evidence suggests that CPAP treatment is effective in restoring cognitive function but with results that are not consistent across studies. This may be due to variability in study design and sampling methodology. However, it has been reported that the usage of CPAP in the early stage of dementia may slow down the progression of the disease. Therefore, a timely diagnosis and treatment in these cases might be crucial.

Up to now, it is well established that OSA patents' brain is characterized by several tissue damages including alterations of WM integrity, free water content, brain metabolites, and regional GM volume changes. Moreover, structural and functional alterations have been widely reported in cortical and subcortical structures such as frontal regions and hippocampus.

In conclusion, MRI studies have substantially contributed to identify the mechanisms underlying OSA pathogenesis and demonstrate the reversible nature of brain damage after CPAP treatment. A further important contribution of neuroimaging is the possibility to early detect brain alterations in a subclinical condition, when neuropsychological symptoms are not yet manifest. Intervening in this temporal window with adequate CPAP treatment really is a great therapeutic opportunity. Nevertheless, future research should be performed on longitudinal studies and in larger OSA populations in order to better correlate clinical data and neuroimaging evidences as result of CPAP treatment.

References

1. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien: American Academy of Sleep Medicine; 2014.
2. Jackson ML, Howard ME, Barnes M. Cognition and daytime functioning in sleep-related breathing disorders. Prog Brain Res. 2011;190:53–68.
3. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev. 2017;34:70–81.
4. Baril AA, Carrier J, Lafrenière A, Warby S, Poirier J, Osorio RS, Ayas N, Dubé MP, Petit D, Gosselin N. Canadian sleep and circadian network biomarkers of dementia in obstructive sleep apnea. Sleep Med Rev. 2018;42:139–48.
5. Ferini-Strambi L, Marelli S, Galbiati A, Castronovo C. Effects of continuous positive airway pressure on cognition and neuroimaging data in sleep apnea. Int J Psychophysiol. 2013;89(2):203–12.
6. Stranks EK, Crowe SF. The cognitive effects of obstructive sleep apnea: an updated meta-analysis. Arch Clin Neuropsychol. 2016;31(2):186–93.
7. Lim DC, Pack AI. Obstructive sleep apnea and cognitive impairment: addressing the blood-brain barrier. Sleep Med Rev. 2014;18:35–48.
8. Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. J Clin Endocrinol Metab. 2005;90:4510–5.
9. Canessa N, Castronovo V, Cappa SF, Aloia MS, Marelli S, Falini A, Alemanno F, Ferini-Strambi L. Obstructive sleep apnea: brain structural changes

and neurocognitive function before and after treatment. Am J Respir Crit Care Med. 2011;183(10):1419–26.
10. Kylstra WA, Aaronson JA, Hofman WF, Schmand BA. Neuropsychological functioning after CPAP treatment in obstructive sleep apnea: a meta-analysis. Sleep Med Rev. 2013;17(5):341–7.
11. Joyeux-Faure M, Naegelé B, Pépin JL, Tamisier R, Lévy P, Launois SH. Continuous positive airway pressure treatment impact on memory processes in obstructive sleep apnea patients: a randomized sham-controlled trial. Sleep Med. 2016;24:44–50.
12. Jackson ML, McEvoy RD, Banks S, Barnes M. Neurobehavioral impairment and CPAP treatment response in mild-moderate obstructive sleep apneas. J Clin Sleep Med. 2018;14:47–56.
13. Zhou J, Camacho M, Tang X, Kushida CA. A review of neurocognitive function and obstructive sleep apnea with or without daytime sleepiness. Sleep Med. 2016;23:99–108.
14. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, Ancoli-Israel S, Stone KL. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA. 2011;306(6):613–9.
15. Osorio RS, Gumb T, Pirraglia E, Varga AW, Lu SE, Lim J, Wohlleber ME, Ducca EL, Koushyk V, Glodzik L, Mosconi L, Ayappa I, Rapoport DM, de Leon MJ. Alzheimer's disease neuroimaging initiative sleep-disordered breathing advances cognitive decline in the elderly. Neurology. 2015;84:1964–71.
16. Richards KC, Gooneratne N, Dicicco B, Hanlon A, Moelter S, Onen F, Wang Y, Sawyer A, Weaver T, Lozano A, Carter P, Johnson J. CPAP adherence may slow 1-year cognitive decline in older adults with mild cognitive impairment and apnea. J Am Geriatr Soc. 2019;67(3):558–64.
17. Troussière AC, Charley CM, Salleron J, Richard F, Delbeuck X, Derambure P, Pasquier F, Bombois S. Treatment of sleep apnoea syndrome decreases cognitive decline in patients with Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2014;85(12):1405–8.
18. Macey PM, Kumar R, Woo MA, Valladares EM, Yan-Go FL, Harper RM. Brain structural changes in obstructive sleep apnea. Sleep. 2008;31(7):967–77.
19. Aloia MS, Arnedt JT, Davis JD, Riggs RL, Byrd D. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. J Int Neuropsychol Soc. 2004;10(5):772–85.
20. Colrain IM, Bliwise D, DeCarli C, Carmelli D. The contribution of oxygen desaturation to the development of white matter hyperintensities in elderl male twins. Sleep. 2002;25:A3.
21. Del Brutto OH, Mera RM, Zambrano M, Castillo PR. Relationship between obstructive sleep apnea and neuroimaging signatures of cerebral small vessel disease in community-dwelling older adults. The Atahualpa Project. Sleep Med. 2017;37:10–2.
22. Sapin E, Peyron C, Roche F, Gay N, Carcenac C, Savasta M, Levy P, Dematteis M. Chronic intermittent hypoxia induces chronic low-grade neuroinflammation in the dorsal hippocampus of mice. Sleep. 2015;38(10):1537–46.
23. Gu XQ, Haddad GG. Decreased neuronal excitability in hippocampal neurons of mice exposed to cyclic hypoxia. J Appl Physiol. 2001;91(3):1245–50.
24. Owen JE, BenediktsdÓttir B, Gislason T, Robinson SR. Neuropathological investigation of cell layer thickness and myelination in the hippocampus of people with obstructive sleep apnea. Sleep. 2019;42(1)
25. Huang X, Tang S, Lyu X, Yang C, Chen X. Structural and functional brain alterations in obstructive sleep apnea: a multimodal meta-analysis. Sleep Med. 2019;54:195–204.
26. Song X, Roy B, Kang DW, Aysola RS, Macey PM, Woo MA, Yan-Go FL, Harper RM, Kumar R. Altered resting-state hippocampal and caudate functional networks in patients with obstructive sleep apnea. Brain Behav. 2018;8(6):e00994.
27. Yaouhi K, Bertran F, Clochon P, Mézenge F, Denise P, Foret J, Eustache F, Desgranges B. A combined neuropsychological and brain imaging study of obstructive sleep apnea. J Sleep Res. 2009;18(1):36–48.
28. Castronovo V, Scifo P, Castellano A, Aloia MS, Iadanza A, Marelli S, Cappa SF, Strambi LF, Falini A. White matter integrity in obstructive sleep apnea before and after treatment. Sleep. 2014;37(9):1465–75.
29. Maresky HS, Shpirer I, Klar MM, Levitt M, Sasson E, Tal S. Continuous positive airway pressure alters brain microstructure and perfusion patterns in patients with obstructive sleep apnea. Sleep Med. 2019;57:61–9.
30. Kim H, Joo EY, Suh S, Kim JH, Kim ST, Hong SB. Effects of long-term treatment on brain volume in patients with obstructive sleep apnea syndrome. Hum Brain Mapp. 2016;37(1):395–409.
31. O'Donoghue FJ, Wellard RM, Rochford PD, Dawson A, Barnes M, Ruehland WR, Jackson ML, Howard ME, Pierce RJ, Jackson GD. Magnetic resonance spectroscopy and neurocognitive dysfunction in obstructive sleep apnea before and after CPAP treatment. Sleep. 2012;35(1):41–8.

26 Advances in Positive Pressure Therapy and Noninvasive Ventilation in the Treatment of Sleep Disorders

William B. LeMaster, Armand Ryden, Melisa Chang, and Michelle Zeidler

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Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea–hypopnea index
APAP	Automatic positive airway pressure
ASV	Adaptive servo-ventilation
BNP	Brain natriuretic peptide
BPAP	Bilevel positive airway pressure
CAD	Coronary artery disease
CHF	Congestive heart failure
CKD	Chronic kidney disease
CMT	Conservative medical therapy
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CSA	Central sleep apnea
EF	Ejection fraction
EPAP	Expiratory positive airway pressure
mIBG	I-metaiodobenzylguanidine
NIV	Noninvasive ventilation
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PSG	Polysomnogram
SDB	Sleep-disordered breathing
T2D	Type 2 diabetes mellitus
VAPS	Volume-assured pressure support

26.1 Introduction

Positive airway pressure (PAP) devices have been commonly used for the treatment of sleep-disordered breathing (SDB) since the 1980s. Continuous positive airway pressure (CPAP) has been the treatment of choice for the most common type of SDB—obstructive sleep apnea (OSA). With the evolution and improvement of technology, newer modalities of portable devices such as automatic positive airway pressure (APAP) and various modalities of noninvasive ventilation (NIV) (e.g., bilevel, adaptive servo-ventilation, and volume-assured pressure support) have emerged to better treat various forms of sleep-disordered breathing (Fig. 26.1). The goal of this article is to discuss the recent updates in the use of PAP and the various NIV therapies

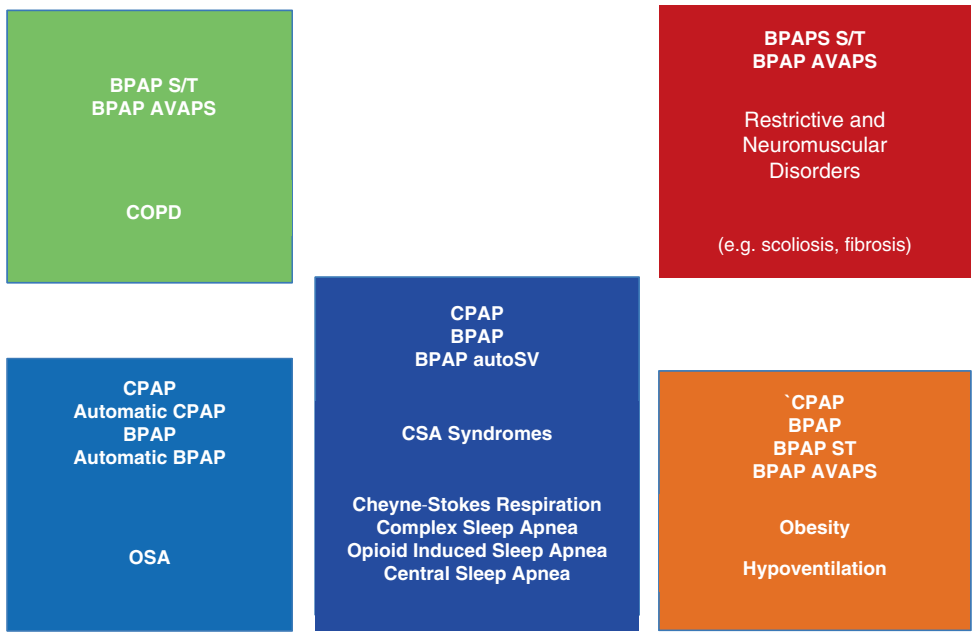

Fig. 26.1 Positive airway pressure and noninvasive ventilation modalities used for varied sleep disorders

in the treatment of SDB particularly with regard to cardiovascular and respiratory comorbidities. The focus will be on controlled trials and meta-analyses. This paper will be structured based on device modalities. Table 26.1 summarizes the key clinical trials over the last 2 years.

26.2 Methodology

We searched PubMeb for articles written in English and published between January 2017 and March 2019. We searched for different PAP and NIV modalities by name, different sleep disorders by

Table 26.1 Summary of Important Clinical Trials

Association of Positive Airway Pressure With Cardiovascular Events and Death in Adults With Sleep Apnea: A Systematic Review and Meta-analysis [8]
A systematic review and meta-analysis was performed to evaluate the incidence of acute coronary syndrome, stroke, vascular death, and death among pts on CPAP and ASV. 10 trials were included (9 of CPAP, 1 of ASV). There were 356 major cardiovascular events and 613 deaths. CPAP/ASV use did not decrease major adverse cardiovascular events, cardiovascular death, stroke, acute coronary syndrome, heart failure, or death from any cause.
Association of Positive Airway Pressure Prescription With Mortality in Patients With Obesity and Severe Obstructive Sleep Apnea: The Sleep Heart Health Study [9]
In a population based cohort study following obese patients with severe OSA for a mean of 11.1 years, the hazard ratio of all cause mortality for PAP therapy was 0.58 after propensity matching. This difference in mortality appears 6–7 years after initiation of PAP.
Autoadjusted versus Fixed CPAP for Obstructive Sleep Apnoea: a Multicentre, Randomised Equivalence Trial [13]
In a multicenter equivalence trial, patients were randomized to APAP or CPAP to evaluate changes in subjective and objective sleepiness from baseline to 2 years after treatment initiation. Reduction in sleepiness and blood pressure were similar between the two groups.
Fixed But Not Autoadjusting Positive Airway Pressure Attenuates the Time-dependent Decline in Glomerular Filtration Rate in Patients With OSA [14]
Knowing that patients with OSA have time-dependent decline in glomerular filtration rate, this study compared patients not on treatment, those with CPAP, and those with APAP. The decline in GFR was attenuated or absent only in the subgroup on fixed CPAP but not with APAP.
A Randomised Controlled Trial of CPAP versus Noninvasive Ventilation for Initial Treatment of Obesity Hypoventilation Syndrome [16]
A multicenter, parallel, double-blind trial for initial treatment of OHS with patients randomized to BPAP or CPAP for 3 months with primary outcome being frequency of treatment failure. 60 patients were randomized and 57 completed follow up. No difference in treatment failure was found between groups (hospital admission, persistent ventilatory failure, non-adherence). Adherence and morning $PaCO_2$ were similar at 3 months as were health related quality of life and sleepiness.
Long-term Clinical Effectiveness of Continuous Positive Airway Pressure Therapy versus Noninvasive Ventilation Therapy in Patients with Obesity Hypoventilation Syndrome: a Multicentre, Open-label, Randomised Controlled Trial [18]
In this multicenter open-label randomized controlled trial, patients with OHS and severe OSA were randomized to NIV or CPAP. Both modalities were found to have similar long term effectiveness at decreasing the number of hospitalization days per year.
Cardiovascular Outcomes With Minute Ventilation-Targeted Adaptive Servo-Ventilation Therapy in Heart Failure: The CAT-HF Trial [23]
The CAT-HF trial investigated whether ASV improved cardiovascular outcomes in hospitalized heart failure patients with moderate to severe OSA. 126 of 215 planned patients were randomized but enrollments stopped early after SERVE-HF resulted. Primary endpoints (death, cardiovascular hospitalization, and changes in 6-min walk distance) were unchanged at 6 months.

A review of the most impactful clinical trials and systematic reviews. *APAP* Automatic positive airway pressure, *ASV* Adaptive servo-ventilation, *BPAP* Bilevel positive airway pressure, *CPAP* Continuous positive airway pressure, *NIV* Noninvasive ventilation, *OHS* Obesity hypoventilation syndrome, *OSA* Obstructive sleep apnea, *PAP* Positive airway pressure

name, and combinations of each modality and disorder (e.g., CPAP, OSA, and CPAP + OSA). Based on this search, we recovered 3110 papers. We also reviewed the most recent society sleep guidelines with regard to positive pressure therapy for sleep disorders. We excluded papers that were not clinical trials or meta-analyses. Further articles which did not meet the stated criteria were included if they provided pivotal updates to the use of currently available NIV methodologies in sleep disorders or newer technologies not explicitly discussed in the clinical trials or guidelines.

26.3 Findings

26.3.1 Continuous Positive Airway Pressure (CPAP) and Automatic Positive Airway Pressure (APAP)

Continuous positive airway pressure provides a constant pressure during the entire breathing cycle, which acts as a pneumatic splint to maintain patency of the upper airway during sleep. APAP uses a proprietary algorithm to provide the lowest pressure needed to achieve patency of the upper airway within a pressure range prescribed by the treating physician. The American Academy of Sleep Medicine (AASM) recommends both CPAP and APAP for the initial treatment of OSA [1]. While CPAP was the initial mainstay therapy for OSA, many patients are now treated with APAP as first-line therapy. Since 2006 the AASM has published guidelines recommending the use of PAP for the treatment OSA in adults with excessive daytime sleepiness, impaired sleep-related quality of life, or comorbid hypertension [1]. The guidelines have since been updated to discuss the use of other treatment modalities such APAP, but the recommendation for PAP therapy over no therapy in individuals with moderate-to-severe obstructive sleep apnea remains constant based on published data. Treatment with CPAP and APAP results in a modest reduction in blood pressure and significantly improves sleepiness and quality of life in OSA patients. While there is strong data linking moderate-to-severe OSA to cardiovascular disease and metabolic disorders, to date, only observational data has shown an improvement in these disease outcomes with the use of PAP. Controlled randomized data showing an improvement in cardiovascular and metabolic disease outcomes in these patients is lacking, and additional large randomized studies are needed. Recent data has also elucidated the role of CPAP in the role of treating obesity hypoventilation syndrome (OHS).

26.3.2 Obstructive Sleep Apnea

26.3.2.1 Continuous Positive Airway Pressure for OSA

Hypertension and diastolic dysfunction are common among patients with sleep apnea, and the effect of CPAP on cardiovascular risk reduction has been a topic of significant investigation. One recent investigation randomized 244 patients with coronary artery disease (CAD) and non-sleepy OSA [defined as Apnea–Hypopnea Index (AHI) >15, and Epworth Sleepiness Scale (ESS) <10] to therapy with CPAP versus no CPAP and obtained echocardiograms at 3 and 12 months following randomization. In the 171 patients included in the final analysis, CPAP had no effect on echocardiographic parameters of diastolic dysfunction. However, a post hoc analysis did show significant association between CPAP usage >4 h/night and improvement in diastolic relaxation velocity at 12-month follow-up [2]. This suggests that nonadherence may be a factor in the negative outcome of the study. Hypertension and PAP therapy have also been evaluated at a more basic level. A study of 117 patients with OSA and resistant hypertension who were randomized to CPAP versus no CPAP showed that baseline aldosterone was higher in severe OSA than moderate OSA. After CPAP therapy, there was a trend toward reduction in aldosterone, which did not meet statistical significance [3]. A smaller study evaluated the effect of CPAP on brain natriuretic peptide (BNP) and troponin levels in 28 patients with moderate-to-severe OSA and/or significant nighttime hypoxemia. Subjects were randomized to CPAP or sham

CPAP for 8 weeks, each in a crossover design, with a 1-month washout period. Sleep studies were performed at the end of each 8-week treatment period, and blood samples were collected at 8PM, 3AM, and 8AM over the course of the sleep study. The authors found that CPAP lowered N-Terminal-pro-BNP significantly over the course of 8 weeks of therapy but a nonsignificant trend for lower Troponin-T levels as compared to sham CPAP was noted [4]. These studies continue to confirm that there is a strong physiological basis to argue that PAP therapy should have cardiovascular benefits; however, clinically significant outcomes are difficult to achieve in part because of difficulty with treatment adherence.

Type 2 diabetes mellitus (T2D) is also a common comorbid disorder among patients with OSA and is another avenue of investigation into the benefits of PAP therapy. Lam et al. randomized 64 diabetic patients with a new diagnosis of OSA to CPAP or no CPAP for 3 months. At the end of 3 months, there was no significant change in glycosylated hemoglobin, but there was a significant reduction in systolic and diastolic blood pressure in the CPAP group [5]. Another study evaluated 23 patients with OSA and T2D who were assigned to either CPAP or sham CPAP for 30 days. Adherence was similar in both groups, and they found that serum fructosamine (measure of glycemia over a 30-day period) decreased with active but not sham CPAP. Though mean serum blood glucose as measured by a continuous glucose monitor did not improve with active CPAP therapy, sham CPAP was associated with an increase in mean blood glucose [6].

There has also been an effort to evaluate the efficacy of PAP therapy in improving overall quality of life. Zhao et al. looked at the effects of CPAP use on health-related quality of life in individuals with high risk for cardiovascular disease and moderate-to-severe OSA by performing a parallel group randomized controlled trial of 169 participants assigned to conservative medical therapy (CMT) alone, CMT plus CPAP, CMT plus sham CPAP, and CMT plus CPAP plus motivational enhancement. The mixed effects linear regression analysis of the data showed that CPAP improved several domains of health-related quality of life including bodily pain, general health, physical functioning, and physical health summary score over 6–12 months follow-up. It also resulted in less daytime sleepiness [7].

Cardiovascular and all-cause mortality remain important topics of research in treatment of OSA. In 2017, a systematic review and meta-analysis were performed to evaluate the incidence of acute coronary syndrome, stroke, vascular death, and death among patients on CPAP and adaptive servo-ventilation (ASV). Ten trials were included (nine of CPAP, one of ASV). There were 356 major cardiovascular events and 613 deaths, but there was no significant reduction in major adverse cardiovascular events, cardiovascular death, or all-cause death with CPAP use. The authors also found that the same is true for stroke, acute coronary syndrome, and heart failure, concluding that PAP does not decrease the likelihood of death as compared to no treatment or sham treatment [8]. A recently published population-based cohort study evaluating the all-cause mortality of 392 patients with obesity and severe OSA showed conflicting results. In a recent analysis of the Sleep Heart Health Study, patients were followed for a mean of 11.1 years, and the hazard ratio of all-cause mortality for those on PAP therapy (81/392) was 0.58 after propensity matching. This difference in mortality appears 6–7 years after initiation of PAP [9]. This data differs from the aforementioned meta-analysis as only individuals with severe OSA were included in this analysis and the length of follow-up exceeds that seen in randomized studies.

Acknowledging that women are often underrepresented in trials of OSA and PAP therapy (80.6% of participants were male in the Sleep Heart Health Study, for instance), a multicenter randomized controlled clinical trial looking at 307 women diagnosed with moderate-to-severe OSA was performed. In this study subjects were randomized to CPAP or conservative treatment for 12 weeks. As compared to the conservative treatment group, women on CPAP had significantly greater decrease in diastolic blood pressure but a nonsignificant decrease in systolic and mean blood pressure. There was no difference in lipid profiles or blood sugar between groups [10].

PAP compliance remains the Achilles' heel of treatment of OSA, and additional work is needed to understand patterns of use within divergent groups of patients. Luyster et al. analyzed data from the RICCADSA trial and found that ongoing use of CPAP at 2 years was greater in patients with moderate-to-severe OSA who were sleepy (OSA and ESS>/= 10) when compared to those that were not sleepy (ESS < 10). The percentage of sleepy patients remaining on CPAP at 2 years was 77% when compared to 60% in the non-sleepy [11].

Based on the current published data on benefits and limitations of PAP therapy in treating OSA, the European Respiratory Society convened an ad hoc committee to review the challenges in treating OSA. The committee recommended that going forward, it will be important to further differentiate clinical and pathophysiologic phenotypes of OSA to tailor treatment. They suggested that severity thresholds should be revised given the discrepancy of events measured between polysomnogram (PSG) and home sleep apnea testing. They also stated that as AHI does not correlate well with outcomes, measures other than AHI should be considered in stratifying patients that would take into account the various clinical and pathophysiologic phenotypes [12].

26.3.2.2 Automatic Positive Airway Pressure vs. Continued Positive Airway Pressure for OSA

In a multicenter equivalence trial, 208 patients were randomized to APAP or CPAP to evaluate changes in subjective and objective sleepiness from baseline to 2 years after initiating treatment. In an intention-to-treat analysis, reduction in sleepiness and reduction in blood pressure were similar between both groups [13]. Another study looked at the effects of CPAP and APAP on GFR as patients with OSA experience a time-dependent decline in GFR. The study compared patients not on treatment, those using CPAP, and those using APAP. The decline in GFR was attenuated or absent only in the subgroup on fixed CPAP [14]. This study raises the question if APAP and fixed CPAP are equivalent in modulating OSA outcomes and will require additional investigation.

APAP has also recently been compared with CPAP in regard to efficacy of therapy in reducing obstructive events and in regard to sleep disruption. In a double-blind, randomized, crossover study, 61 patients with moderate-to-severe OSA underwent 2 full-night attended PSGs in random order with manually titrated CPAP or APAP (specifically the System One RemStar Auto A-Flex; ResMed, Australia). Fifty-one participants completed a titration PSG followed by 1 night of APAP therapy and 1 night of fixed CPAP in random order. The authors found that APAP therapy had similar efficacy to CPAP at a pressure determined by titration PSG at decreasing obstructive events during sleep, that the pressure adjustments made by the APAP machine had no negative effect on sleep architecture, and that the residual AHI measured by the APAP machine correlated well with the residual AHI measured by a PSG [15].

26.3.3 Hypoventilation

26.3.3.1 Continuous Positive Airway Pressure vs. Noninvasive Ventilation for Nocturnal Hypoventilation

Data regarding the efficacy of NIV compared with CPAP in nocturnal hypoventilation has been eagerly anticipated and recently published. Over the last 2 years, there have been several studies published which evaluated the use of PAP, as opposed to NIV, in patients with nocturnal hypoventilation syndromes such as OHS. One multicenter, parallel, double-blind trial randomized 60 subjects with newly diagnosed OHS to bilevel positive airway pressure (BPAP) or CPAP for 3 months and evaluated frequency of treatment failure defined as hospital admission, persistent ventilatory failure, or nonadherence. In the 57 subjects who completed follow-up, there was no difference in treatment failure rates between the two groups. Adherence to prescribed therapy and morning $PaCO_2$ levels was similar between the two groups at 3 months follow-up,

and there were no significant differences in health-related quality of life or sleepiness between the groups [16]. However, a secondary analysis of the Pickwick Project looked at echocardiographic changes over 2 months in 221 OHS patients randomized to NIV (volume-assured pressure support), CPAP, or lifestyle modification alone. They found that treatment with NIV but not CPAP lowered systolic pulmonary artery pressure and only NIV therapy decreased left ventricular hypertrophy and led to improvement in a 6-min walk distance [17].

Patients with combined OHS and OSA have also been evaluated with regard to the efficacy of CPAP vs. NIV (volume assured pressure support). A multicenter, open-label, randomized controlled trial evaluated 215 patients with both OHS and severe OSA. Over median follow-up of 5.4 years, the authors found that patients on NIV or CPAP had similar rates of hospitalization and no significant differences between groups in regard to secondary outcomes such as blood gas changes, pulmonary function changes, and changes in quality of life [18]. The authors concluded that CPAP may be a better first choice therapy for OHS/OSA patients given the lower complexity and cost of CPAP compared with NIV. Another, much smaller prospective study, of 15 stable patients with OHS with moderate-to-severe concomitant OSA on NIV for at least 2 months showed no difference in diurnal blood gases, nocturnal oximetry and capnometry, mean compliance, AHI, measures of quality of life, and sleep after switching to CPAP for more than a month. Furthermore, 80% of subjects preferred CPAP over NIV [19].

26.3.4 Adaptive Servo-Ventilation (ASV)

26.3.4.1 Adaptive Servo-Ventilation and Heart Failure

ASV is a form of positive airway ventilation that monitors the patient's respiratory cycle and provides positive airway pressure to treat obstructive sleep apnea as well as pressure support and a backup rate to treat central sleep apneas. This modality is used to treat central sleep apnea (CSA) disorders such as CSA, complex sleep apnea, and periodic breathing. ASV has been the subject of scrutiny since the SERVE-HF trial (September 2015, *The New England Journal of Medicine*) concluded all-cause and cardiovascular mortality were higher among patients with CSA in the setting of congestive heart failure and with reduced ejection fraction (EF) who were treated with ASV therapy. In response to these findings, the AASM updated the guidelines for treatment of CSA in 2016. The guidelines now recommend the use of ASV targeted to normalize AHI for the treatment of CSA related to congestive heart failure (CHF) only if left ventricular ejection fraction is greater than 45% [20]. The reason for the increased all-cause mortality in the SERVE-HF study remains unclear. Knitter et al. sought to investigate the mechanisms by which ASV therapy may have increased all-cause mortality by comparing four different ASV devices (including the S7 device; Resmed, Australia, used during SERVE-HF trial). In this study 14 patients underwent PSG 4 nights in a row, once with each device. Nightly AHI was not different among devices, but the S7 device resulted in greater minute ventilation, especially while individuals were awake. The authors postulate that hypocapnia resulting from the increased minute ventilation may have led to hypokalemia from intracellular shifts which may have led to a prolonged QT and a higher incidence of potentially fatal arrhythmias [21]. An on-treatment analysis of the SERVE-HF cohort was also performed to better understand the increased all-cause mortality in the intervention (ASV) group. This study found that patients randomized to ASV who crossed over to the control group (optimal medical therapy for heart failure) were at higher risk of cardiovascular death than controls, while control patients who crossed over to ASV therapy showed a trend toward lower risk of cardiovascular death than those randomized to ASV. Cardiovascular risk did not increase as ASV usage increased. Overall, the on-treatment analysis corroborated the intention-to-treat analysis which showed increased all-cause and cardiovascular mortality in those using ASV

[22]. The CAT-HF trial was contemporary with the SERVE-HF trial and investigated whether ASV improved cardiovascular outcomes in hospitalized heart failure patients (preserved or reduced EF) with moderate-to-severe sleep apnea. Subjects were randomized to optimal medical therapy alone or optimal medical therapy plus ASV therapy, and 126 of 215 planned patients were randomized before enrollment stopped early after SERVE-HF resulted. AHI decreased significantly in the treatment group. The primary endpoints (death, cardiovascular hospitalization, and percentage changes in 6-min walk distance) were not significantly different between the two groups at 6 months [23].

Despite the concerns about the potential mortality with ASV use in this patient population, a number of studies showed that ASV continues to have some benefits. One retrospective study of 44 patients with severe heart failure initiated on ASV compared the hospitalization frequency of these patients in the 12 months before and 12 months after ASV initiation. They found a significant decrease in the number of hospitalizations after initiation of ASV [24]. A small (35 patients) prospective sub-study of the CAT-HF trial randomized patients with sleep apnea and pacemakers or implanted defibrillators to either optimal medical therapy or optimal medical therapy plus ASV. They found that ASV reduced the incidence of atrial fibrillation, ventricular fibrillation, and ventricular tachycardia as compared to optimal medical therapy alone [25]. Another analysis of the CAT-HF trial looked at a group of patients who underwent echocardiography at baseline and on follow-up 6 months later. Of the 126 enrolled, 95 subjects had echocardiograms available for analysis. This analysis found that left ventricle remodeling was seen equally in both the control group and the ASV group but that there were reductions in left atrial volume in the ASV group suggesting it may help with diastolic function [26]. In response to the SERVE-HF trial, a prospective observational study to evaluate tolerance of ASV discontinuation was performed. Fourteen patients with ejection fraction less than 45% with median 68 months of ASV machine use were asked to stop ASV treatment. In this group, AHI increased significantly, and quality of life decreased. The authors found no change in NYHA functional class, but patients reported increased dyspnea, reduced concentration, and reduced memory after discontinuation. There were no objective changes in ejection fraction, heart rhythm data, or physical capacity [27]. In another study, 35 patients with frequent hospitalization for congestive heart failure were initiated on ASV treatment for 12 months to evaluate the cost-effectiveness of the therapy. The authors found significant decreases in NYHA class, BNP, left atrial size, and mitral regurgitation after 12 months of ASV therapy. Hospitalization frequency and medical cost per patient both decreased [28]. D'Elia looked at the effect of ASV therapy on ten patients admitted for acute heart failure exacerbation with a history of SDB. Half of the patients received standard care, and half received standard care plus ASV therapy. The authors found that patients on ASV therapy had a reduced AHI, improved diastolic function, improved RV function, and decreased BNP levels [29]. These studies should be interpreted with caution since there were many smaller studies prior to the SERVE-HF trial showing benefits for ASV in quality-of-life measures and surrogate markers.

Additional studies have evaluated patients for functional and sympathetic changes after ASV therapy. Tokuda et al. performed extensive evaluation on nine heart failure patients both before and 6 months after starting ASV treatment including BNP levels, echocardiogram, C-hydroxyephedrine positron emission tomography (HED/PET) (a marker of presynaptic function), and I-metaiodobenzylguanidine (mIBG) scan (a means of evaluating cardiac sympathetic nerve function). Data analysis showed reduced AHI and lower BNP concentrations after 6 months of ASV therapy. Based on HED/PET and mIBG, ASV might improve cardiac sympathetic nervous function as well [30]. Another study evaluated 31 patients with Cheyne–Stokes respirations or CSA in patients with an ejection fraction of less than or equal to 40%. Subjects were randomized to either ASV or conservative therapy for 6 months. mIBG and Tc-Sestamibi scans were performed to assess cardiac sympathetic nerve activity and cardiac

function. The ASV group had improved AHI, improved cardiac sympathetic nerve activity (based off of mIBG data), increased ejection fraction, and decreased functional limitations after 6 months of ASV therapy as compared to the control group [31].

Further work has been done to assess what factors make ASV more versus less effective. Potential predictors of ASV effectiveness were evaluated using data from ASV titrations as well as compliance downloads. Markers of reduced ASV clinical efficacy were (1) an arousal index which markedly exceeded the respiratory event index during positive pressure titration; (2) persistent pressure cycling (i.e., changing pressure support rather than stable levels of pressure support) during long-term ASV therapy; (3) the ASV-associated pressure cycling induced arousals, sleep fragmentation, and blood pressure surges; and (4) elevated ratios of 95th percentile to median tidal volume, minute ventilation, and respiratory rate were associated with pressure cycling [32]. This provides some insight as to why some patients do not have a good clinical response to ASV therapy.

26.3.5 Bilevel Positive Airway Pressure (BPAP)

AASM guidelines recommend BPAP as an option for treatment in both OSA and CSA related to CHF in patients who do not respond to other modalities (CPAP, ASV, oxygen therapy) [1, 20]. The latest AASM guidelines on treatment of chronic alveolar hypoventilation syndromes (central respiratory control disturbances, restrictive thoracic disorders, neuromuscular disorders, and obesity hypoventilation syndrome) were published in 2010 and recommend the use of NIV to prevent worsening hypoventilation during sleep [33]. BPAP is the most common type of NIV prescribed for this indication. In September 2018, a systematic review was published which evaluated the efficacy of BPAP for treatment of OHS versus lifestyle counseling, CPAP therapy, and average volume-assured pressure support (VAPS) therapy. BPAP was superior to lifestyle counseling in improving $PaCO_2$, PaO_2, HCO_3, percentage of total sleep time, ESS, and Functional Outcomes of Sleep Questionnaire but performed similarly to both CPAP and VAPS [34].

26.3.6 Volume-Assured Pressure Support (VAPS)

VAPS is a mode of bilevel positive pressure ventilation which seeks to target a designated tidal volume with each breath by changing the inspiratory positive airway pressure based on the tidal volume generated by the previous breaths. In a recent meta-analysis of 8 trials (64 patients with chronic obstructive pulmonary disease (COPD) and 61 patients with OHS), VAPS was compared to BPAP with regard to parameters of gas exchange, efficiency of sleep, and compliance. The authors found that there was no difference between the two modalities in blood gas measurements of $PaCO_2$ and PaO_2, sleep efficiency defined as the percentage of time in bed spent sleeping, or compliance as measured on a scale from 0 (lack of symptoms and best comfort) to 100 (worst symptoms and lack of comfort) in patients with chronic respiratory failure [35].

26.3.7 Emerging Technologies in Noninvasive Ventilation

Newer modes of NIV therapy have been developed as well, one being auto-trilevel ventilation which allows for adjustments in expiratory positive airway pressure (EPAP) (Prisma25ST, Weinmann Inc., Germany). In one randomized, double-blind, crossover study of 25 patients with chronic hypoventilation and OSA, VAPS with fixed EPAP was compared to VAPS with auto-adjusting EPAP to ensure upper airway patency (AutoEPAP) over 2 nights of attended PSG. The study showed AutoEPAP was noninferior to fixed EPAP at improving AHI [36]. A different trilevel mode of ventilation has recently been explored. In this instance there are two EPAP pressures with a lower pressure at the beginning of exhalation to facilitate CO_2 removal and a higher EPAP and the end of expiration to better stabilize the airway. In one study,

such an auto-trilevel ventilation was compared to BPAP in patients with combined OHS and moderate-to-severe OSA. Twenty-three patients used three different modes of ventilation over the course of 3 days—BPAP with EPAP set at a level which stopped snoring (mode 1), BPAP with EPAP set 3 cmH_2O higher than the first group (mode 2), and BPAP with auto-adjusting EPAP to ensure upper airway patency (mode 3, auto-trilevel ventilation). All modalities improved oxygenation and sleep efficiency. Auto-trilevel ventilation resulted in the lowest arousal index, lowest ESS, and highest sleep efficiency. It also resulted in a significantly lower $PaCO_2$ as compared to mode 2 [37]. Another study evaluated the efficacy of auto-trilevel PAP in patients with both OSA and COPD with hypercapnia. Thirty-two patients with overlap OSA and hypercapnia were evaluated using the same 3 modes of ventilation described in the previous trial with a 2-night washout period in between. The results were similar to those among patients with combined OHS and OSA. Auto-trilevel PAP resulted in the lowest arousal index, daytime ESS, and highest sleep efficiency. AHI was lower and SpO_2 higher in both modes 2 and 3. There was no difference in morning $PaCO_2$ [38].

26.4 Final Conclusions

Table 26.2 summarizes conclusions and future perspectives of this paper.

Learning Points

1. CPAP therapy for OSA may have clinical benefits beyond reduction of daytime sleepiness and improvement in quality of life. It may also help with cardiovascular risk, improvement in metabolic disease, and prevention of kidney disease progression in some populations.
2. CPAP therapy for OSA has been shown to improve health parameters such as bodily pain, general health quality of life, and physical functioning as compared to conservative medical therapy.
3. For patients with obesity hypoventilation or mixed obesity hypoventilation and OSA, CPAP therapy may be of similar clinical efficacy to BPAP.
4. In patients with obesity and severe OSA, PAP therapy significantly decreased all-cause mortality, and the effect appears between 6 and 7 years after initiation of therapy in an observational study.

Table 26.2 Conclusions and Future Perspectives

Main Conclusions
• PAP therapy for sleep apnea may have benefits beyond improvement in daytime sleepiness. It may be helpful to prevent or treat cardiovascular disease, metabolic disorders and renal disease and may decrease mortality in obese patients.
• CPAP may be used as first line of therapy in patients with obesity hypoventilation or mixed obesity hypoventilation and OSA as it may be of similar efficacy to BPAP.
• New technologies continue to develop and offer new modalities of ventilation that may improve compliance.
Future perspective
• Further research is necessary to elucidate the utility of NIV in patients with heart failure with reduced EF and central sleep apnea.
• Large prospective randomized trials to evaluate the benefits of PAP and NIV for the treatment or prevention of co-morbid conditions in patients with SDB are necessary.
• Large trials evaluating emerging modalities for treatment of OSA and hypoventilation need to be evaluated for efficacy in comparison to currently available modalities.

Main conclusions and future perspectives for NIV in the treatment of sleep disorders. *ASV* Adaptive servo-ventilation, *BPAP* Bilevel positive airway pressure, *CPAP* Continuous positive airway pressure, *NIV* Noninvasive ventilation, *OSA* Obstructive sleep apnea, *PAP* Positive airway pressure, *SDB* Sleep disordered breathing

Critical Points

1. The reason that ASV increased mortality among patients with heart failure and SDB remains unclear, though it may be related to increased minute ventilation associated with the particular device used during the SERVE-HF study.
2. Discontinuation of ASV in patients with SDB and heart failure is associated with subjectively decreased quality of life but no worsening in objective measures of physical capacity or echocardiographic parameters.
3. In meta-analyses, CPAP and ASV did not decrease the incidence of cardiovascular events, cardiovascular death, stroke, heart failure, or death from any cause.
4. Auto-trilevel ventilation is a new ventilation modality with two EPAP pressures—a lower pressure at the beginning of exhalation to facilitate CO_2 removal and a higher EPAP and the end of expiration to better stabilize the airway. This modality shows promise of improving nighttime sleep and daytime sleepiness.

26.5 Summary

Recent research in the treatment of sleep disorders with PAP and NIV has looked at the benefits of therapy beyond the treatment of daytime sleepiness. While observational data suggests decreased all-cause mortality in patient with severe OSA treated with PAP, randomized controlled data is still lacking. The jury remains out on the effect of PAP on cardiovascular risk and metabolic disorders in patients with OSA, and large randomized studies are needed. Recent data suggests that PAP is as beneficial as NIV for the treatment of OHS with or without OSA. In light of the results of the SERVE-HF trial in 2015, a great deal of research is ongoing to elucidate the role of NIV in patients with concomitant heart failure and central sleep apnea. As well, new modes of ventilation offer promise for improved sleep parameters and compliance.

References

1. Patil SP, Ayappa IA, Caples SM, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an American academy of sleep medicine systematic review, meta-analysis, and grade assessment. J Clin Sleep. 2019;15(2):301–34.
2. Glantz H, Johansson MC, Thunström E, et al. Effect of CPAP on diastolic function in coronary artery disease patients with nonsleepy obstructive sleep apnea: a randomized controlled trial. Int J Cardiol. 2017;241:12–8.
3. de Souza F, Muxfeldt ES, Margallo V, et al. Effects of continuous positive airway pressure treatment on aldosterone excretion in patients with obstructive sleep apnoea and resistant hypertension: a randomized controlled trial. J Hypertens. 2017;35(4):837–44.
4. Chang Y-S, Yee BJ, Hoyos CM, et al. The effects of continuous positive airway pressure therapy on troponin-T and N-terminal pro B-type natriuretic peptide in patients with obstructive sleep apnoea: a randomised controlled trial. Sleep Med. 2017;39:8–13.
5. Lam JCM, Lai AYK, Tam TCC, et al. CPAP therapy for patients with sleep apnea and type 2 diabetes mellitus improves control of blood pressure. Sleep Breath. 2017;21(2):377–86.
6. Morariu EM, Chasens ER, Strollo PJ, et al. Effect of continuous positive airway pressure (CPAP) on glycemic control and variability in type 2 diabetes. Sleep Breath. 2017;21(1):145–7.
7. Zhao YY, Wang R, Gleason KJ, et al. Effect of continuous positive airway pressure treatment on health-related quality of life and sleepiness in high cardiovascular risk individuals with sleep apnea: Best Apnea Interventions for Research (BestAIR) trial. Sleep. 2017; 40(4).
8. Yu J, Zhou Z, McEvoy RD, et al. Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea: a systematic review and meta-analysis. JAMA. 2017;318(2):156–66.
9. Lisan Q, Van Sloten T, Marques Vidal P, et al. Association of positive airway pressure prescription with mortality in patients with obesity and severe obstructive sleep apnea: the sleep heart health study. JAMA Otolaryngol Head Neck Surg. 2019;145(6):509–15.
10. Campos-Rodriguez F, Gonzalez-Martinez M, Sanchez-Armengol A, et al. Effect of continuous positive airway pressure on blood pressure and metabolic profile in women with sleep apnoea. Eur Respir J. 2017; 50(2).
11. Luyster FS, Strollo PJ, Thunström E, et al. Long-term use of continuous positive airway pressure therapy in coronary artery disease patients with nonsleepy obstructive sleep apnea. Clin Cardiol. 2017;40(12):1297–302.

12. Randerath W, Bassetti CL, Bonsignore MR, et al. Challenges and perspectives in obstructive sleep apnoea: report by an ad hoc working group of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society. Eur Respir J. 2018;52(3).
13. Bloch KE, Huber F, Furian M, et al. Autoadjusted versus fixed CPAP for obstructive sleep apnoea: a multicentre, randomised equivalence trial. Thorax. 2018;73(2):174–84.
14. Marrone O, Cibella F, Pépin J-L, et al. Fixed but not autoadjusting positive airway pressure attenuates the time-dependent decline in glomerular filtration rate in patients with OSA. Chest. 2018;154(2):326–34.
15. Gagnadoux F, Pevernagie D, Jennum P, et al. Validation of the system one RemStar auto A-flex for obstructive sleep apnea treatment and detection of residual apnea-hypopnea index: a European randomized trial. J Clin Sleep Med. 2017;13(2):283–90.
16. Howard ME, Piper AJ, Stevens B, et al. A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax. 2017;72(5):437–44.
17. Corral J, Mogollon MV, Sánchez-Quiroga M-Á, et al. Echocardiographic changes with non-invasive ventilation and CPAP in obesity hypoventilation syndrome. Thorax. 2018;73(4):361–8.
18. Masa JF, Mokhlesi B, Benítez I, et al. Long-term clinical effectiveness of continuous positive airway pressure therapy versus non-invasive ventilation therapy in patients with obesity hypoventilation syndrome: a multicentre, open-label, randomised controlled trial. Lancet. 2019;393(10182):1721–32.
19. Orfanos S, Jaffuel D, Perrin C, et al. Switch of noninvasive ventilation (NIV) to continuous positive airway pressure (CPAP) in patients with obesity hypoventilation syndrome: a pilot study. BMC Pulm Med. 2017;17(1):50.
20. Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. 2012;35(1):17–40.
21. Knitter J, Bailey OF, Poongkunran C, et al. Comparison of physiological performance of four adaptive servo ventilation devices in patients with complex sleep apnea. Am J Respir Crit Care Med. 2019;199(7):925–8.
22. Woehrle H, Cowie MR, Eulenburg C, et al. Adaptive servo ventilation for central sleep apnoea in heart failure: SERVE-HF on-treatment analysis. Eur Respir J. 2017;50(2).
23. O'Connor CM, Whellan DJ, Fiuzat M, et al. Cardiovascular outcomes with minute ventilation-targeted adaptive servo-ventilation therapy in heart failure: the CAT-HF trial. J Am Coll Cardiol. 2017;69(12):1577–87.
24. Yoshida M, Ando S-I, Kodama K, et al. Adaptive servo-ventilation therapy reduces hospitalization rate in patients with severe heart failure. Int J Cardiol. 2017;238:173–6.
25. Piccini JP, Pokorney SD, Anstrom KJ, et al. Adaptive servo-ventilation reduces atrial fibrillation burden in patients with heart failure and sleep apnea. Heart Rhythm. 2019;16(1):91–7.
26. Daubert MA, Whellan DJ, Woehrle H, et al. Treatment of sleep-disordered breathing in heart failure impacts cardiac remodeling: insights from the CAT-HF Trial. Am Heart J. 2018;201:40–8.
27. Hetland A, Lerum TV, Haugaa KH, et al. Patients with Cheyne–Stokes respiration and heart failure: patient tolerance after three-month discontinuation of treatment with adaptive servo-ventilation. Heart Vessels. 2017;32(8):909–15.
28. Hiasa G, Okayama H, Hosokawa S, et al. Beneficial effects of adaptive servo-ventilation therapy on readmission and medical costs in patients with chronic heart failure. Heart Vessels. 2018;33(8):859–65.
29. D'Elia E, Ferrero P, Vittori C, et al. Beneficial effects of adaptive servo-ventilation on natriuretic peptides and diastolic function in acute heart failure patients with preserved ejection fraction and sleep-disordered breathing. Sleep Breath. 2019;23(1):287–91.
30. Tokuda Y, Sakakibara M, Yoshinaga K, et al. Early therapeutic effects of adaptive servo-ventilation on cardiac sympathetic nervous function in patients with heart failure evaluated using a combination of 11C-HED PET and 123I-MIBG SPECT. J Nucl Cardiol. 2019;26(4):1079–89.
31. Toyama T, Hoshizaki H, Kasama S, et al. Adaptive servo-ventilation therapy improves cardiac sympathetic nerve activity, cardiac function, exercise capacity, and symptom in patients with chronic heart failure and Cheyne-Stokes respiration. J Nucl Cardiol. 2017;24(6):1926–37.
32. Gunn S, Naik S, Bianchi MT, et al. Estimation of adaptive ventilation success and failure using polysomnogram and outpatient therapy biomarkers. Sleep. 2018;41(9).
33. Berry RB, Chediak A, Brown LK, et al. Best clinical practices for the sleep center adjustment of noninvasive positive pressure ventilation (NPPV) in stable chronic alveolar hypoventilation syndromes. J Clin Sleep Med. 2010;6(5):491–509.
34. Royer CP, Schweiger C, Manica D, et al. Efficacy of bilevel ventilatory support in the treatment of stable patients with obesity hypoventilation syndrome: systematic review and meta-analysis. Sleep Med. 2019;53:153–64.
35. Huang XA, Du YP, Li LX, et al. Comparing the effects and compliance between volume-assured and pressure support non-invasive ventilation in patients with chronic respiratory failure. Clin Respir J. 2019;13(5):289–98.

36. McArdle N, Rea C, King S, et al. Treating chronic hypoventilation with automatic adjustable versus fixed EPAP intelligent volume-assured positive airway pressure support (iVAPS): a randomized controlled trial. Sleep. 2017;40(10).
37. Zou C, Sheng W, Huai D, et al. Comparison between auto-trilevel and bilevel positive airway pressure ventilation for treatment of patients with concurrent obesity hypoventilation syndrome and obstructive sleep apnea syndrome. Sleep Breath. 2019;23(3):735–40.
38. Su M, Huai D, Cao J, et al. Auto-trilevel versus bilevel positive airway pressure ventilation for hypercapnic overlap syndrome patients. Sleep Breath. 2018;22(1):65–70.

Central Sleep Apnoea Treatment: When and How?

27

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27.1 Introduction

Central breathing disorders (CBD) are a complex entity that present as central sleep apnoeas (CSA) and hypopnoeas, periodic breathing with apnoea or irregular breathing. Central sleep apnoea is defined by a cessation or decrease of airflow without respiratory effort, in contrast with obstructive sleep apnoea (OSA). The condition can be primary (idiopathic CSA) or secondary. Secondary CSA can arise, for example, in association with medical disorders (such as heart failure (HF), stroke, end-stage renal disease (ESRD)), drug/substance usage or high altitude. Furthermore, it can also appear in patients under positive airway pressure treatment.

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Pathophysiology of CSA is complex and incompletely understood. There is growing evidence that CSA can be related to unstable breathing, caused by high loop gain or decreased output from central neurons leading to hyperventilatory or hypoventilatory disturbances, respectively. For instance, Cheyne–Stokes respiration (CSR) is a form of periodic breathing commonly observed in patients with chronic heart failure (CHF). It is characterized by oscillations of ventilation between central apnoeas and hyperpnoea with a crescendo–decrescendo pattern. It remains unclear if CSR-CSA is simply a manifestation of worsening CHF, a cause of HF progression or a compensatory mechanism to maintain stroke volume (SV) in severe HF. Some characteristics, such as the cycle length and pattern (positive or negative—if end-expiratory lung volume (EELV) is above or below the functional residual capacity

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(FRC), respectively) may have some prognosis implications in CHF [1].

Full polysomnography (PSG) with oesophageal pressure measurement is the gold standard to diagnose CSA. However, because it is an invasive measure, different surrogates of respiration and/or respiratory effort are used in routine practice, including flow, thoracoabdominal movement, pulse transit time (PTT), electromyography (EMG) of the diaphragmatic muscle, suprasternal pressure, jaw movement and forehead venous pressure. To assess hypoventilation during routine PSG, transcutaneous carbon dioxide or end-tidal carbon dioxide is used.

Untreated CSA disrupts sleep which may lead to daytime symptoms that include excessive sleepiness, lack of concentration, morning headaches and increased risk of accidents. The goals of therapy for patients with CSA are to normalize sleep-related breathing patterns and oxygen desaturation, thereby improving symptoms and quality of sleep.

Most studies regarding treatment were conducted in HF patients, and the results were posteriorly extrapolated for the other causes of CSA. There are many treatment strategies described, such as optimizing the underlying condition for CSA or removal of the offending medication/substance, positive airway pressure treatment, supplemental oxygen or respiration stimulants. Regarding positive airway pressure (PAP), there have been two major clinical trials in the last years that have marked the course of treatment of CSA: CanPAP (Canadian Positive Airway Pressure for Heart failure and Sleep apnoea) [2] for continuous positive airway pressure (CPAP) therapy and SERVE-HF (Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo-Ventilation in Patients with Heart Failure) [3] for adaptive servo-ventilation (ASV). In CanPAP, patients with CSA associated with heart failure—mean apnoea–hypopnoea index (AHI) of 40 events per hour and mean left ventricular ejection fraction (LVEF) of 24%—were randomly assigned to receive treatment with CPAP and without CPAP and followed for 2 years. The group of patients treated with CPAP had superior improvement in the AHI, LVEF, mean nocturnal oxygen saturation and exercise capacity. However, there were no differences in quality of life, transplant-free survival or number of hospitalizations [2]. Additionally, the increased caution raised when considering the use of ASV in patients with heart failure is based on results of SERVE-HF, a multicentre, open-label trial that randomly assigned patients with moderate-to-severe predominant CSA and symptomatic heart failure to ASV plus standard medical therapy or medical therapy alone. However, it showed a significant increase in all-cause and cardiovascular mortality in the ASV group [3].

Despite the intense research in CBD field, many questions remain open, and treatment is still suboptimal, perhaps owing due to its etiological and pathophysiological heterogeneity. Consequently, we aimed to review recent evidence regarding patient selection and treatment options in CSA (Table 27.1).

27.2 Methods

The literature research was performed in the electronic data sources MEDLINE/PubMed, PubMed Central® (PMC), through a combination of descriptors from January 2016 to March 2019. The descriptors chosen to use together were "central sleep apnoea" *or* "sleep disordered breathing" *or* "central breathing disturbances" *or* "central disordered breathing" *or* "central apnoea" *and* "treatment". Articles from hand search of relevant papers and screening of references were included.

The main inclusion criteria were articles published in English; data on human subjects; subjects older than 18 years old; not being letters, guidelines or case reports; and individuals with confirmed diagnosis of central sleep apnoea.

Two independent researchers read the titles and abstracts of each preselected articles, separately identifying the ones that met the inclusion and exclusion criteria. After this stage, each researcher read the complete articles that respected the criteria and selected only those compatible with the aim of the review.

Table 27.1 Main studies published in the last 3 years regarding central sleep apnoea treatment

Author	Design	vPopulation	Results	Main conclusion/future perspective
Heart failure with reduced ejection fraction				
Oldenburg O, et al., 2018 [4]	Prospective registry Intervention: investigate whether treatment of CSA with ASV improved survival in HFrEF patients	550 Patients with CSA (AHI ≥15/h) and HFrEF ASV group: 224 patients; mean LVEF 31.3 ± 7.8% Control group: 326 patients; mean LVEF 28.0 ± 8.0%	Patient reported NYHA functional class improved in the ASV group, but LVEF, 6MWD, natriuretic peptides and blood gases remained unchanged. 109 (48.7%) ASV-treated patients and 191 (58.6%) controls died (adjusted Cox modelling hazard ratio (HR) of 0.95, 95% confidence interval (CI) 0.68–1.24; $p = 0.740$); older age, lower LVEF, impaired renal function, low sodium concentration and nocturnal hypoxemia were significant predictors of mortality.	Long-term ASV treatment of predominant CSA in HFrEF patients included in our registry had no statistically significant effect on survival
Woehrle H, et al., 2017 [5]	Multicentre, randomized, parallel-group trial (on-treatment analyses of SERVE-HF) Intervention: Effect of ASV in CSA in HFrEF (group ASV vs. group control)	1325 Patients with HFrEF and CSA (AHI ≥10/h) ASV group: 666 patients; mean LVEF 32.2 ± 7.9% Control group: 659 patients; mean LVEF: 32.5 ± 8.0%	Increased cardiovascular death hazard ratios during ASV usage periods, slightly lower than those in the SERVE-HF intention-to-treat analysis (1.27 (95% CI 1.00–1.62); $p = 0.051$ vs. 1.37 (95% CI 1.10–1.69); $p = 0.004$). Cardiovascular risk did not increase as nightly ASV usage increased	On-treatment analysis showed similar results to the SERVE-HF intention-to-treat analysis, with an increased risk of cardiovascular death in heart failure with reduced ejection fraction patients with predominant central sleep apnoea treated with ASV
Cowie M, et al., 2017 [6]	Multicentre, randomized, parallel-group trial—subanalysis of SERVE-HF Intervention: Evaluate effects of ASV, including assessment of changes in left ventricular function, ventricular remodelling and cardiac, renal and inflammatory biomarkers	312 Patients with HFrEF and CSA (AHI ≥10/h) ASV group: 159 patients; mean LVEF 32.2 ± 8.3% Controls group: 153 patients; mean LVEF 33.8 ± 8.1%	No change between groups in LVEF, left ventricular dimensions, wall thickness, diastolic function or right ventricular dimensions and ejection fraction (by echocardiography or cMRI), plasma N-terminal pro B-type natriuretic peptide, renal or inflammatory markers at 12 months after ASV	In patients with HFrEF and CSA, addition of ASV to guideline-based medical management had no statistically significant effect on cardiac structure and function or on cardiac biomarkers, renal function and systemic inflammation over a 12-month period
Fox H, et al., 2017 [7]	Observational, retrospective Intervention: long-term effects of PAP therapy on pulmonary function, including respiratory muscle strength	350 Patients with stable HFrEF with SDB (AHI ≥15, 58% with CSA) PAP group: 231 patients; mean LVEF 34.2 ± 7.5% Control group: 119 patients; mean LVEF 34.5 ± 7.9%	Inspiratory vital capacity, 3.3 ± 0.9 vs. 3.2 ± 0.8 L; forced expiratory volume in 1 s, 2.5 ± 0.7 vs. 2.4 ± 0.7 L; lung diffusion capacity, 6.2 ± 1.9 vs. 5.9 ± 1.8 mmol/min/kPa	PAP therapy had no negative nor positive impact on lung function, including respiratory muscle strength, in stable HFrEF patients with SDB

(continued)

Table 27.1 (continued)

Author	Design	Population	Results	Main conclusion/future perspective
Heart failure with preserved ejection fraction				
Heider K, et al., 2018 [8]	Retrospective, bicentric study Intervention: Changes in sleep fragmentation and sleep quality in patients with HFpEF treated with ASV for treatment of emergent central sleep apnoea (TECSA) or CSA	114 Patients with HFpEF and SDB TECSA: 60 patients CSA: 54 patients Mean LVEF: TECSA, 57 ± 9%; CSA, 55 ± 8%	In both groups ASV therapy led to a significant reduction in ΔAHI (−43 ± 21 vs. −47 ± 22/h), Δarousal index (−11 ± 15, vs. −11 ± 21/h;) and longer-stage N3 and REM sleep (ΔN3, 8 ± 11 vs. 9 ± 13%; ΔREM 7 ± 9 vs. 3 ± 8%) Increase in sleep efficiency only in TECSA group (ΔSE, 10 ± 19 vs. 1 ± 18%, $p = 0.019$)	In patients with HFpEF, whose TECSA and CSA were treated with ASV, a significant reduction of AHI and arousal index as well as an increase of N3 and REM sleep was observed
Heart failure in acute/hospitalized setting				
Daubert MA, et al., 2018 [9]	Randomized, controlled, multicentre trial—a subanalysis of CAT-HF trial Intervention: patients hospitalized with HF and moderate-to-severe sleep apnoea were randomized to ASV plus optimized medical therapy (OMT) or OMT alone	95 HF hospitalized patients (HFpEF and HFrEF) with SDB (AHI ≥15/h) ASV + OMT group: 40 patients; CSA 27(77.1%); mean LVEF 25.9 ± 10.8%; OMT group: 37 patients; CSA 28 (84.9%); mean LVEF 28.4 ± 9.5%	HFrEF: a significant increase in LVEF, +4.3% in the ASV group ($p = 0.0004$) and +4.6% in OMT alone ($p = 0.007$); a significant decrease in LV end-systolic volume index, −9.4 mL/m^2 in the ASV group ($p = 0.01$) and −8.6 mL/m^2 in OMT alone ($p = 0.003$) Reductions in left atrial (LA) volume and E/e′ were greater in the ASV arm, whereas patients receiving OMT alone demonstrated more improvement in right ventricular function HFpEF: treated with ASV also had a decrease in LA size that was greater than those receiving OMT alone	Significant reverse LV remodelling was seen amongst HFrEF patients with SDB regardless of treatment allocation. Substantial reductions in LA volume amongst HFrEF and HFpEF patients receiving ASV suggest that ASV treatment may improve diastolic function
O'Connor CM, et al., 2017 [10]	Randomized, controlled, multicentre trial Intervention: patients hospitalized with HF and moderate-to-severe sleep apnoea were randomized to ASV plus OMT or OMT alone	126 HF hospitalized patients (HFpEF and HFrEF) with SDB (AHI ≥15/h) ASV + OMT group, 65 patients; CSA, 7 (72%); mean LVEF 30.5 ± 15.4% OMT group: 61 patients; CSA 48 (79%); mean LVEF 33.7 ± 15.7	Composite global rank score (hierarchy of death, cardiovascular hospitalizations, and percent changes in 6-min walk distance) did not differ significantly between the ASV and control groups at 6 months ($p = 0.92$); a subgroup analysis suggested a positive effect of ASV in patients with HF with preserved ejection fraction ($p = 0.036$) AHI: decreased from 35.7 to 2.1/h at 6 months in the ASV group versus 35.1 to 19.0/h in the control group ($p < 0.0001$)	In hospitalized HF patients with moderate-to-severe sleep apnoea, adding ASV to OMT, did not improve 6-month cardiovascular outcomes

Basic K, et al., 2016 [11]	Prospective, observational Interventional: Effect of medical compensation in SBD in acute decompensated heart failure	105 Patients with acute decompensated HF and SBD (AHI ≥5/h, 77% with CSA); mean LVEF 38.5 ± 13.3%	AHI, 54 ± 17 to 48 ± 9/h ($p = 0.06$); central hypopnoea index 20.9 ± 14 to 17.1 ± 6.2/h ($p < 0.01$) time spent in CSR, 65.5 ± 28.4 to 63.7 ± 17.8 min ($p < 0.01$); oxygenation, 91.4 ± 0.6% to 92.0 ± 1.5% ($p < 0.05$). No significant change in cycle length (CL)	Cardiac compensation non-significantly improved the AHI but had no clear impact on CSR CL
Bitter T, et al., 2016 [12]	Randomized, controlled, double-blind, crossover Intervention: intravenous (IV) glyceryl trinitrate (GTN) to a maximum tolerable dosage and inhalation of iloprost 10 µg/mL after a washout phase	21 Patients with CHF and CSA/CSR (AHI ≥15/h) Mean LVEF 44.3 ± 9.6%	GTN and iloprost significantly lowered mean pulmonary artery pressure (20.1 ± 9.0 to 11.6 ± 4.2 mmHg, $p < 0.001$ and 16.9 ± 7.9 to 14.2 ± 6.4 mmHg, $p < 0.01$, respectively). Pulmonary capillary wedge pressure was only reduced by GTN (14.0 ± 5.6 to 7.2 ± 3.9 mmHg, $p < 0.001$). No significant change in the cardiac index. Sleep studies revealed no significant improvement in AHI, central apnoea index and CSR cycle length	Acute improvement of pulmonary congestion by GTN had no immediate impact on CSR severity
Neurostimulation				
Constanzo MR, et al., 2018 [13]	Prospective, multicentre, randomized, controlled trial Intervention: Evaluate safety and effectiveness of unilateral neurostimulation in patients with central sleep apnoea at 12 months	151 Subjects with CSA (AHI ≥20/h, with >50% central events) Treatment group: 58 patients; mean LVEF 40 ± 12% Control group: 73 patients; mean LVEF 40 ± 12%	AHI decrease ≥50% at 12 months: Treatment group vs. control (67% (95% CI 53–78%) vs. 55% (95% CI 43–67%))	Phrenic nerve stimulation produced sustained improvements in sleep indices and quality of life to at least 12 months in patients with CSA

(continued)

Table 27.1 (continued)

Author	Design	Population	Results	Main conclusion/future perspective
Constanzo MR, et al., 2016 [14]	Prospective, multicentre, randomized, controlled trial Intervention: Evaluate safety and effectiveness of unilateral neurostimulation in patients with central sleep apnoea at 6 months	151 Subjects with CSA (AHI ≥20/h, with >50% central events) Treatment group: 73 patients; mean LVEF 39.7 ± 12.1% Control group: 78 patients; mean LVEF 39.4 ± 12.2%	AHI reduction from baseline of 50% or greater: treatment group (35 (51%)); control group (8 (11%)); difference between groups 41%, 95% CI 25–54, p < 0.0001 Adverse events: 13 patients had serious-related adverse events at 12 months. Treatment group, 6 (8%); control group, 7 (9%) cases of. 27 (37%) of 73 Patients in the treatment group reported non-serious therapy-related discomfort that was resolved with simple system reprogramming; 7 deaths were reported through 12 months and were unrelated to the implant procedure, the device or the delivered therapy	Transvenous neurostimulation resulted in significant reductions in the severity of central sleep apnoea as well as improvements in the arousal index, self-reported sleepiness, REM sleep, and quality-of-life measures at 6 months
Jagielski D, et al., 2016 [15]	Prospective, multicentre, nonrandomized trial Intervention: evaluate the 12-month clinical outcomes of patients with CSA treated with unilateral transvenous phrenic nerve stimulation	47 Subjects CSA (AHI ≥20/h, with >50% central events)	AHI, 49.9 ± 15.1 vs. 27.5 ± 18.3 events/h, p <0.001; central apnoea index, 28.2 ± 15.0 vs. 6.0 ± 9.2 events/h, $p < 0.001$; ODI, 46.1 ± 19.1 vs. 26.9 ± 18.0 events/h, $p < 0.001$); REM sleep, (11.4 ± 6.1% vs. 17.1 ± 8.0%, $p < 0.001$); sleep efficiency, (69.3 ± 16.9% vs. 75.6 ± 17.1%, $p = 0.024$) Adverse events: Three deaths unrelated to therapy and five serious adverse events	CSA, unilateral transvenous phrenic nerve stimulation is associated with sustained improvement in key sleep parameters, sleep symptoms and quality of life over 12 months of follow-up

6MWD 6-min walking distance, *AHI* apnoea hypopnoea index, *ASV* adaptive servo-ventilation, *CSR* Cheyne–Stokes respiration, *CL* cycle length, central sleep apnoea, *HFpEF* Heart failure with preserved ejection fraction, *HFrEF* Heart failure with reduced ejection fraction, *GTN* glyceryl trinitrate, *LA* left atrial, *LEVF* left ventricular ejection fraction, *LV* left ventricule, *MRI* magnetic resonance imaging, *NYHA* New York Heart Association, *ODI* oxygen desaturation index, *OMT* optimized medical therapy, *PAP* positive airway pressure, *SDB* sleep-disordered breathing, *REM* rapid eye movement, *TECSA* treatment-emergent central sleep apnoea

The authors followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16].

27.3 Results

27.3.1 When to Treat Central Sleep Apnoea?

According to International Classification of Sleep Disorders, 3rd edition (ICSD-3) [17], CSA diagnosis needs the presence of symptoms (sleepiness, difficulty in initiating or maintaining sleep, frequent awakenings or nonrestorative sleep, awakening with short of breath, snoring or witnessed apnoeas) and a PSG revealing five or more central apnoeas and/or central hypopnoeas per hour of sleep, and the number of central apnoeas and/or central hypopnoeas has to be superior to 50% of the total number of apnoeas and hypopnoeas. However, many authors in the literature choose to initiate treatment if AHI ≥15 events/h with predominance of central events, as in the recent statement published by the European Respiratory Society (ERS) Task Force [18]. This choice arises mainly from previous prognostic studies in heart failure which have demonstrated that patients with heart failure with reduced ejection fraction (HFrEF) and CSA have an increased mortality risk. Furthermore, this risk was more significant in CSA with AHI superior to 22.5 events/h [19]. It is important to understand if CSA is a marker of disease severity or progression in heart failure in order to improve the offered treatment.

27.3.2 How to Treat Central Sleep Apnoea?

27.3.2.1 Chronic Heart Failure (CHF)

CSA is highly prevalent not only in patients with stable congestive heart failure with reduced ejection fraction (HFrEF) but also in those with preserved ejection fraction (HFpEF). Therefore, most studies regarding treatment of CSA were conducted in these populations.

Heart Failure Medication and Devices

No recent controlled randomized trials were found regarding the effect of medication, medical devices or cardiac transplant in CSA.

Previous studies have shown that treatments of heart failure that increase LVEF can alleviate or abolish CSA (e.g. medical management, mitral valvuloplasty, cardiac resynchronization therapy or left ventricular assist device and cardiac transplantation). Mainly, such interventions do not lead to complete resolution of the abnormal breathing pattern [11], for example, normalization of LVEF by cardiac transplantation is associated with a resolution of CSA in 50% of cases [18, 20].

Recently, in a randomised controlled trial, it was evaluated the impact of intravenous glyceryl trinitrate (GTN) in CSA/CSR. The authors verified an acute improvement of pulmonary congestion glyceryl trinitrate; however, it had no immediate impact on CSA/CSR severity [12].

The ENTRESTO-SAS trial is including patients to evaluate the role of sacubitril–valsartan in the outcome of SDB, including CSA in CHF patients (ClinicalTrials.gov Identifier: NCT02916160) [21].

Continuous Positive Airway Pressure (CPAP)

The rationale for CPAP as first-line therapy is based on results of a limited number of small randomized trials which have consistently demonstrated that CPAP decreases the frequency of central apnoeas in patients with CSA associated with heart failure. As mentioned before, the largest study about CSA and CPAP use was CanPAP [2].

A post hoc analysis of CanPAP has indicated that patients whose AHI was suppressed below 15 events/h had a significant improvement in LVEF and transplant-free survival. However, despite CPAP treatment if CSA persisted, the mortality was increased [22].

No recent controlled randomized trials were found regarding the effect of CPAP in CSA.

Adaptive Servo-Ventilation

Adaptive servo-ventilation (ASV) was designed to address several aspects of the respiratory

disturbance associated with CSA, including ventilatory overshoot and undershoot. Similar to CPAP, an expiratory pressure is applied to facilitate the maintenance of upper airway patency. Additionally, a variable inspiratory pressure support and a backup rate are applied. The device is equipped with a feedback circuit that allows it to measure the respiratory output (either in the form of peak flow or minute ventilation) to individually regulate delivered pressure support. The devices attempt to maintain a target minute ventilation/flow just below the long-term average ventilation of the patient to prevent the decrease of CO_2 below the apnoea threshold. Some ASV devices have auto-titrating technology capable of regulating expiratory pressure, and its use is being evaluated in clinical trials.

According to the literature, ASV seems to suppress central apnoea and hypopnoea more efficiently than oxygen, CPAP or BPAP in heart failure [18].

However, as previously stated, the SERVE-HF [3] was a multicentre, open-label trial that randomly assigned 1325 patients with moderate-to-severe predominant CSA (AHI ≥15, central apnoea index >10) and symptomatic heart failure to ASV plus standard medical therapy or medical therapy alone. Compared with controls, patients assigned to ASV had significantly higher all-cause mortality and cardiovascular mortality. Based on the results of this trial, most medical societies recommend against the use of ASV in heart failure patients with reduced ejection fraction (LVEF <45%).

The mechanism whereby ASV led to an increase in mortality in this trial is unknown. One possibility is that ASV could lead to a decrease in cardiac output and stroke volume in susceptible patients, such as those with low preload. Some authors have proposed ASV-induced alkalosis with subsequent hypokalaemia to potentially explain sudden cardiac death associated with ASV use, lowering the threshold for malignant arrhythmias. Another option is that Cheyne–Stokes respiration serves as a compensatory function in heart failure and that ASV proved detrimental by diminishing this compensatory respiratory pattern. In the SERVE-HF trial, a subgroup analysis found a positive association between the proportion of Cheyne–Stokes breathing and the risk of cardiovascular mortality [3].

Other possibility raised in the literature by Xie J. et al. was the impact of periodic limb movements (PLMS) in CSA due to heart failure treated with ASV [23]. The authors reported that PLMS may rise in HF patients after suppression of CSA by ASV. Nevertheless, the clinical significance of augmented post-ASV PLMS in HF prognosis needs to be determined, as well as if these increases may contribute to worsening outcomes in HF patients with CSA treated with ASV.

Additionally, one aspect to take in consideration was the poor adherence to ASV therapy in SERVE-HF trial (an average usage of 3.7 h/night overall) which may limit the interpretation of the results [3].

After the SERVE-HF trial, research with ASV diminished. Still, some subanalysis of the SERVE-HF population was made in order to try to justify the increased mortality findings. Woehrle H. et al. performed a time-dependent on-treatment analyses (unadjusted and adjusted for predictive covariates) and verified an amplified cardiovascular death hazard ratio during ASV usage periods, slightly lower than those in the SERVE-HF intention-to-treat analysis [5]. However, the cardiovascular risk did not rise as nightly ASV usage increased. Additionally, Cowie M. et al. analyzed 312 patients with HFrEF and CSA from the SERVE-HF [6]. No statistically significant difference on cardiac structure or function, cardiac biomarkers, renal function and systemic inflammation was found between de ASV group or the control group during the 12 months follow-up. In addition to that positive airway, pressure therapy has recently been shown not to affect other organs like the lung function [7].

In contrast to the results of SERVE-HF trial, the Bad Oeynhausen registry data did not document an increase in mortality during long-term ASV treatment for predominant CSA in HFrEF

patients [4]. As in the SERVE-HF, ASV therapy did effectively control nocturnal respiratory events, whilst adherence to therapy was larger in the registry. The authors verified improvements in HF symptoms, but ASV did not seem to improve objective measures of exercise capacity, LVEF or N-terminal pro B-type natriuretic peptide (NT-proBNP) plasma levels.

In the literature exists some conflicting evidence regarding the effect of ASV in HF symptoms, exercise capacity and LVEF in patients with HFrEF. Some authors have reported improvement of this variables with ASV therapy, and others have stating no significant difference [18].

Regarding the treatment of CSA in hospitalized patients with CHF, the CAT-HF (Cardiovascular Improvements with Minute Ventilation-targeted Adaptive Servo-Ventilation Therapy in Heart Failure) trial, which was interrupted due to SERVE-HF results, included 126 hospitalized heart failure patients with predominant CSA (81% with HFrEF) and randomized patients to receive ASV plus optimal medical therapy or medical therapy alone [10]. Whilst the trial showed no difference in the primary outcome of death, cardiovascular hospitalizations and timed walk distance, the confidence intervals were wide, and there was a suggestion of increased harm in the ASV group. Though prespecified subgroup analysis suggested a positive effect of ASV in patients with HF with preserved ejection fraction, this study had some limitations, such as the limited sample and the fact that adherence to ASV therapy was below the recommended level.

A subanalysis of the CAT-HF trial was performed evaluating the impact of treatment of CSA in cardiac remodelling of heart failure patients [9]. A significant reverse left ventricular remodelling was seen amongst HFrEF patients with sleep-disordered breathing (SDB) regardless of treatment. Substantial reductions in left atrial volume amongst HFrEF and HFpEF patients receiving ASV suggested that ASV treatment may also improve diastolic function.

No prospective trials were found regarding ASV in HFpEF. One recent retrospective study confirmed the impact of ASV in reducing AHI, arousal index and sleep architecture (increase stage N3 e rapid eye movement (REM) sleep) [8].

At the moment, the Effect of ASV on Survival and Hospital Admissions in HF (ADVENT-HF) study (ClinicalTrials.gov identifier, NCT01128816) is examining a type of ASV therapy with an algorithm that should maintain lower pressures [24]. It is enrolling both OSA and CSA patients with a HFrEF and may give some additional knowledge about the treatment of CSA.

Supplemental Nocturnal Oxygen

No recent controlled randomized trials were found regarding the effect of oxygen therapy in CSA. In previous studies including patients with CHF and CSA, nocturnal oxygen supplementation has been shown to improve O_2 saturation, AHI and LVEF. The Chronic Heart Failure—Home Oxygen Therapy (CHF-HOT) studies were randomized, open-label, multicentre trials designed to determine efficacy of nocturnal oxygen in patients with CHF and CSA. One recent post hoc analysis, that considered the short-term (12 weeks) and the long-term (52 weeks) CHF-HOT studies confirmed the previous results and described a decrease in the number of hourly episodes of ventricular arrhythmia by 12 weeks of home oxygen therapy in patients with marked elevation in AHI and severe ventricular dysfunction [25].

There are small studies aiming to evaluate the role of high-flow nasal oxygen in HFrEF associated CSA (ClinicalTrials.gov Identifier, NCT03085641).

Bilevel Positive Airway Pressure (BPAP)

No recent controlled randomized trials were found regarding the effect of bilevel positive pressure in CSA due to heart failure.

Trials of BPAP are typically reserved for those who have failed or not tolerated trials of oxygen, CPAP or ASV. However, if we extrapolate the

results regarding ASV, the use of BPAP in patients with CSA due to HFrEF should be approached with caution and on a case-by-case basis [18].

There is a paucity of data regarding the effects of BPAP in patients with other hyperventilation-related CSA.

Respiratory Stimulants

Respiratory stimulants, such as theophylline, acetazolamide and carbon dioxide, augment ventilation in HFrEF with normocapnic or hypocapnic CSA. These agents can alter respiratory control instability, decrease the likelihood of crossing the apnoea threshold and diminish the propensity for central apnoeas and hypopnoeas [18].

Transvenous Neurostimulation

Despite the association between CSA and mortality in HF, some patients do not tolerate modifications of heart failure medication or positive airway pressure. Therefore, a novel treatment method has been recently studied: unilateral phrenic nerve stimulation by the Remedē® System, a transvenously implantable neurostimulation device. In a multicentre randomized controlled trial, Constanzo M.R. et al. demonstrated that transvenous neurostimulation resulted in significant reductions in the severity of central sleep apnoea as well as improvements in the arousal index, self-reported sleepiness, REM sleep and quality-of-life measures at 6 months [14]. No major differences in safety or tolerability were reported during the follow-up. Additionally, sustained benefits were verified in sleep parameters, sleep symptoms and quality of life over a 12-month period [13, 15].

27.3.2.2 Stroke

Several studies have reported an association between stroke and CSA. After the stroke, the number of central apnoeas decreases over time, unless the cause of CSA is another condition such as heart failure. One single centre retrospective study in patients with CSA in post-acute ischaemic stroke patients without concomitant CHF reported that ASV improved AHI, after a trial of CPAP or bilevel positive pressure with unsatisfactory results [26]. Furthermore, other studies raised concerns about the low CPAP tolerability in these post-stroke patients [18, 27].

Literature is scant regarding the pathophysiology, the role of CSB in the recovery or if treatment should be offered—no recent controlled trials were found regarding the treatment of CSA in stroke.

27.3.2.3 End-Stage Renal Disease

Sleep-disordered breathing (SDB) is increasingly recognized amongst patients with end-stage renal disease (ESRD). OSA is the most commonly reported disorder, followed by CSA. Nevertheless, the pathogenesis of sleep apnoea in ESRD remains unclear. Previous work on features of sleep apnoea in ESRD patients suggested that fluid retention seems to play a central role and its pathogenesis may be related to both upper airway occlusion and destabilization of central respiratory control.

Concerning CSA, there are a few studies in the literature addressing therapy aspects. Nocturnal haemodialysis seems to be superior in reducing CSA over conventional haemodialysis during daytime. Regarding subjective sleep assessments, improved sleep quality was found in the prospective pre–post intervention studies and cohort studies, whilst no significant improvements were found in the randomized controlled trials. Oxygen therapy, CPAP and ASV have proven efficacious in reducing central events in ESRD [28].

No structured studies were found evaluating the effect of renal transplant in CSA.

27.3.2.4 High Altitude

CSA that appears with altitude is named high-altitude periodic breathing (HABP). Previous studies could be divided in two groups: evaluating the effect of high altitude in healthy subjects and in patients with pre-existing breathing disorders. Few studies suggested that acetazolamide, dexamethasone or nocturnal oxygen may reduce HABP in healthy subjects. Furthermore, studies evaluating patients with a pre-existing sleeping disorder were performed mainly in OSA.

No recent controlled randomized trials were found regarding the effect of bilevel positive pressure in CSA. In a small prospective study, 18 healthy subjects were brought from sea level to 3800 m and underwent polysomnography on 3 consecutive nights [29]. Each night the randomized received no treatment, supplemental oxygen or ASV. The authors did not observe consistent efficacy in the use of ASV for treatment of CSA due to high-altitude periodic breathing in nonacclimatized individuals. In contrast, oxygen was efficacious during sleep in preventing sleep apnoea, oxygen desaturation and arousal index. Taking in consideration the major limitation of these studies, the authors stated that adjustment in the ASV algorithm may improve efficacy and ASV may have utility in acclimatized persons or with previous sleep breathing disorder.

27.3.2.5 Opioids/Substance Usage

No recent controlled randomized trials were found regarding the treatment of CSA related to opioids/substances usage.

Literature support a dose-response relationship between opioid daily dose and severity of CBD; therefore, the first approach should be, if possible, to diminish the opioid dosage. Secondly, medications that may contribute for SDB should be excluded, such as benzodiazepines [18].

About PAP therapy, there is scant direct evidence upon which to base treatment recommendations in patients chronically using opioids [30]. Still, most data suggested that both ASV therapies are superior to conventional CPAP for elimination of opioid-associated CSA [18, 31].

27.3.2.6 Treatment-Emergent/ Treatment-Persistent CSA

Recently, an ERS task force reported that the term treatment-emergent CSA should be used for patients with CSA newly developed under treatment with PAP that disappear under continuous use and the term treatment-persistent for CSA that persists under continuous use of PAP therapy [18]. No other cause should explain these events (e.g. underlying cardiovascular, renal or neurological diseases or pre-existing CSA prior to initiation of PAP). The authors also stated the importance of confirming the previous diagnosis by reviewing the initial PSG and excluding avoidable causes of CSA under PAP, for example excessive titration, post-hyperventilation apnoea, post-arousal apnoea, overestimation due to split-night error and misclassification of central hypopnoeas.

Studies revealed conflicting definitions of treatment-emergent CSA which makes it impossible to extrapolate therapy results regarding this condition. Recently, Liu D. et al. identified different trajectories during CPAP therapy (transient, emerging, persistent CSA) using a US positive airway pressure (PAP) device telemonitoring database. In this study, older patients, higher residual AHI and leak appear to be risk factors for emergent CSA during CPAP [32].

Despite these definition issues, literature stated that CPAP and ASV have improved effectively treatment-emergent/treatment-persistent CSA; however, ASV seems to be superior than the other PAP therapies.

27.3.2.7 Idiopathic CSA

Idiopathic central sleep apnoea is a rare disease of unknown prevalence that typically presents as hypocapnic CSA. Concerning its treatment, no recent trials were found, and there is very limited data, mainly about the use of zolpidem, acetazolamide or PAP (CPAP or ASV) [18].

27.3.2.8 Other Diseases Related to CSA

Certain endocrine, neurological or pulmonary diseases have been reported to be associated with CSA, such as acromegaly, diabetes mellitus, Parkinson's disease, Alzheimer's disease, interstitial lung disease and pulmonary hypertension. However, limited scientific evidence regarding treatment is available. Therefore, treatment decisions must be individualized based on disease and symptom severity and patient willingness to accept therapy.

27.4 Conclusions

In CSA, many doubts remain about which patients should be treated. Some authors started treatment with PAP if AHI ≥15/h, others if AHI ≥5/h with symptoms. Furthermore, studies have demonstrated that the detrimental effects of CSA increase with the higher number of CSA events and in one study was observed an augmented mortality risk when AHI was superior to 22.5/h [19]. Hence, trials are needed to evaluate long-term prognostic relevance of CSA and to try to define clearer indications for treatment initiation.

In terms of treatment in clinical practice, a recent algorithm was published by an ERS task force [18]. Firstly, as previously stated, most cases of CSA are secondary to an underlying medical condition, such as heart failure or stroke, high altitude or opioids/substance usage. In such cases, treatment of the underlying condition or removal of the offending medication/substance may result in improvement in the CSA.

Because CSA often persists despite treatment of the underlying cause, targeted treatment with positive airway pressure must be considered. CPAP is the preferred first-line therapy for symptomatic patients with hyperventilation-related CSA. In the algorithm, the authors proposed that if AHI remains superior to 15/h despite CPAP usage or in case of poor tolerance, treatment with ASV should be tried, except if LVEF ≤45%. However, for other authors, the definition of CPAP "failure" can be the presence of AHI ≥5/h, with >50% of residual central events.

If possible, patients should undergo titration for PAP in a sleep laboratory setting, which offers an opportunity to adjust parameters to correct all breathing events and verify interfaces or other problems related to PAP.

Unlike CPAP or ASV, nocturnal oxygen therapy is not effective in eliminating upper airway obstruction that may accompany central apnoeas. Given these findings, its use is likely best reserved for those patients whose pressure support therapies are found to be insufficient or are poorly tolerated.

Regarding medication in CSA, potential adverse effects of theophylline and acetazolamide limit its use in clinical practice in CHF, at least until studies can demonstrate its long-term safety and efficacy. Acetazolamide may have a role in CSA associated with high altitude since it seems to reduce central events in health subjects. Additionally, it appears to prevent central events and to improve oxygen saturation in combination with automatic continuous positive pressure (APAP) in OSA patients.

Furthermore, phrenic nerve stimulation also may offer a promising new way to treat CSA in HF. The therapy was found to be well tolerated, and therapeutic efficacy was maintained at 12-month follow-up. However, this device has not yet been compared with CPAP or other therapies for CSA, and further studies are needed to help define optimal patient selection and long-term safety.

Research advances in the last years have allowed to improve our understanding about pathophysiology and aetiology of central breathing disorders. Still, several questions related to pathophysiology and treatment remain open, mainly indications for treatment and long-term efficacy and safety of the different therapies used in CSA (Fig. 27.1). Active research in CSA treatment is currently ongoing and will be presenting results in a recent future (ADVENT-HF, phrenic nerve stimulation).

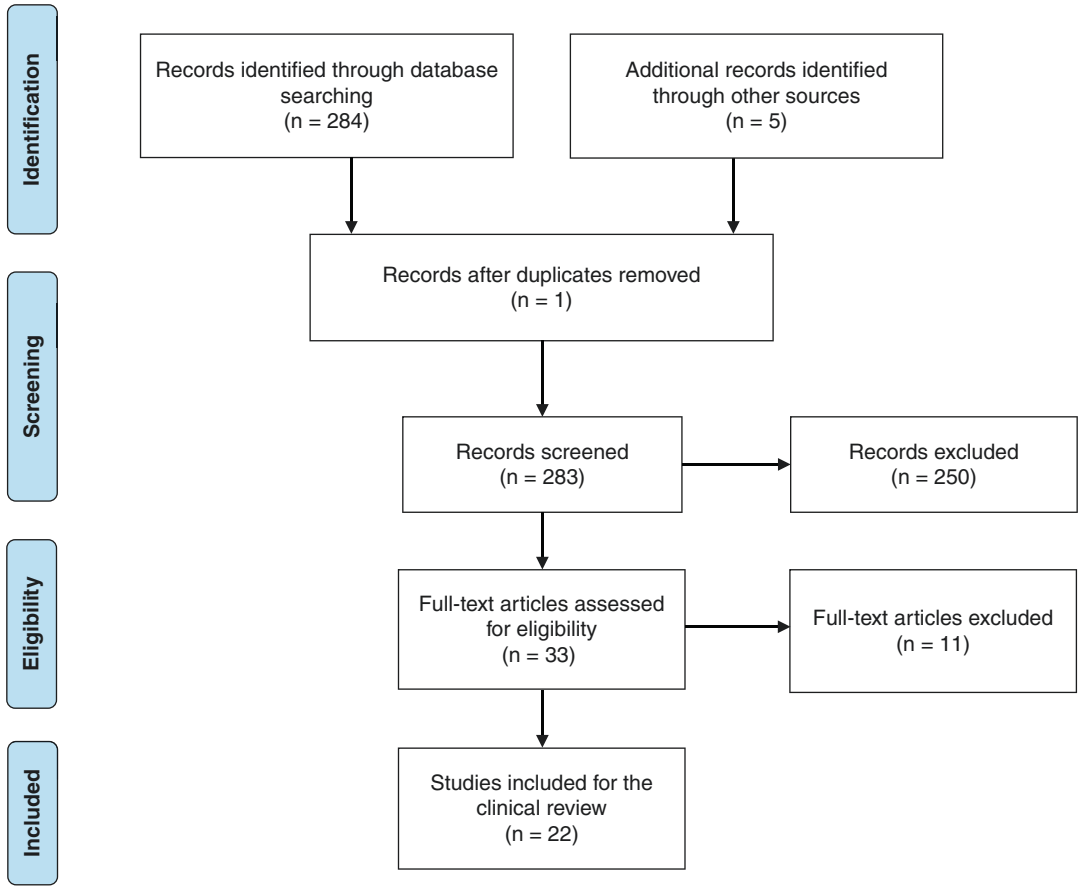

Fig. 27.1 Diagram of search methodology. (Adapted from PRISMA [16])

References

1. Perger E, Inami T, Lyons OD, et al. Distinct patterns of hyperpnea during Cheyne-Stokes respiration: implication for cardiac function in patients with heart failure. J Clin Sleep Med. 2017;13(11):1235–41.
2. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med. 2005;353:2025–33.
3. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373:1095–105.
4. Oldenburg O, Wellmann B, Bitter T, et al. Adaptive servo-ventilation to treat central sleep apnea in heart failure with reduced ejection fraction: the Bad Oeynhausen prospective ASV registry. Clin Res Cardiol. 2018;107(8):719–28.
5. Woehrle H, Cowie MR, Eulenburg C, et al. Adaptive servo ventilation for central sleep apnoea in heart failure: SERVE-HF on-treatment analysis. Eur Respir J. 2017;50:1601692.
6. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnoea in systolic heart failure: results of the major substudy of SERVE-HF. Eur J Heart Fail. 2018;20(3):536–44.
7. Fox H, Witzel S, Bitter T, et al. Positive airway pressure therapy in heart failure patients: long-term effects on lung function. Respir Physiol Neurobiol. 2017;238:41–6.
8. Heider K, Arzt M, Lerzer C, et al. Adaptive servo-ventilation and sleep quality in treatment emergent central sleep apnea and central sleep apnea in patients with heart disease and preserved ejection fraction. Clin Res Cardiol. 2018;107(5):421–9.
9. Daubert MA, Whellan DJ, Woehrle H, et al. Treatment of sleep-disordered breathing in heart failure impacts cardiac remodeling: insights from the CAT-HF Trial. Am Heart J. 2018;201:40–8.
10. O'Connor CM, Whellan DJ, Fiuzat M, et al. Cardiovascular outcomes with minute ventilation-targeted adaptive servo-ventilation therapy in heart failure: the CAT-HF Trial. J Am Coll Cardiol. 2017;69(12):1577–87.

11. Basic K, Fox H, Spießhöfer J, et al. Improvements of central respiratory events, Cheyne-Stokes respiration and oxygenation in patients hospitalized for acute decompensated heart failure. Sleep Med. 2016;27-28:15–9.
12. Bitter T, Fox H, Schmalgemeier H, et al. Acute improvement of pulmonary hemodynamics does not alleviate Cheyne-Stokes respiration in chronic heart failure—a randomized, controlled, double-blind, crossover trial. Sleep Breath. 2016;20(2):795–804.
13. Costanzo MR, Ponikowski P, Javaheri S, et al. Sustained 12 month benefit of phrenic nerve stimulation for central sleep apnea. Am J Cardiol. 2018;121(11):1400–8.
14. Costanzo MR, Ponikowski P, Javaheri S, et al. Transvenous neurostimulation for central sleep apnoea: a randomized controlled trial. Lancet. 2016;388(10048):974–82.
15. Jagielski D, Ponikowski P, Augostini R, et al. Transvenous stimulation of the phrenic nerve for the treatment of central sleep apnoea: 12 months' experience with remedē® System. Eur J Heart Fail. 2016;18(11):1386–93.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
17. American Academy of Sleep Medicine. The international classification of sleep disorders, third edition (ICSD-3). Darien: American Academy of Sleep Medicine; 2014. ISBN 978-0991543410.
18. Randerath W, Verbraecken J, Andreas S, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J. 2017;49:1600959.
19. Jilek C, Krenn M, Sebah D, et al. Prognostic impact of sleep disordered breathing and its treatment in heart failure: an observational study. Eur J Heart Fail. 2011;13:68–75.
20. Mansfield DR, Solin P, Roebuck T, et al. The effect of successful heart transplant treatment of heart failure on central sleep apnea. Chest. 2003;124:1675–81.
21. Jaffuel D, Molinari N, Berdague P, et al. Impact of sacubitril-valsartan combination in patients with chronic heart failure and sleep apnoea syndrome: the ENTRESTO-SAS study design. ESC Heart Fail. 2018;5(3):222–30.
22. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation. 2007;115:3173–80.
23. Xie J, Covassin N, Chahal AA, et al. Effect of adaptive servo-ventilation on periodic limb movements in sleep in patients with heart failure. Am J Cardiol. 2019;123(4):632–7.
24. Lyons OD, Floras JS, Logan AG, et al. Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. Eur J Heart Fail. 2017;19(4):579–87.
25. Nakao YM, Ueshima K, Yasuno S, Sasayama S. Effects of nocturnal oxygen therapy in patients with chronic heart failure and central sleep apnea: CHF-HOT study. Heart Vessels. 2016;31(2):165–72.
26. Brill AK, Rösti R, Hefti JP, et al. Adaptive servo-ventilation as treatment of persistent central sleep apnea in post-acute ischemic stroke patients. Sleep Med. 2014;15(11):1309–13.
27. Brill AK, Horvath T, Seiler A, et al. CPAP as treatment of sleep apnea after stroke: a meta-analysis of randomized trials. Neurology. 2018;90:e1222.
28. Nigam G, Pathak C, Riaz M. A systematic review of central sleep apnea in adult patients with chronic kidney disease. Sleep Breath. 2016;20(3):957–64.
29. Orr JE, Heinrich EC, Djokic M, et al. Adaptive servoventilation as treatment for central sleep apnea due to high-altitude periodic breathing in nonacclimatized healthy individuals. High Alt Med Biol. 2018;19(2):178–84.
30. Reddy R, Adamo D, Kufel T, et al. Treatment of opioid-related central sleep apnea with positive airway pressure: a systematic review. J Opioid Manag. 2014;10:57.
31. Javaheri S, Harris N, Howard J, Chung E. Adaptive servoventilation for treatment of opioid-associated central sleep apnea. J Clin Sleep Med. 2014;10:637.
32. Liu D, Armitstead J, Benjafield A, et al. Trajectories of emergent central sleep apnea during CPAP therapy. Chest. 2017;152(4):751–60.

28 Impact of Positive Airway Pressure on Quality of Life, Excessive Daytime Sleepiness and Depressive Mood in Patients with Obstructive Sleep Apnea

Baran Balcan

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Abbreviations

APAP	Auto-adjusting positive airway pressure
AHI	Apnea–hypopnea index
BPAP	Bi-level positive airway pressure
CES-D	Center for Epidemiologic Studies Depression Scale
CPAP	Continuous positive airway pressure
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
HADS	Hospital Anxiety and Depression Scale
HDRS	Hamilton Depression Rating Scale
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PICO	Patient, population or problem, intervention, comparison, and outcomes
POMS	Profile of Mood States
QSQ	Quebec Sleep Questionnaire
RDI	Respiratory disturbance index
REI	Respiratory event index
SF-36	Short Form of the Medical Outcomes Survey
ZDS	Zung Self-rating Depression Scale

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28.1 Introduction

Obstructive sleep apnea syndrome (OSAS) is repeated obstruction of the upper airway which results in cessation of airflow, with disturbance in saturation followed by arousals from sleep [1]. Although protective by nature, this mechanism leads to fragmented, poor-quality sleep. Untreated OSA is a common condition in patients with coronary artery disease (CAD), causing episodic hypoxemia and nocturnal sympathetic nervous system activation, elevated blood pressure and markers of oxidative stress, inflammation, and hypercoagulation [2]. OSA can also result in undesirable physiological, behavioral, and cognitive squeal, excessive daytime sleepiness (EDS), hyperactivity, and behavioral disturbances, learning and memory deficits, increased risk-taking and injury risk and have impacts impact on daily life with sleep deprivation, which may result in altered mood, impaired cognition, and decreased energy [3].

Cardinal symptoms of OSA are loud snoring, witnessed apnea, and excessive daytime sleepiness. Sometimes daytime symptoms (excessive daytime sleepiness), depression, and impaired quality of life may be the presenting symptoms of OSA rather than cardinal symptoms [4]. OSA patients with excessive daytime sleepiness may have reduced health-related quality of life (HRQoL) compared to the general population [3].

First-line treatment in OSA is positive airway pressure (PAP), which eliminated apneas and hypopneas. PAP treatment in OSA is known to be beneficial, if usage of the device is at least 4 h per night 70% of all nights, which means 2.8 h/night adjusted usage. In this section the association between quality of life, excessive daytime, and depression with OSA will be discussed; moreover, response to PAP treatment will be evaluated (Fig. 28.1).

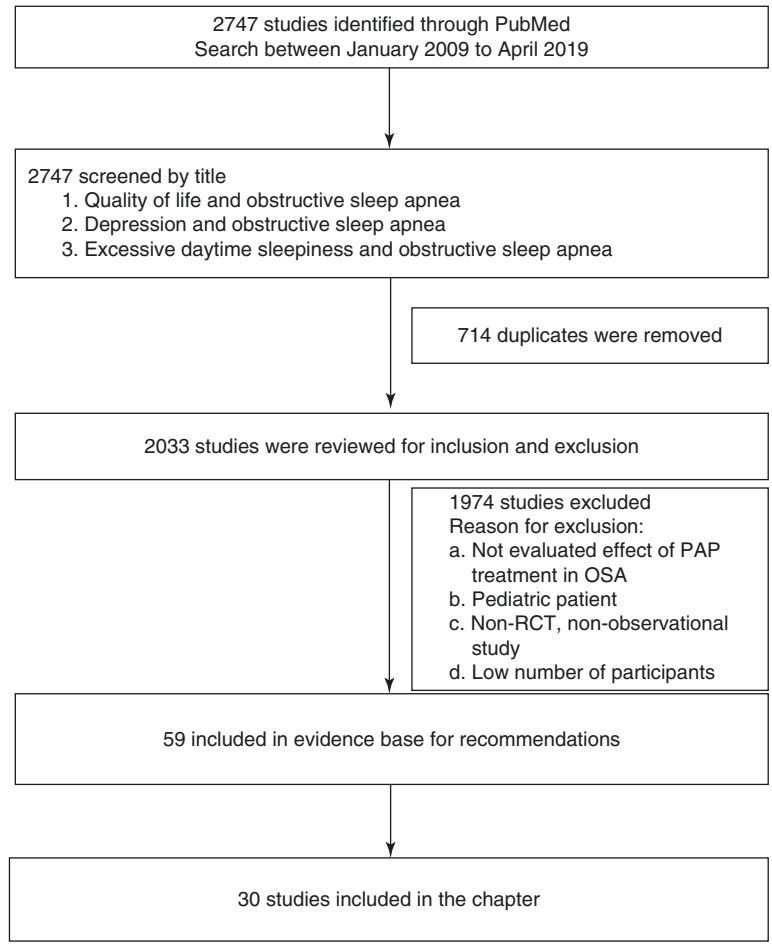

Fig. 28.1 Screening procedure for studies included in this chapter

28.2 Excessive Daytime Sleepiness, Quality of Life and Depression

28.2.1 Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) is a common problem which is mostly a self-reported symptom of OSA. Uncontrolled need of sleep and falling asleep during daytime are the characteristics of EDS [5]. EDS is a serious condition which leads to problems such as poor work performance, motor vehicle accidents, and work injuries. Quality-of-life outcomes are affected negatively, and people with EDS may have poor cognitive function and depressive mood [5]. EDS may be the only symptom of impaired quality of life, observed in sleep-related breathing disorder, and may also be related with chronic pain, nocturnal angina, chronic pulmonary symptoms, urinary dysfunction, psychological disorders, and the effects of the medications [5].

Excessive daytime sleepiness is a usually self-reported, questionnaire-based condition, and the mostly used questionnaire is Epworth Sleepiness Scale (ESS). Dozing of the questionnaire are 0 = would never doze, 1 = slight chance of dozing, 2 = moderate change of dozing, and 3 = high chance of dozing. There are eight questions that evaluate the situation of chance of dozing: (1) sitting and reading; (2) watching TV; (3) situation sitting, inactive in a public place (e.g., a theater or a meeting); (4) as a passenger in a car for an hour without a break; (5) lying down to rest in the afternoon when circumstances permit; (6) sitting and talking to someone; (7) sitting quietly after a lunch without alcohol, and (8) in a car, while stopped for a few minutes in the traffic. Total score over 10 is mostly accepted as sleepy.

Other questionnaires used for evaluation of sleepiness is the Stanford Sleepiness Scale (SSS). This questionnaire is more complicated than ESS, and also the results are not as homogeneous as ESS; therefore, it is not preferred to evaluate the condition of sleepiness anymore.

28.2.2 Quality of Life

In recent years, there has been an increased interest in evaluation of quality of life (QoL) in patients with chronic illnesses [6]. OSA has been shown to be associated with cardiovascular and other chronic diseases as well as motor vehicle accidents; moreover, it has also be reported that there is a relationship between OSA and QoL [6]. Excessive daytime sleepiness, loud snoring, and witnessed apnea are the cardinal symptoms of OSA. Beside these cardinal symptoms, fatigue and social or emotional difficulties, which affect life negatively, may be the presentation of OSA in some patients. Evaluation of QoL based on questionnaires such as Short Form of the Medical Outcomes Survey (SF-36) that contains eight domains (physical function, role-physical, bodily pain, general health, energy/vitality, role-emotional, social function, and mental health), and two composite scores (mental component score [MCS] and physical component score [PCS]), Functional Outcomes of Sleep Questionnaire (FOSQ), Quebec Sleep Questionnaire (QSQ), and the Calgary Sleep Apnea Quality of Life Index (SAQLI), etc. Although results have varied, most of the studies has shown significant association between OSA and quality of life [7].

28.2.3 Depressive Mood

The prevalence of depression is high in patients with OSA; it was reported that in community-based studies, its rates were estimated as 17%, and in studies from sleep cohorts, it was observed as high as 40% [8]. It was also reported that depression may be a risk factor of OSA; on the other hand, depression may be caused by OSA. In the sleep-EVAL study, a population-based telephone interviews with 18,980 patients, it was reported that prevalence of major depression in OSA patients according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria was 17% and 4.3% for the whole population [9].

Wandeputte et al. reported the prevalence of depression as 41%, and Wahner-loedler et al. reported depression 38% for women and 26% for men in sleep clinic cohorts [10, 11].

28.3 Positive Airway Pressure Treatment

Continuous positive airway pressure (CPAP) therapy, which has a stable pressure through the whole respiration (inspiration and expiration) to secure the airway, is used commonly in OSA. Bi-level PAP, the other option used in treatment of OSA, supplies different levels of pressure in inspiration (IPAP) and expiration (EPAP). Flow sensors, built in recently developed CPAP (called auto-adjusting PAP [APAP]) devices, has the capability of detection of respiratory events; thus they can increase the pressure when respiratory events sensed and decrease the support when respiratory events does not occur. Auto-adjusting procedures were also developed for BiPAP devices, and they are called auto-BiPAP.

Adherence to PAP therapy is very important for the success of the OSA treatment. Minimum accepted compliance is 4 h per night; besides, there are many studies that recommended the success of dose response relationship of the PAP therapy [12, 13]. Therefore, it is suggested to use the device as much as possible, preferably the whole sleep period. In order to promote the compliance, it is essential to favor the comfort of the patient. Different choices of masks, oronasal, nasal, and nasal pillows, provide options to patients to feel comfortable and reduce the leak. Furthermore, humidifiers used in the PAP devices promote heated system and defend against dryness. Most of the new-generation PAP devices include SD cards or online connection systems which provide physicians the chance to evaluate the compliance of the patients in follow-ups after initiation of OSA treatment.

PICO Questions

PICO (patient, population or problem, intervention, comparison, and outcomes) questions were developed in order to evaluate the effectiveness of PAP treatment in OSA patients. As summarized in Table 28.1, PICO questions consist of 11 items. Nine of 11 questions excluding second and third evaluate quality of life, and eight questions excluding second, third, and tenth evaluate daytime sleepiness (Table 28.1).

28.3.1 Impact of Positive Airway Pressure Treatment on Sleepiness

Evaluation of sleepiness is done subjectively by self-reported questionnaires and mostly used one is ESS. When previous literature especially randomized controlled trials (RCT) is analyzed, it is observed that PAP treatment significantly improves excessive daytime sleepiness [7, 14, 15]. Significant improvement in excessive daytime sleepiness is observed in both sleepy and non-sleepy populations; however, improvement in sleepy ones was more compared to non-sleepy patients [7]. In a randomized controlled trial, McMillian et al. evaluated benefits of CPAP in moderate-to-severe OSA in elderly (age ≥65 years) 278 participants. They reported that CPAP treatment reduces ESS scores significantly at third and twelfth months; moreover, they observed greater decline in ESS scores in patients with higher levels of ESS scores at baseline [14]. They recommend CPAP treatment in moderate-to-severe OSA subjects in elderly population with excessive daytime sleepiness. In another randomized controlled trial, Campos Rodriguez and colleagues evaluated daytime sleepiness, mood, and quality of life in 307 females with diagnosis of moderate-to-severe OSA (AHI ≥ 15 events/h). At the end of twelfth week, they observed a significant improvement in daytime sleepiness in CPAP group compared to conservative therapy [15]. In an observational study Weaver et al. evaluated dose–response relationship for improvement of daytime sleepiness in 149 patients, and they have reported that CPAP usage should be at least 4 h for significant decline in ESS scores [13]. Most of the studies in the literature suggest that excessive daytime sleepiness improves with satisfactory CPAP usage; however

Table 28.1 PICO questions

1. In adult patients with OSA, does CPAP versus no treatment improve AHI/RDI/REI, daytime sleepiness, neurocognitive function, quality of life, sleep quality, mood, and motor vehicle crashes?
2. In adult patients with OSA, does PAP versus no therapy improve left ventricular ejection fraction, blood pressure control, and glucose control (hemoglobin A1c; fasting glucose)?
3. In adult patients with OSA, does PAP versus no therapy reduce cardiovascular event rates (incident hypertension, myocardial infarction, coronary revascularization procedures, stroke, atrial fibrillation, sudden death, hospitalization for heart failure, and cardiovascular mortality), all-cause hospitalization, and all-cause mortality?
4. In adult patients with OSA, does initiation of PAP based on an in-laboratory versus ambulatory APAP-based strategy improve AHI/RDI, adherence to PAP therapy, sleepiness, and quality of life?
5. In adult patients with OSA, does APAP versus CPAP improve AHI/RDI, adherence, sleepiness, neurocognitive function, and quality of life and reduce side effects?
6. In adult patients with OSA, does BPAP or auto-BPAP versus CPAP improve AHI/RDI, adherence to PAP therapy, sleepiness, neurocognitive function, and quality of life and reduce side effects?
7. In adult patients with OSA, does the addition of modified pressure profile PAP to PAP therapy improve adherence to PAP therapy, sleepiness, and quality of life and reduce side effects?
8. In adult patients with OSA, does oral CPAP versus nasal (nasal mask versus intranasal) CPAP versus oronasal CPAP improve AHI/RDI, adherence to PAP therapy, sleepiness, and quality of life and reduce side effects?
9. In adult patients with OSA, does humidified PAP versus standard PAP improve adherence to PAP therapy, sleepiness, quality of life and reduce side effects?
10. In adult patients with OSA, do educational or behavioral interventions versus no intervention prior to or during PAP treatment improve adherence to PAP therapy, sleepiness, and quality of life?
11. In adult patients with OSA, do interventions guided by monitoring of OSA and PAP parameters during PAP treatment versus no monitoring improve adherence to PAP therapy, sleepiness, and quality of life, and reduce side effects?

AHI apnea–hypopnea index, *APAP* auto-adjusting positive airway pressure, *BPAP* bilevel positive airway pressure, *CPAP* continuous positive airway pressure, *OSA* obstructive sleep apnea, *PAP* positive airway pressure, *PICO* patient, population or problem, intervention, comparison, and outcomes, *RDI* respiratory disturbance index, *REI* respiratory event index

in some studies, residual daytime sleepiness was reported even if the participants used their devices at least 4 h. Foster et al. observed residual daytime sleepiness in OSA patients who underwent CPAP treatment. Twenty-nine OSA patients receiving CPAP therapy were included in this study; they evaluated daytime sleepiness with ESS subjectively and by multiple sleep latency test (MSLT) objectively. They suggested that there is a different phenotype of OSA which may be associated with persistent excessive daytime sleepiness despite appropriate treatment received OSA [16]. Impact of CPAP treatment on daytime sleepiness was summarized in Table 28.2.

28.3.2 Impact of Positive Airway Pressure on Quality of Life

As it was mentioned above, there are many studies that suggested significant association between OSA and quality of life. Evaluation of quality of life is based on subjective questionnaires such as Short Form of the Medical Outcomes Survey (SF 36), Functional Outcomes of Sleep Questionnaire (FOSQ), Calgary Sleep Apnea Quality of Life Index (SAQLI), etc. As described in Table 28.2, there are many studies (most of them RCTs) that favor the effectiveness of PAP treatment in improvement in quality of life [14, 15, 17, 18]; on the other hand, in some studies no benefit of PAP treatment was observed for improvement of quality of life [19–21]. In some randomized controlled trials evaluating quality of life with SF-36 questionnaires, no significant improvement with PAP treatment in OSA patients was observed in physical component summary, mental component summary, and vitality score. In this chapter, some of those RCTs in which association of quality of life and PAP therapy in OSA will be discussed.

Campos Rodriguez and colleagues evaluated 307 (randomized to CPAP [n = 151] and conservative treatment [n = 156]) women who had moderate-to-severe OSA. They used short-form

Table 28.2 Summary of articles addressing impact of CPAP treatment on excessive daytime sleepiness, impaired quality of life, and depressive mood

First author, year	Questionnaire	OSA	Sample size	Main finding	Study design
Excessive daytime sleepiness					
T. E. Weaver, 2007	ESS	AHI ≥ 15	149	CPAP improves EDS	Observational
A. McMillan, 2014	ESS	ODI ≥ 7.5	278	CPAP improves EDS	RCT
Campos-F. Rodriges, 2016	ESS	AHI ≥ 15	307	CPAP improves EDS	RCT
S. N. Foster, 2019	ESS	AHI ≥ 5	29	CPAP does not improve EDS	
Quality of life					
A. McMillan, 2014	SF-36	ODI ≥ 7.5	278	CPAP improves QOL	RCT
Campos-F. Rodriges, 2016	QSQ	AHI ≥ 15	307	CPAP improves QOL	RCT
E. F. Lewis, 2017	SF-36	AHI ≥ 15	318	CPAP improves QOL	RCT
Y. Y. Zhao, 2017	SF-36	AHI ≥ 15	169	CPAP improves QOL	RCT
F. Barbe, 2001	FOSQ	AHI ≥ 30	55	CPAP does not improve QOL	RCT
M. Barnes, 2002	FOSQ	AHI ≥ 5	114	CPAP does not improve QOL	RCT
C. L. Phillips, 2011	FOSQ	AHI ≥ 30	38	CPAP does not improve QOL	RCT
Depression					
Campos-F. Rodriges, 2016	HADS	AHI ≥ 15	307	CPAP improves depression	RCT
S. Redline, 1998	POMS	AHI ≥ 5	111	CPAP improves depression	RCT
B. Balcan, 2019	ZDS	AHI ≥ 15	244	CPAP improves depression	RCT
El Sherbini, 2011	HDRS	AHI ≥ 15	37	CPAP improves depression	Observational
A. Haensel, 2007	POMS	AHI ≥ 15	50	CPAP improves depression	Observational
C. Diamanti, 2013	CES-D	AHI ≥ 15	41	CPAP improves depression	Observational
M. Barnes, 2002	BDI	AHI ≥ 5	114	CPAP does not improve depression	RCT
F. Gagnadoux, 2014	Pichot	AHI ≥ 30	300	CPAP does not improve depression	Observational

AH apnea–hypopnea index, *CES-D* Center for Epidemiologic Studies Depression Scale, *CPAP* continuous positive airway pressure, *EDS* excessive daytime sleepiness, *ESS* Epworth Sleepiness Scale, *FOSQ* Functional Outcomes of Sleep Questionnaire, *HADS* Hospital Anxiety and Depression Scale, *HDRS* Hamilton Depression Rating Scale, *ODI* oxygen desaturation index, *POMS* Profile of Mood States, *QSQ* Quebec Sleep Questionnaire, *SF-36* Short Form of the Medical Outcomes Survey, *ZDS* Zung Self-rating Depression Scale

health survey (SF-12) in order to evaluate the quality of life. After 12 weeks of follow-ups, they have demonstrated that there was a significant improvement in each domain of quality-of-life measurements compared to no-CPAP group. They reported this improvement in both moderate and severe OSA; moreover, they suggested that improvement was more with increased CPAP adherence [15]. In another randomized controlled trial, McMillan et al. evaluated 278 elderly (Age ≥65 years) participants, who were randomized to CPAP (n = 140) and no CPAP (n = 138). Quality of life was evaluated by SF-36 questionnaire in this study. At baseline there was no significant difference between the groups regarding the quality-of-life evaluation; after 3 and 12 months, they observed an improvement in vitality and energy domains of SF-36 in CPAP group [14]. Another randomized controlled trial which evaluated quality-of-life change after CPAP treatment in OSA patients evaluated 169 patients (CPAP group [n = 83], controls [n = 86]). They reported improvement at sixth and twelfth months in vitality, general health, physical functioning, bodily pain, and physical health summary score domains of SF-36 [18]. HEARTBEAT

study is the other randomized controlled trial that used SF-36 for evaluation of impact of CPAP on health-related quality of life. They evaluated OSA patients with coronary heart disease, and they observed improvement in vitality and mental status domains in CPAP group regarding health-related quality of life; moreover, they reported participants with higher ESS scores had better improvement in quality-of-life measures [17].

In a few studies, benefit of CPAP treatment was not observed on quality of life in OSA patients [19–21]. Arandomized controlled trial by Barbe and colleagues evaluated 54 sleepy (ESS ≥ 11), severe (AHI ≥ 30 events/h) OSA subjects and compared 29 cases with 25 controls, and they did not report a significant improvement in quality of life at the end of 6 weeks [19]. In another randomized controlled, trial no improvement was observed in mild and moderate OSA participants after CPAP therapy. Phillips et al. and Barns et al. also did not report improvement in quality of life after CPAP treatment in OSA patients [21]. Impact of CPAP treatment on quality of life was summarized in Table 28.2.

28.3.3 Impact of Positive Airway Pressure on Depression

Association between OSA and depression has been recognized and evaluated for 40 years [22]. Although association between depressive mood and OSA had been established many times, mechanism between this relationship is unclear. Evaluation of depression is done by measures such as Beck Depression Inventory (BDI), Montgomery–Asberg Depression Rating Scale (MADRS), Hospital Anxiety and Depression Scale (HADS), Hamilton Depression Rating Scale (HAM-D), and Zung Self-rating Depression Scale. Previously it was demonstrated that there is a connection between depressive mood, quality of life, and excessive daytime sleepiness and OSA. The best improvement in depression and excessive daytime sleepiness is observed after 3 months of CPAP therapy in OSA [22]. There are studies addressing the benefits of CPAP on depression in OSA [15, 23–26]; on the other hand, in some studies, no effect of CPAP on depression has been observed in sleep clinic cohorts [27–29].

Campos Rodriguez and colleagues conducted a multicenter randomized controlled trial with 307 women. They evaluated daytime sleepiness, quality of life, as well as depressive mood in moderate-to-severe OSA participants. Assessment of mood and depression was done by Hospital Anxiety and Depression (HADS) questionnaire and Abbreviated Profile of Mood States (POMS). They reevaluated participants after 3 months of CPAP therapy, and they reported improvement in mood state and depression besides the improvement of quality of life and daytime sleepiness in both moderate and severe OSA [15]. In another randomized controlled trial, Redline et al. assessed the effect of CPAP treatment versus conservative treatment on depression in 111 mild-to-moderate OSA participants. They measured depressive mood with POMS; 50% of the CPAP group and 25% of the controls had shown improvement in depressive mood after 8 weeks of follow-ups. Improvement in CPAP group was significantly better compared to conventional therapy group [26]. Another randomized controlled trial conducted by Balcan and colleagues evaluated 244 coronary artery disease patients with non-sleepy (ESS < 10) OSA. Assessment of depression was done by Zung Self-rating Depression Scale score questionnaire. In the follow-ups, they reported a significant decline in depression scores; however in no-CPAP group, scores remained unchanged at 3 and 12 months; moreover, they observed that improvement in depressive mood was better by increased CPAP adherence [30]. El Sherbini et al. evaluated 37 OSA adults with mean AHI = 27.7 events/h prospectively; they performed Hamilton Depression Rating Scale (HDRS) for assessment of depression and reevaluated them after 2 months of CPAP treatment. Nearly 60% of the participants diagnosed as depressive clinically; they reported significant correlation between depression and OSA parameters such as AHI and ODI; moreover, they observed significant improvement in depression after CPAP treatment [23]. Haensel and

colleagues designed a double-blinded placebo controlled study with OSA (AHI ≥ 15 events/h) patients; after 2 weeks of treatment (CPAP and sham-CPAP [a device that gives pressure in untherapeutic dose]), they evaluated mood. They used POMS for assessment of depression, and they observed improvement after treatment; however, there was decline in depression scores in both groups, and there was no difference between group analysis [24]. In another observational study, Diamanti et al. evaluated 41 OSA patients; they assessed depression with the Center for Epidemiologic Studies Depression Scale (CES-D); finally after 6 months of treatment, they reported a significant decrease in depressive mood in the participants [25].

In some sleep clinic cohorts, no significant correlation was demonstrated between CPAP treatment and improvement in depressive mood. In a randomized controlled trial, the efficacy of CPAP treatment on depressive mood in mild-to-moderate OSA was evaluated. One hundred and fourteen participants were recruited for 3 months of CPAP therapy, a mandibular advancement splint, and a placebo tablet. Sleep parameters (AHI, ODI, etc.), as well as quality-of-life measures, were improved at the end of the follow-ups in treatment groups; however, improvement in depressive measures in treatment groups was not significantly better than control group [29]. Gagnadoux et al. evaluated 300 OSA patients with depressive mood diagnosed by 13-item, self-rated Pichot Depression Scale [QD2A]7 questionnaire. After 1 year of CPAP treatment, they assessed persistent depressive symptoms and reported that there was no resolution in depressive symptoms after CPAP therapy; moreover, there was a strong association with persistent depression and excessive daytime sleepiness [27].

28.4 Conclusion

Loud snoring and witnessed apnea are the most decisive symptoms of OSA, but these symptoms cannot be self-reported. Quality of life, excessive daytime sleepiness, and depressive mood are the associates and are the self-reported symptoms of OSA. Clinic may be presented by only with impaired quality of life or together with excessive daytime sleepiness and depressive mood. The definite treatment option is PAP in OSA; apneas, hypopneas, and desaturations can be healed by positive pressure. But beside the nature of the disease, it is also important to heal the presenting symptoms of the patients. There are many studies which evaluated progress in quality-of-life depression and daytime sleepiness in OSA populations. Most of the studies favor CPAP treatment for improvement of those symptoms in OSA patients. Very few of the studies had reported no improvement in daily symptoms after CPAP treatment. Effectiveness of CPAP therapy depends on some factors: compliance, duration of devise usage, and comfortable mask. Fort an effective treatment in quality of life and daily symptoms, PAP device should be used at least 4 h per night with a comfortable mask, and probable improvement can usually be observed after 3 months of PAP treatment.

References

1. Bradley TD, Phillipson EA. Pathogenesis and pathophysiology of the obstructive sleep apnea syndrome. Med Clin North Am. 1985;69:1169–85.
2. Thunstrom E, Manhem K, Yucel-Lindberg T, Rosengren A, Lindberg C, Peker Y. Neuroendocrine and inflammatory responses to losartan and continuous positive airway pressure in patients with hypertension and obstructive sleep apnea. A randomized controlled trial. Ann Am Thorac Soc. 2016;13:2002–11.
3. Lynch MK, Elliott LC, Avis KT, Schwebel DC, Goodin BR. Quality of life in youth with obstructive sleep apnea syndrome (osas) treated with continuous positive airway pressure (cpap) therapy. Behav Sleep Med. 2019;17:238–45.
4. Balcan B, Thunstrom E, Strollo PJ Jr, Peker Y. Determinants of depressive mood in coronary artery disease patients with obstructive sleep apnea and response to continuous positive airway pressure treatment in non-sleepy and sleepy phenotypes in the riccadsa cohort. J Sleep Res. 2019;28:e12818.
5. Brewster GS, Hirschman KB, Riegel BJ, Hanlon AL, Huang L, McPhillips MV, et al. Association of health related quality of life domains with daytime sleepiness among elderly recipients of long-term services and supports. Geriatr Nurs. 2019;40:417.
6. Batool-Anwar S, Goodwin JL, Kushida CA, Walsh JA, Simon RD, Nichols DA, et al. Impact of continuous positive airway pressure (cpap) on quality of life in patients with obstructive sleep apnea (osa). J Sleep Res. 2016;25:731–8.

7. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an american academy of sleep medicine systematic review, meta-analysis, and grade assessment. J Clin Sleep Med. 2019;15:335–43.
8. Hoyos CM, Bartlett DJ, Phillips CL. Is obstructive sleep apnea a risk factor for depression in coronary artery disease? Ann Am Thorac Soc. 2019;16:49–50.
9. Ohayon MM. The effects of breathing-related sleep disorders on mood disturbances in the general population. J Clin Psychiatry. 2003;64:1195–200. quiz: 274–6.
10. Vandeputte M, de Weerd A. Sleep disorders and depressive feelings: a global survey with the beck depression scale. Sleep Med. 2003;4:343–5.
11. Wahner-Roedler DL, Olson EJ, Narayanan S, Sood R, Hanson AC, Loehrer LL, et al. Gender-specific differences in a patient population with obstructive sleep apnea-hypopnea syndrome. Gend Med. 2007;4:329–38.
12. Antic NA, Catcheside P, Buchan C, Hensley M, Naughton MT, Rowland S, et al. The effect of cpap in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe osa. Sleep. 2011;34:111–9.
13. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, et al. Relationship between hours of cpap use and achieving normal levels of sleepiness and daily functioning. Sleep. 2007;30:711–9.
14. McMillan A, Bratton DJ, Faria R, Laskawiec-Szkonter M, Griffin S, Davies RJ, et al. Continuous positive airway pressure in older people with obstructive sleep apnoea syndrome (predict): a 12-month, multicentre, randomised trial. Lancet Respir Med. 2014;2:804–12.
15. Campos-Rodriguez F, Queipo-Corona C, Carmona-Bernal C, Jurado-Gamez B, Cordero-Guevara J, Reyes-Nunez N, et al. Continuous positive airway pressure improves quality of life in women with obstructive sleep apnea. A randomized controlled trial. Am J Respir Crit Care Med. 2016;194:1286–94.
16. Foster SN, Hansen SL, Scalzitti NJ, Matsangas P, Moore BA, Mysliwiec V. Residual excessive daytime sleepiness in patients with obstructive sleep apnea treated with positive airway pressure therapy. Sleep Breath. 2019;22:589.
17. Lewis EF, Wang R, Punjabi N, Gottlieb DJ, Quan SF, Bhatt DL, et al. Impact of continuous positive airway pressure and oxygen on health status in patients with coronary heart disease, cardiovascular risk factors, and obstructive sleep apnea: a heart biomarker evaluation in apnea treatment (heartbeat) analysis. Am Heart J. 2017;189:59–67.
18. Zhao YY, Wang R, Gleason KJ, Lewis EF, Quan SF, Toth CM, et al. Effect of continuous positive airway pressure treatment on health-related quality of life and sleepiness in high cardiovascular risk individuals with sleep apnea: best apnea interventions for research (bestair) trial. Sleep. 2017;40(4)
19. Barbe F, Mayoralas LR, Duran J, Masa JF, Maimo A, Montserrat JM, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. A randomized, controlled trial. Ann Intern Med. 2001;134:1015–23.
20. Barnes M, Houston D, Worsnop CJ, Neill AM, Mykytyn IJ, Kay A, et al. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. Am J Respir Crit Care Med. 2002;165:773–80.
21. Phillips CL, Yee BJ, Marshall NS, Liu PY, Sullivan DR, Grunstein RR. Continuous positive airway pressure reduces postprandial lipidemia in obstructive sleep apnea: a randomized, placebo-controlled crossover trial. Am J Respir Crit Care Med. 2011;184:355–61.
22. Gupta MA, Simpson FC, Lyons DC. The effect of treating obstructive sleep apnea with positive airway pressure on depression and other subjective symptoms: a systematic review and meta-analysis. Sleep Med Rev. 2016;28:55–68.
23. El-Sherbini AM, Bediwy AS, El-Mitwalli A. Association between obstructive sleep apnea (osa) and depression and the effect of continuous positive airway pressure (cpap) treatment. Neuropsychiatr Dis Treat. 2011;7:715–21.
24. Haensel A, Norman D, Natarajan L, Bardwell WA, Ancoli-Israel S, Dimsdale JE. Effect of a 2 week cpap treatment on mood states in patients with obstructive sleep apnea: a double-blind trial. Sleep Breath. 2007;11:239–44.
25. Diamanti C, Manali E, Ginieri-Coccossis M, Vougas K, Cholidou K, Markozannes E, et al. Depression, physical activity, energy consumption, and quality of life in osa patients before and after cpap treatment. Sleep Breath. 2013;17:1159–68.
26. Redline S, Adams N, Strauss ME, Roebuck T, Winters M, Rosenberg C. Improvement of mild sleep-disordered breathing with cpap compared with conservative therapy. Am J Respir Crit Care Med. 1998;157:858–65.
27. Gagnadoux F, Le Vaillant M, Goupil F, Pigeanne T, Chollet S, Masson P, et al. Depressive symptoms before and after long-term cpap therapy in patients with sleep apnea. Chest. 2014;145:1025–31.
28. Borak J, Cieslicki J, Szelenberger W, Wilczak-Szadkowska H, Koziej M, Zielinski J. Psychopathological characteristics of the consequences of obstructive sleep apnea prior to and tree months after cpap. Psychiatr Pol. 1994;28:33–44.
29. Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med. 2004;170:656–64.
30. Balcan B, Thunstrom E, Strollo PJ Jr, Peker Y. Continuous positive airway pressure treatment and depression in adults with coronary artery disease and nonsleepy obstructive sleep apnea. A secondary analysis of the riccadsa trial. Ann Am Thorac Soc. 2019;16:62–70.

Part III

Pulmonary Critical Care

Bushra Mina and Jun Duan

NIV Modes and Settings

29

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Abbreviations

6MWT	6-min walk tests
A mode	Assist mode
A/C mode	Assist–control mode
AHI	Apnea–hypopnea index
AHRF	Acute hypercapnic respiratory failure
ARF	Acute respiratory failure
ASV	Adaptive servo ventilation
AVAPS	Average volume-assured pressure support
BPAP	Bilevel positive airway pressure
Bpm	Breaths per minute
C mode	Control mode
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continue positive airway pressure
CSAS	Central sleep apnea syndrome
EAdi	Electrical activity of the diaphragm
EPAP	Expiratory positive airway pressure
FA	Flow assist
FiO_2	Fractional inspired oxygen concentration
HF	Heart failure
I/*E* ratio	Inspiratory/expiratory ratio
IBW	Ideal body weight
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
LVEF	Left ventricular ejection fraction
n	Number of patients
NAVA	Neurally adjusted ventilator assist
NIV	Noninvasive mechanical ventilation
NPPV	Noninvasive positive pressure ventilation
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PAP	Positive airway pressure
PAV	Proportional assist ventilation
Paw	Airway pressure
PEEP	Positive end-expiratory pressure
PS	Pressure support
PSV	Pressure support ventilation
PTM	Pressure-targeted mode
QoL	Quality of life
RCT	Randomized control trial
S mode	Spontaneous mode
SBT	Spontaneous breathing trial
SMC	Standard medical care
T mode	Timed mode
V/*Q*	Ventilation/perfusion
VA	Volume assist
Vt	Tidal volume
VTM	Volume-targeted mode

29.1 Introduction

Noninvasive mechanical ventilation (NIV) is a ventilator support which provides ventilation via the patient's nose, mouth, or both without the use of an artificial airway (endotracheal tube, tracheostomy). NIV has been increasingly used in the acute care setting for acute respiratory failure (ARF) and plays an important role in these patients. NIV decreases work of breathing and improves gas exchange and lung compliance. The use of NIV reduces need for intubation. That's why it is decreased in the incidence of complications of positive pressure ventilation such as ventilatory-associated pneumonia, baro-

trauma, and volutrauma. Besides, NIV preserves airway defense mechanisms and allows patients to speak, eat, drink, and expectorate secretions. This chapter will mainly focus on the classic and new NIV modes and their settings.

29.2 Terms Used in NIV

It is important to understand the terminology used in NIV.

1. **Positive end-expiratory pressure (PEEP):** PEEP is a positive airway pressure at end-expiratory phase. There are mechanical breaths.
2. **Expiratory positive airway pressure (EPAP):** EPAP controls end-expiratory pressure. It is used as continuous positive airway pressure (CPAP) when inspiratory positive airway pressure (IPAP) = EPAP. Moreover, it is used as PEEP when IPAP > EPAP.
3. **IPAP:** IPAP controls peak inspiratory pressure during inspiration. IPAP = Pressure Support (PS) + PEEP or PS + EPAP.
4. **CPAP:** CPAP provides positive airway pressure during spontaneous breaths. There are no mechanical breaths. CPAP is active when IPAP = EPAP.
5. **Bilevel positive airway pressure (BPAP):** BPAP provides IPAP and EPAP. CPAP is active when IPAP = EPAP.

29.3 How Is Inspiratory and Expiration Determined in the Ventilator During NIV?

Either the patient or the ventilator can control both the onset (e.g., triggering) and the end of inspiration (e.g., cycling into expiration).

29.3.1 Spontaneous Mode (S Mode)

This mode only can be used in pressure-targeted mode (PTM) and is also called pressure support ventilation (PSV) [1]. The initiation and end of inspiration are controlled by the patient. The patient triggers the ventilator and inspiration starts. During the low-level expiratory pressure (EPAP), the patient's inspiratory effort modifies the pressure and flow into the circuit, starting the change to the higher inspiratory pressure (IPAP). The pressure is maintained so long as a minimal preset inspiratory flow is occurring. Inspiratory flow reaches a predetermined percentage of peak inspiratory flow, and the pressure in the circuit reverses to EPAP, and then inspiration finishes. The levels of ventilatory support, trigger sensitivity, and peak flow are the main variables determining the patient's work of breathing. In some ventilators, the clinician can select a targeted inspiratory pressure, inspiratory trigger sensitivity, fractional inspired oxygen concentration (FiO_2), and a percentage threshold of peak flow for cycling to expiration. However, in other ventilators, only the inspiratory pressure can be set.

29.3.2 Assist Mode (A Mode)

When using A mode, in mechanical ventilator settings, FiO_2, inspiratory trigger sensitivity, inspiratory time or inspiratory: expiratory ratio (*I*:*E*), a target pressure or volume are set. The patient controls the initiation of inspiration, and the clinician regulates the inspiratory length.

29.3.3 Assist–Control Mode (A/C Mode)

In this mode the patient triggers the ventilator, and the inspiration begins with the patient's effort. However, if the patient doesn't initiate breathing in the predefined time interval, the ventilator starts the inspiration. In this mode, the backup respiratory rate is selected which is different from the A mode. If the patient's spontaneous respiratory rate is lower than the preset ventilatory backup respiratory rate, the ventilator moves to control mode. This situation prevents apnea and related complications.

29.3.4 Control Mode (C Mode)

In some ventilators, this mode is also called "Timed (T) mode" and is seldom used [1]. There is a predefined automatic cycle based on time. In this mode, only the ventilator initiates and ends inspiration. All of the work of breathing is performed by the ventilator. The clinician selects FiO_2, a respiratory rate, inspiratory and expiratory times or *I*/*E* ratio, a targeted pressure, or volume.

29.4 The Ventilatory Cycle

Appropriate settings of NIV are vital to provide optimal patient–ventilator synchrony and an appropriate tolerance by the patient. Hence, we must know how a ventilator acts and how patient–ventilator synchronize and must analyze the different phases of a typical positive pressure ventilatory cycle.

29.4.1 Triggering

The initiation of inspiration can be triggered by patient effort or time. As the patient begins to inhale, the ventilator detects a change in flow or pressure, which triggers the ventilator change from expiratory to inspiratory pressure. NIV devices have two types of triggers which are pressure-based trigger or flow-based trigger. The pressure-based trigger is based on a fall in proximal airway pressure and needs a closed circuit. Older NIV ventilators have it. The flow-based trigger is based on detection of an inspiratory flow in the presence of a continuous flow washing out the circuit during expiration, and new NIV devices have it.

Asynchrony during the inspiratory phase is quite common during sleep in patients under NIV. It may affect sleep quality and ventilatory efficacy. It is affected by trigger sensitivity, delay duration, and pre-inspiratory effort. The inspiratory trigger should have a short delay of response. Even in the presence of leaks, inspiratory trigger should be sensitive enough to permit the patient to trigger easily. It should be <100 ms [1]. If it is high value, the work of breathing increases, and asynchrony develops. This situation causes NIV failure.

Triggering depends on the circuit type used, the intrinsic PEEP level, the presence of the leaks, and the patient profile. Leaks may cause a pressure or flow drop resulting in auto-triggering. They may also contribute to ineffective inspiratory effort by preventing the detection of the patients inspiratory effort. Some ventilators enable the clinicians to set the trigger sensitivity in order to overcome these issues.

29.4.2 Pressurization

The pressurization for patient is vital to decrease inspiratory effort and improve synchronization. Inspiratory flow should be sufficient to meet inspiratory demand. Situations affecting pressurization are the inspiratory effort of patient, compliance, and resistance of the respiratory system, the rise time, and the level of ventilatory support.

Rise time is the time taken to reach IPAP after the onset of the inspiratory phase and is also called pressurization slope. COPD patients tend to prefer relatively rapid rise time (0.05–0.1 s), whereas patients with neuromuscular diseases prefer a slower one (0.3–0.4 s) [1]. If there is a high ventilatory demand of patient, short rise time should be set. For example, patients with COPD need a shorter inspiratory and a longer expiratory time. In patients with a slower respiratory rate, increasing rise time can improve comfort. A long rise time can result in a decrease in the effective tidal volume (Vt) delivered to the patient. The actual rise time achieved is affected by lung compliance, leaks, and patient breathing patterns.

Fall time is the time taken for the inspiratory pressure to fall after the ventilator cycles into expiration [2]. Some ventilators enable the clinicians to set the fall time.

29.4.3 IPAP

IPAP is the pressure delivered by the ventilator as the patient is inhaling. This establishes the PS (IPAP minus EPAP) that provides assistance to inspiration and decreases the work of breathing by leading to increased Vt and minute ventilation, unloading respiratory muscles and improving gas exchange.

29.4.4 EPAP

PEEP is an above-atmospheric (positive) pressure applied during expiration. When positive pressure is applied during machine breaths, it is called PEEP. When the positive pressure is applied during spontaneous breathing, the term CPAP is used. PEEP is called EPAP in bilevel devices. PEEP during NIV provides many advantages. It flushes dead space CO_2, prevents rebreathing, and reduces dynamic hyperinflation. So, PEEP reduces inspiratory work required to trigger assisted inspiration. PEEP assists with the maintenance of upper airway patency during sleep in patients with unstable upper airway, helps to recruit and maintain lung volume, and improves oxygenation. Since inspiratory pressure must be increased in parallel if inspiratory assistance is to be maintained, which can lead to intolerance and favor leaks [1], the PEEP setting may interfere with either PS or IPAP levels. The application of a high level of PEEP may result in hemodynamic impairment.

29.4.5 Volume

Vt or minute volume can be set in some ventilators.

29.4.6 Backup Rate

A backup rate can be set by the clinician to ensure a minimum ventilation level for the patient in some modes. When the patient's spontaneous breathing rate falls below the backup rate level, the ventilator delivers timed breaths. This situation is crucial to patients with impaired central respiratory drive during sleep.

29.4.7 Cycling

Respiratory cycling is the length of one complete breathing cycle. Switching from inspiration to expiration can be flow cycled or time cycled. If the ventilators use a time criteria set by the clinician, it is called time-cycled mode. In the flow-cycled mode, cycling occurs as inspiratory flow decreases to a preadjusted percentage of the peak inspiratory flow, which is supposed to indicate the end of inspiratory effort [1]. Ideally, cycling should coincide with the end of patient effort. Patient–ventilator asynchrony may occur if the flow at which the ventilator cycles to exhalation does not coincide with the termination of neural inspiration. Leaks can affect cycling, as though the leak flow is greater than the ventilator's flow cycle criteria, the inspiratory phase will continue. In some modes, cycling can occur after a preset time through the setting of inspiratory time limits, as described earlier [2].

29.4.8 Inspiratory Time Limits

Some ventilators enable the clinician to set an inspiratory time. It ensures that the ventilator delivers the inspiratory pressure for a set time only, regardless of the patient's spontaneous breathing pattern. Another ventilator mode may require parameters such as minimum and maximum inspiratory time for inspiratory time to be set. Inspiratory time limits aim to avoid the problems of premature and late cycling. Premature cycling is simply when the ventilator terminates the breath while the patient requires a longer inspiratory period. That is, the inspiratory time is too short for adequate respiratory support. Inspiratory muscles continue to contract, causing the mechanical ventilator to sense a second effort and possibly resulting in a second breath, com-

monly referred to as double triggering. Asynchrony may causes decreased Vt, increased inspiratory load, and inaccurate display respiration of respiratory rate. Often as a result of circuit leaks, inspiratory time may be too long; it causes insufficient time for expiration and leads to the development of intrinsic PEEP. This situation means late cycling.

29.5 Effect of the Ventilatory Mode

NIV can be delivered using the same modes used for invasive mechanical ventilation. Basically, the Vt can be given either as a volume target or as a pressure target. Additionally, hybrid modalities can be used for NIV.

29.5.1 Volume-Targeted Mode (VTM)

The ventilator delivers a fixed Vt throughout a given time, and the pressure is variable to achieve the fixed volume. Pressure in the airways (Paw) results from the interaction between spontaneous inspiratory efforts, compliance and resistance of the respiratory system, and ventilatory settings. VTM is also called the flow-limited mode.

29.5.2 Pressure-Targeted Mode (PTM)

PTM is also called the pressure-limited mode [1]. The ventilator in the PTM mode is set to deliver air flow via generating a predefined positive pressure in the airways for a given time. The airflow is set so as to establish and maintain a constant Paw according to the preset pressure. Constant analysis of the flow rate and airway pressure determines the flow variations which are necessary to maintain square wave pressure. Flow is active at the beginning of inspiration when the gradient between the circuit pressure and the pressure target is great. As the gradient narrows, the flow decelerates until driving pressure no longer exists and flow ceases. The volume delivered to the patient during PTM depends on the interaction between the preset pressure, inspiratory time, the patient's inspiratory effort, compliance, and resistance of respiratory system of the patient. Therefore, the volume delivered to the patient during PTM is not constant.

PTM ventilators may use circuits with or without an expiratory valve. Simple-circuit PTM ventilators without an expiratory valve are used the most for NIV. These devices are provided with a calibrated leak and cycle between IPAP and EPAP. The levels of IPAP and EPAP are set independently. An important advantage of PTM is the ability to compensate for mild–moderate leaks.

29.5.3 Which Will We Select: Volume or Pressure-Targeted Mode?

VTM and PTM have been commonly used with great success. However, both of them have advantages and disadvantages. Initially, the majority were ventilated successfully using volume-targeted ventilators. Currently, most patients are ventilated using pressure-targeted ventilators, since the PTM setting is better tolerated by the patient. Clear data showing benefits for PTM in high-impact endpoints such as improvements in gas exchange or sleep quality, in health-related quality of life (QoL), and mortality are not available [2]. Even so, due to the higher comfort, PTM has become the mode most frequently used in surveys and scientific studies [2]. With the rapid development of technology, the advantages of volume and pressure mode have been combined in one mode (hybrid mode).

An individualized approach is usually necessary to apply the best mode and setting for the patient. First of all, the pathology causing respiratory failure and the presence of sleep-related breathing disorders should be investigated. The

ventilator modes and settings should be targeted with respect to this information.

29.5.4 Volume-Targeting Pressure Mode

PTM has an disadvantage that cannot guarantee a Vt delivered to the patient [1]. Volume targeting is a feature available in some bilevel ventilators that can allow overweighting of this limitation. Volume-targeting pressure mode is a hybrid mode which combines the advantages of the pressure and volume modes. During this mode, the ventilator estimates the delivered tidal volume and adjusts parameters to achieve a target Vt. Some ventilators adjust a target volume; each breath starts as a pressure-limited breath, and the breath converts to a flow-cycled mode by prolonging the inspiratory time if the preset Vt is not reached. The PS should be determined to provide a Vt as close as possible to the set target volume.

29.6 Classic Modes and Settings for NIV

29.6.1 CPAP

CPAP is a spontaneous breathing mode. Patients are required to start all of their breaths; no mandatory breaths are delivered. When the CPAP is adjusted, the airflow is introduced into the airways to maintain a pressure to continuously stent the airways open, in people who are breathing spontaneously. PEEP is the pressure in the alveoli that is above atmospheric pressure at the end of expiration. CPAP, a way of delivering PEEP, also maintains the set pressure during both inspiration and expiration unlike PEEP. It is recommended to set the flow triggering when using CPAP. Because while in flow triggering, ventilator performance is better than pressure triggering. CPAP can increase functional residual capacity, decrease atelectasis, increase the surface area of the alveoli, improve ventilation/perfusion (*V*/*Q*) matching, reduce work of breathing, and, thus, improve oxygenation.

CPAP is suggested for patients with ARF due to cardiogenic pulmonary edema in the prehospital setting, early for immunocompromised patients with ARF and for patients with postoperative ARF and for chest trauma patients with ARF [3]. The patients with obesity hypoventilation syndrome (OHS) have coexisting obstructive sleep apnea (OSA). CPAP during sleep is the first-line treatment mode used in this patients [4]. In OSA, CPAP affects mainly the maintenance of upper airway patency. So, it prevents obstructive and hypopneic events. For fixed CPAP, the optimal settings are obtained during an attended laboratory polysomnogram with the patient wearing their device. CPAP starting level as 4 cm H_2O is recommended. Until upper airway obstruction is eliminated, the CPAP level is increased by 1–2 cm H_2O with at least 5-min intervals. The recommended maximum level of CPAP is 20 cm H_2O for adults. If the upper airway obstruction continues at 20 cm H_2O, transition to BPAP should be considered.

Lynch et al. studied QoL in youth with OSA syndrome treated with CPAP therapy. They found that CPAP adherence appears to be associated with positive changes in OSA syndrome-specific QoL domains [5].

29.6.2 BPAP

BPAP is a pressure-cycled mode used during NIV. It delivers both a preset IPAP and EPAP. IPAP and EPAP are independently titrated and set. The Vt correlates with the difference between the IPAP and the EPAP. A sensor in the airflow circuit detects a pressure change through the electronic transducer when the patient starts inspiration or expiration. It automatically switches between IPAP and EPAP settings. There is a continuous flow of air in the breathing circuit to facilitate the patient's breathing. When the patient starts to inhale, a decrease in current in the breathing circuit is

detected. The system thus supports ventilation in such a way that the amount of airflow in the circuit increases to the IPAP pressure level. The desired Vt is reached. The system supports breathing to at the EPAP level at the end of inspiration. When the inspiratory flow is reduced, the pressure in the circuit is rapidly decreased to the baseline level, and expiration of the patient is provided. EPAP prevents airway collapse. As an example, the Vt is greater using an IPAP of 14 cm H_2O and an EPAP of 5 cm H_2O (difference or delta of 9 cm H_2O), than an IPAP of 10 cm H_2O and an EPAP of 5 cm H_2O (difference or delta of 5 cm H_2O). Alveolar ventilation is enhanced by a larger Vt, assuming that the respiratory rate is constant. Most BPAP devices also allow a backup respiratory rate to be set.

Bilevel NIV is recommended NIV for patients with ARF leading to acute or acute-on-chronic respiratory acidosis (pH $\leq$ 7.35) due to COPD exacerbation and for patients with ARF due to cardiogenic pulmonary oedema [3]. Bilevel NIV is suggested for patients with ARF due to cardiogenic pulmonary edema in the prehospital setting, early for immunocompromised patients with ARF, for patients with postoperative ARF, for terminal cancer patients with ARF, for chest trauma patients with ARF, and to prevent post-extubation respiratory failure for high-risk patients post-extubation [3]. The patients with OHS, who fail CPAP, should be treated with BPAP. EPAP is set to overcome upper airway occlusion. IPAP is increased to augment ventilation further. Initial IPAP and EPAP are usually started at 8 cm H_2O and 4 cm H_2O, respectively. Their levels are increased until airway obstruction is resolved and hypoventilation is eliminated (maximum IPAP is typically 20–30 cm H_2O for adults). Increased IPAP in 1–2 cm H_2O increments provide more ventilatory assistance and larger Vt. Increased EPAP in 1–2 cm H_2O increments improve oxygenation or to relieve upper airway obstruction.

BPAP levels are started with low initial pressures, and thus tolerance of NIV is better. Initially IPAP and EPAP are 8–10 cm H_2O and 4–5 cm H_2O, respectively, for the patients with neuromuscular and chest wall disease. Inspiratory PS (IPAP minus EPAP) is 4–6 cm H_2O. Backup rate is set 2 bpm below resting respiratory rate.

For nocturnal ventilatory support in stable patients with COPD, the clinicians typically start with EPAP of 5 cm H_2O and IPAP of 10 cm H_2O, and level of IPAP and EPAP can gradually be increased. The maximum IPAP is 12–20 cm H_2O.

There are many studies about BPAP modes. Vasquez and coworkers performed a retrospective analysis of administrative claims data of hospitalizations in patients with COPD who received or did not receive positive airway pressure (PAP) therapy—CPAP, BPAP, and NIV using a home ventilator [6]. Prescription of BPAP (1.5%), CPAP (5.6%), and NIV (<1%) in patients with COPD demonstrated geographic, sex, and age-related variability. After adjusting for confounders and propensity score, NIV, BPAP, and CPAP were individually associated with lower hospitalization risk in the 6 months posttreatment when compared with the 6 months pretreatment but not when compared with the baseline period between 12 and 6 months prior to treatment initiation. The analysis suggested that comorbid sleep-disordered breathing, chronic respiratory failure, heart failure (HF), and age <65 years were associated with greater benefits from PAP therapy. They concluded that initiation of PAP therapy was associated with reduction in hospitalization among patients with COPD.

Elgebaly investigated whether BPAP improves the outcome of ARF after open-heart surgery. This study showed superiority of invasive over noninvasive mode of ventilator support. However, NIV was proven to be a safe method [7].

Neto et al. investigated the effects of NIV with BPAP exercise tolerance and dyspnea in HF patients [8]. The patients with New York Heart Association class I/II/III HF were randomly assigned either to a NIV group (n = 20) or control group (n = 20). All patients underwent two 6-min walk tests (6MWT), with a 30-min interval between them. In the NIV group, the patients performed BPAP with an IPAP of 12 cm H_2O and EPAP of 6 cm H_2O for 30 min. The NIV group showed a significant improvement in the 6MWT distance and dyspnea compared with the control group. They concluded that BPAP showed bene-

ficial effects on exercise tolerance and dyspnea. They thought that it was safe and well tolerated by HF patients. They suggested that it should be considered for inclusion in cardiac rehabilitation programs.

29.7 New Modalities and Settings for NIV

29.7.1 Proportional Assist Ventilation (PAV)

PAV is a new mode of ventilation being developed to improve patient–ventilator interaction. During PAV, the ventilator instantaneously delivers positive pressure throughout inspiration in proportion to patient-generated flow (flow assist, units cm H_2O/L/s) and volume (volume assist, units cm H_2O/L) [9]. PAV generates pressure in proportion to the patient's effort by amplifying the patient's inspiratory effort without a preselected pressure or volume target. PAV requires a spontaneously breathing patient. By varying the pressure generated from breath to breath, PAV preserves respiratory variability during breathing. PAV provides automatic synchrony between the patient and the ventilatory cycle. Thus, one of the most important causes of NIV failure is prevented.

There are several studies in which PAV is used as NIV and compared with other modes. Gay et al. compared noninvasive PAV with PSV [10]. With ARF, 44 patients (21 PAV and 23 PSV) were enrolled in the study. Firstly, patients were fitted with a standard nasal mask. PAV settings included flow assist (FA), the integrated flow signal (volume assist, VA), and a proportional adjustment of both signals. Standard initial settings (FA 2 cm H_2O/L/s, VA 5 cm H_2O/L, proportional assist 100%, and end-expiratory pressure of 4 cm H_2O) were used for all patients receiving PAV therapy. PSV was begun at an inspiratory pressure of 10 cm H_2O and an expiratory pressure of 4 cm H_2O. Settings were gradually adjusted upward as tolerated in both modes. FiO_2 was adjusted to maintain O_2 saturation ≥88%. Mortality and intubation rates were similar, but refusal rate was lower, reduction in respiratory rate was more rapid, and there were fewer complications in the PAV group. They concluded that the use of the PAV mode was feasible for noninvasive therapy of ARF. They found that compared with PSV, PAV is associated with more rapid improvements in some physiologic variables and is better tolerated. This study is the first randomized, prospectively designed study to demonstrate the feasibility of using PAV to deliver NPPV, administered using a practical initiation strategy based on simple clinical indices.

Fernández-Vivas et al. compared the effects of PSV and PAV during NIV in the treatment of ARF [11]. This prospective randomized study included 117 adult patients with ARF (59 PSV and 58 PAV). No significant differences were observed between PSV and PAV in the frequency of intubation, mortality rate, and mean length of stay. Subjective comfort (0–10 visual analog scale) was rated higher, and intolerance occurred less frequently (3.4% vs. 15%, $p < 0.05$) in the PAV than in the PSV mode. They thought that no major differences exist in terms of physiological improvement or in terms of outcomes when comparing PSV and PAV, although PAV seems more comfortable, and intolerance occurred less frequently.

Rusterholtz and coworkers found that PAV was not superior to CPAP for NIV in severe cardiogenic pulmonary edema with regard to either efficacy and tolerance [12].

In a study, Tawfeek and Elnabtity evaluated the effectiveness of noninvasive PAV as a method of weaning in patients who could not tolerate spontaneous breathing trial (SBT). They concluded that noninvasive PAV could be added safely and effectively in the mechanical ventilation weaning protocol for patients who meet simple weaning criteria but failed SBT and have no contraindications to NIV [13].

Vijayaraghavan et al. studied about evidence supporting clinical use of PAV [14]. They found that of the four trials evaluating noninvasive applications, all evaluated PAV as an initial support strategy to avoid intubation. They concluded that current evidence did not support the use of noninvasive PAV in critically ill adults.

29.7.2 Neurally Adjusted Ventilator Assist (NAVA)

NAVA is a novel ventilatory mode of ventilation that uses the electrical activity of the diaphragm (EAdi) to control the ventilator [15]. The EAdi represents the neural effort, both with respect to timing and amplitude, and is pneumatically independent. NAVA is associated with a better patient–ventilator synchrony compared to PSV during NIV for ARF.

Beck et al. have become the first researchers to use noninvasive NAVA in rabbits with acute lung injury [16]. In the study, they have found that NAVA can be effective in delivering NIV even when the interface with the patient is excessively leaky and can unload the respiratory muscles while maintaining synchrony with the subject's demand.

The study, researched by Cammarato et al., compared neurally controlled PS with pneumatically controlled PS and NAVA, delivered through two different helmets, in hypoxemic patients receiving NIV for prevention of extubation failure [17]. They have found that neurally controlled PS improves comfort and patient–ventilator interactions.

Seghal et al. performed a systematic review of studies comparing the two modes of NIV [18]. Their search yielded nine studies investigating the use of PSV versus NAVA during NIV for ARF. The results of this study have suggested that PSV during NIV for ARF is associated with a significantly higher asynchrony index and a 3.4% times higher risk of severe asynchrony in comparison to NAVA. They suggested that the results highlight a paucity of clinical data on the use of NAVA during NIV in the management of ARF.

Longhini et al. compared neurally controlled PS with PS during NIV using a facial mask, with respect to patient comfort, gas exchange, and patient–ventilator interaction and synchrony [19]. They found that neurally controlled PS improved comfort and patient–ventilator interaction during NIV by facial mask and also improved synchrony, as opposed to pressure support only.

29.7.3 Average Volume-Assured Pressure Support (AVAPS)

Some mechanical ventilators have hybrid modes, the advantages of pressure and volume settings have combined in these modes. During the use of AVAPS, target Vt is initially determined. Then, maximum IPAP, minimum IPAP, and EPAP are selected. The values of ventilation variables are not certain. If the target Vt is not achieved, IPAP value increases to the set maximum IPAP to reach the target Vt. Otherwise, if the patient's respiratory effort increases and the target Vt value is exceeded, IPAP value decreases to minimum IPAP. These changes occur gradually in minutes to ensure comfort and adaptation of patient.

AVAPS mode is often used in patients with COPD and OHS. There are many studies on the use of AVAPS mode. Briones Claudett et al. reported the first case-control study with benefits in 11 patients with COPD and hypercapnic encephalopathy [20]. Ciftci et al., in a study, determined factors that affected AVAPS's use in 106 patients with COPD and acute hypercapnic respiratory failure (AHRF) and assessed the feasibility of AVAPS [21]. The ventilatory parameters were initially programmed in the AVAPS with IPAP minimum value of 12 cm H_2O, IPAP maximum value of 26 cm H_2O, and EPAP value of 5 cm H_2O. The initial Vt was at 8–10 mL/kg of ideal body weight (IBW) and then adjusted according to patient tolerance and clinical outcome. They found that the use of AVAPS mode was successful in 81 (76.4%) patients. They have suggested that NIV with AVAPS should be instituted early, before severe respiratory acidosis develops in patients with COPD-associated AHRF.

A study in patients with acute or acute-on-chronic hypercapnic respiratory failure compared PS (bilevel pressure ventilation/BiPAP-S) and AVAPS modes [22]. Additionally, short-term effects of body position and obesity within both modes were analyzed. The decrease in the $PaCO_2$ levels in the AVAPS mode per session was remarkably high. However, the course was similar in both modes. Obesity and body positioning had no important effect on the $PaCO_2$ response

and ventilator mechanics in the study. Moreover, its sample size was not adequate to detect a significant difference between the modes.

AVAPS mode is also used in patients with de novo hypoxemic respiratory failure. Briones-Claudett and coworkers have studied the use of the BiPAP S/T-AVAPS ventilatory strategy in patients with mild to moderate de novo hypoxemic respiratory failure in a nonrandomized single-center prospective pilot study [23]. They have found that the BiPAP S/T-AVAPS ventilatory mode can be used in subjects with de novo hypoxemic respiratory failure. They have suggested that high inspiratory pressures and high exhaled tidal volumes could serve as guides in no-responders in order to avoid delays in intubation and higher mortality.

Huang and coworkers investigated a study which compared the effects and compliance between volume-assured and PS NIV in patients with chronic respiratory failure [24]. They found that there was no significant difference in clinical outcomes in spite of theoretical and demonstrable differences in performance. Yet, they have suggested that in clinical practice, individual patients' characteristics and their responses to alternative modes of ventilation differ.

29.7.4 Adaptive Servo-Ventilation (ASV)

ASV is a bilevel device that alternates between an inspiratory pressure and expiratory pressure (constant or variable). The difference between the expiratory and inspiratory pressure varies from breath to breath. The greater the difference in PS, the Vt is delivered the greater. The device is equipped with a feedback circuit which allows it to measure the respiratory output from the patient to individually regulate delivered PS. So, if the patien's respiratory effort increases, the machine's support decreases. The opposite is also true.

ASV targeted to normalize the apnea–hypopnea index (AHI) which can be used for the treatment of central sleep apnea syndrome (CSAS) related to congestive heart failure (CHF) in adults with an ejection fraction >45% or mild CHF-related CSAS. ASV targeted to normalize the AHI should not be used for the treatment of CSAS related to CHF in adults with an ejection fraction ≤45% and moderate or severe CSA predominant, sleep-disordered breathing. The recommendation against using ASV is based on evidence for increased risk of death in CHF patients with left ventricular ejection fraction (LVEF) ≤45%.

In periods of central apnea, the device alternates between expiratory and inspiratory pressure with a physician preset or automatic backup rate. ASV does not perform well when mask leak is high. In the ASV titrations, assuring good mask fit is especially important. Settings for expiratory pressure, PS, and a backup rate need to be set manually before titration. If the pressure needed to overcome airway obstruction is not known, or no obstructive apnea is present, the EPAP is initiated at the lowest setting (4–5 cm H_2O). If the pressure needed to overcome airway obstruction is not known, or no obstructive apnea is present, the EPAP is initiated at the lowest setting (4–5 cm H_2O). Then, EPAP is then gradually increased, typically in 1 cm H_2O increments, to eliminate obstructive apneas (with 20-min intervals at each pressure level). The clinicians set EPAP at the level of CPAP pressure that controlled obstruction or set EPAP on ASV device 2 cm H_2O below the CPAP level known to control obstructive apneas.

The level of PS is uncertain, and there is no agreement among experts [25]. Some experts support all breaths by setting a minimal PS in the 2–3 cm H_2O range. Maximal PS is set between 8 and 15 cm H_2O. Other experts limit the PS range to 5 cm H_2O [25]. The issue of supporting every breath when applying ASV is controversial. Because if PS is continued while hyperpnea is present, hypocapnia may be aggravated, which may increase central apnea. Hypocapnia can also damage cardiovascular function. For this reason, some experts can adjust the minimal PS to 0 cm H_2O.

There are many studies about NIV modes. Table 29.1 summarizes an important part of recent studies on classical and new NIV modes.

Table 29.1 Summaries of recent studies on classical and new NIV modes

Study ID	Study
Nava et al. [26]	NIV to prevent respiratory failure after extubation in high-risk patients
	Multicenter RCT
	PSV (n = 48) versus standard medical treatment (n = 49)
	NIV group had a lower rate of reintubation and a lower ICU mortality
Rusterholtz et al. [12]	CPAP versus PAV for NIV in acute cardiogenic pulmonary edema
	Prospective multicenter randomized study
	CPAP (n = 19) versus PAV (n = 17)
	Failure was observed in 7 (37%) CPAP and 7 (41%) PAV patients
	4 (21%) CPAP and 5 (29%) PAV patients required endotracheal intubation
	Changes in physiological parameters were similar
	Myocardial infarction and ICU mortality rates were strictly similar
	PAV was not superior to CPAP for NIV in severe cardiogenic pulmonary edema with regard to either efficacy or tolerance
Bertrand et al. [27]	NAVA versus PSV for NIV during ARF
	Prospective, crossover study
	NAVA (n = 13) versus PSV (n = 13)
	Significantly fewer asynchrony events during NAVA than during PSV
	Ineffective efforts and delayed cycling were significantly less with NAVA
	No significant differences in arterial blood gases or patient discomfort under PSV and NAVA
Cowie et al. [28]	ASV for central sleep apnea in systolic heart failure
	Multicenter, randomized, parallel-group, event-driven study
	1325 Patients with a LVEF of 45% or less
	ASV (n = 666) versus guideline-based medical treatment (n = 659)
	All-cause mortality and cardiovascular mortality were significantly higher in the ASV group than in the control group
Pagano et al. [29]	PSV versus CPAP for treating of acute cardiogenic pulmonary edema: A pilot study
	Multicenter observational pilot study
	PSV (n = 65) versus CPAP (n = 88)
	No significant differences regarding mortality in the two groups
	PSV group had a significant lower rate of endotracheal intubation and a higher improvement of blood gas analyses parameters
Huang et al. [24]	Comparing the effects and compliance between volume-assured and PS
	NIV in patients with chronic respiratory failure
	Meta-analysis
	No significant difference was observed between AVAPS and PS-NIV groups to compare $PaCO_2$ and PaO_2
	No significant difference between the two groups with sleep efficiency and visual analog scale
Berbenetz et al. [30]	Noninvasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary edema
	Systematic review and meta-analysis
	Compared with standard medical care (SMC), NPPV may reduce hospital mortality
	NPPV probably reduces endotracheal intubation rates
	Adverse events were generally similar between NPPV and SMC groups

CPAP continuous positive airway pressure, *PAV* proportional assist ventilation, *n* number of patients, *NIV* noninvasive mechanical ventilation, *ICU* intensive care unit, *ARF* acute respiratory failure, *NAVA* neurally adjusted ventilator assist, *PSV* pressure support ventilation, *RCT* randomized control trial, *ASV* adaptive servo-ventilation, *LVEF* left ventricular ejection fraction, *PS* pressure support, *AVAPS* average volume-assured pressure support, $PaCO_2$ partial pressure of carbon dioxide, PaO_2 partial pressure of oxygen, *NPPV* noninvasive positive pressure ventilation, *SMC* standard medical care

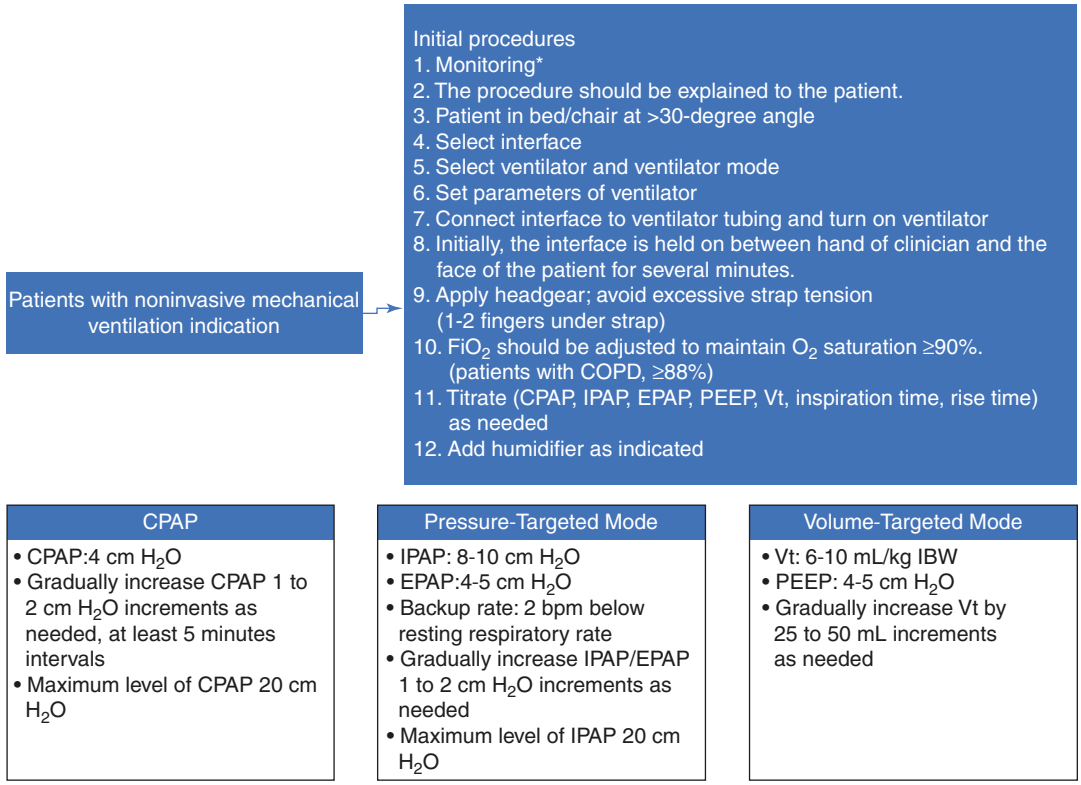

Fig. 29.1 Noninvasive mechanical ventilation algorithm. *FiO_2* fractional inspired oxygen concentration, *O_2* oxygen, *COPD* chronic obstructive pulmonary disease, *CPAP* continuous positive airway pressure, *IBW* ideal body weight, *IPAP* inspiratory positive airway pressure, *EPAP* expiratory positive airway pressure, *PEEP* positive end-expiratory pressure, *Vt* Tidal volume, *bpm* breaths per minute. ∗ The patient comfort, level of dyspnea, vital signs, O_2 saturation, accessory muscle use, patient–ventilatory synchrony, mask leak, and arterial blood gas should be monitored. Be alert to NIV failure symptoms

29.8 NIV Settings

When NIV is indicated for patients, the NIV mode and settings must be performed carefully. The NIV algorithm is shown in Fig. 29.1. The settings of other modes are described above.

29.9 Final Conclusion

The main conclusions of NIV modes and settings are summarized in Table 29.2.

Learning Points

1. Select the appropriate ventilator and ventilator mode.

Table 29.2 Main conclusions of NIV modes and settings

1. NIV is a ventilator support without the use of an artificial airway
2. The patient or the ventilator may control both the onset and the end of inspiration
3. Settings of NIV are important to provide optimal patient ventilatory synchrony
4. NIV may be pressure-targeted or volume-targeted
5. New modalities are able to combine features of both pressure-targeted and volume-targeted ventilator
6. NIV is usually used in the PTM that is better tolerated by the patients
7. Patient tolerance and pathology causing respiratory failure should be considered and settings of pressures must be titrated individually for patients
8. NIV is associated with reduction in morbidity and mortality compared with endotracheal intubation

NIV noninvasive mechanical ventilation, *PTM* pressure-targeted mode

2. Start the IPAP at 8–10 cm H_2O and the EPAP 4–5 cm H_2O.
3. Gradually increase the IPAP and the EPAP 1–2 cm H_2O increments as needed.
4. Monitor the patient for risk of developing NIV failure.

Critical Points

1. The inspiratory and expiratory determiners of the ventilator during NIV should be well known.
2. Patient–ventilator synchronization should always be given importance to prevent NIV failure.
3. Effect of ventilator mode should be well known.
4. The appropriate indication of NIV, the correct NIV mode, and the settings reduce morbidity and mortality.

Key Summary

More current studies are needed on NIV modes and settings. There should be better definition of patient's clinical characteristics to be assisted by NIV. Appropriate criteria should be established when NIV will start and when NIV will stop. The better modes and interfaces should be developed to ensure maximum patient–ventilator synchrony.

References

1. Esquinas AM, editor. Noninvasive mechanical ventilation theory, equipment, and clinical applications. 2nd ed. Cham; Heidelberg; New York, NY; Dordrecht; London: Springer; 2016.
2. Simonds AK. The ERS practical handbook of noninvasive ventilation. Lausanne: The European Respiratory Society; 2015.
3. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2):1602426. https://doi.org/10.1183/13993003.02426-2016.
4. Guan L, Wu W, Huo Y, et al. Efficacy of bilevel positive airway pressure and continuous positive airway pressure therapy in patients with obesity hypoventilation syndrome: protocol for systematic review and meta-analysis. BMJ Open. 2018;8(5):e020832. https://doi.org/10.1136/bmjopen-2017-020832.
5. Lynch MK, Elliott LC, Avis KT, et al. Quality of life in youth with obstructive sleep apnea syndrome (OSAS) treated with continuous positive airway pressure (CPAP) therapy. Behav Sleep Med. 2019;17(3):238–45. https://doi.org/10.1080/15402002.2017.1326918.
6. Vasquez MM, McClure LA, Sherrill DL, et al. Positive airway pressure therapies and hospitalization in chronic obstructive pulmonary disease. Am J Med. 2017;130(7):809–18. https://doi.org/10.1016/j.amjmed.2016.11.045.
7. Elgebaly AS. Does bilevel positive airway pressure improve outcome of acute respiratory failure after open-heart surgery? Ann Card Anaesth. 2017;20(4):416–21. https://doi.org/10.4103/aca.ACA_95_17.
8. Gomes Neto M, Duarte LFG, Rodrigues ES Jr, et al. Effects of noninvasive ventilation with bilevel positive airway pressure on exercise tolerance and dyspnea in heart failure patients. Hell J Cardiol. 2018;59(6):317–20. https://doi.org/10.1016/j.hjc.2017.11.005.
9. Navalesi P, Costa R. New modes of mechanical ventilation: proportional assist ventilation, neurally adjusted ventilatory assist, and fractal ventilation. Curr Opin Crit Care. 2003;9(1):51–8.
10. Gay PC, Hess DR, Hill NS. Noninvasive proportional assist ventilation for acute respiratory insufficiency. Comparison with pressure support ventilation. Am J Respir Crit Care Med. 2001;164:1606.
11. Fernández-Vivas M, Caturla-Such J, González de la Rosa J, et al. Noninvasive pressure support versus proportional assist ventilation in acute respiratory failure. Intensive Care Med. 2003;29:1126.
12. Rusterholtz T, Bollaert PE, Feissel M, et al. Continuous positive airway pressure vs. proportional assist ventilation for noninvasive ventilation in acute cardiogenic pulmonary edema. Intensive Care Med. 2008;34(5):840–6. https://doi.org/10.1007/s00134-008-0998-7.
13. Tawfeek MM, Elnabtity AMA. Noninvasive proportional assist ventilation may be useful in weaning patients who failed spontaneous breathing trial. Egypt J Anaesth. 2012;28(1):89–94.
14. Tirupakuzhi Vijayaraghavan BK, Hamed S, Jain A, et al. Evidence supporting clinical use of proportional assist ventilation: a systematic review and meta-analysis of clinical trials. J Intensive Care Med. 2018;1:885066618769021. https://doi.org/10.1177/0885066618769021.
15. Sinderby C, Navalesi P, Beck J, et al. Neural control of mechanical ventilation in respiratory failure. Nat Med. 1999;5(12):1433–6.
16. Beck J, Brander L, Slutsky AS, et al. Non-invasive neurally adjusted ventilatory assist in rabbits with acute lung injury. Intensive Care Med. 2008;34(2):316–23.
17. Cammarota G, Longhini F, Perucca R, et al. New setting of neurally adjusted ventilatory assist during noninvasive ventilation through a helmet. Anesthesiology. 2016;125(6):1181–9.
18. Sehgal IS, Dhooria S, Aggarwal AN, et al. Asynchrony index in pressure support ventilation (PSV) versus

neurally adjusted ventilator assist (NAVA) during non-invasive ventilation (NIV) for respiratory failure: systematic review and meta-analysis. Intensive Care Med. 2016;42(11):1813–5.
19. Longhini F, Pan C, Xie J, et al. New setting of neurally adjusted ventilatory assist for noninvasive ventilation by facial mask: a physiologic study. Crit Care. 2017;21(1):170. https://doi.org/10.1186/s13054-017-1761-7.
20. Briones Claudett KH, Briones Claudett M, Chung Sang Wong M, et al. Noninvasive mechanical ventilation with average volume assured pressure support (AVAPS) in patients with chronic obstructive pulmonary disease and hypercapnic encephalopathy. BMC Pulm Med. 2013;13:12. https://doi.org/10.1186/1471-2466-13-12.
21. Çiftci F, Çiledağ A, Erol S, et al. Evaluation of the feasibility of average volume-assured pressure support ventilation in the treatment of acute hypercapnic respiratory failure associated with chronic obstructive pulmonary disease: a pilot study. J Crit Care. 2017;39:232–7. https://doi.org/10.1016/j.jcrc.2016.12.023.
22. Türk M, Aydoğdu M, Gürsel G. Effects of modes, obesity, and body position on non-invasive positive pressure ventilation success in the intensive care unit: a randomized controlled study. Turk Thorac J. 2018;19(1):28–35. https://doi.org/10.5152/TurkThoracJ.2017.17036.
23. Briones-Claudett KH, Esquinas Rodriguez A, Briones-Claudett MH, et al. Use of noninvasive mechanical ventilation with pressure support guaranteed with average volume in de novo hypoxaemic respiratory failure. A pilot study. Anaesth Intens Ther. 2018;50(4):283–90. https://doi.org/10.5603/AIT.a2018.0036.
24. Huang XA, Du YP, Li LX, et al. Comparing the effects and compliance between volume-assured and pressure support non-invasive ventilation in patients with chronic respiratory failure. Clin Respir J. 2019;13:289. https://doi.org/10.1111/crj.13009.
25. Kuzniar TJ. Mode selection for positive airway pressure titration in adult patients with central sleep apnea syndromes. https://www.uptodate.com/contents/mode-selection-for-positive-airway-pressure-titration-in-adult-patients-with-central-sleep-apnea-syndromes?search=asv&source=search_result&selectedTitle=1~15&usage_type=default&display_rank=1.
26. Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005;33(11):2465–70.
27. Bertrand PM, Futier E, Coisel Y, et al. Neurally adjusted ventilatory assist vs pressure support ventilation for noninvasive ventilation during acute respiratory failure: a crossover physiologic study. Chest. 2013;143(1):30–6. https://doi.org/10.1378/chest.12-0424.
28. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnoea in systolic heart failure: results of the major substudy of SERVE-HF. Eur J Heart Fail. 2018;20(3):536–44. https://doi.org/10.1002/ejhf.1048.
29. Pagano A, Numis FG, Rosato V, et al. Pressure support ventilation vs Continuous positive airway pressure for treating of acute cardiogenic pulmonary edema: a pilot study. Respir Physiol Neurobiol. 2018;255:7–10. https://doi.org/10.1016/j.resp.2018.04.007.
30. Berbenetz N, Wang Y, Brown J, et al. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database Syst Rev. 2019;4:CD005351. https://doi.org/10.1002/14651858.CD005351.pub4.

30 Measures of Improvement for Noninvasive Positive Pressure Ventilation in the ICU

Fiore Mastroianni and Mangala Narasimhan

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30.1 Introduction

Noninvasive ventilation (NIV) has been used for decades in the ICU to treat acute and chronic respiratory failure from many causes [1]. Multiple randomized, controlled trials have proven the benefits of bi-level noninvasive positive pressure ventilation in patients with hypercapnic respiratory failure from an acute exacerbation of chronic obstructive pulmonary disease (COPD) and in patients with cardiogenic pulmonary edema [2]. In acute hypoxemic respiratory failure from pneumonia and sepsis, bi-level has been shown to improve respiratory status [3]. NIV has also been shown to improve reintubation outcomes in the transition time from invasive ventilation to spontaneous breathing in patients with COPD [4, 5]. The clinician caring for these acutely ill patients on noninvasive ventilation needs to have parameters to measure improvement of respiratory status. This will enable the safe use of noninvasive ventilation for acute respiratory failure and allow the operator to escalate to invasive ventilation when appropriate. In this chapter, we will review these measures of improvement for different types of acute respiratory failure: hypercapnia from COPD, respiratory failure associated with left ventricular dysfunction, and noninvasive positive pressure ventilation for respiratory failure due to pneumonia.

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30.2 NIV in Patients with Hypercapnic Respiratory Failure

- Improvement should occur within 1–2 h.
- Measures of improvement include pH, pCO_2, oxygenation, and neurologic status.

It is important to monitor for improvement in a patient receiving noninvasive ventilation (NIV) because there may be harm through inappropriate treatment. Failure of NIV can lead to intubation and mechanical ventilation, while prolonged failing NIV can increase the risk of aspiration, pneumonia, and life-threatening respiratory failure. NIV is a temporizing measure in patients with abnormal gas exchange. Timely and accurate predictors of success can improve outcomes and better distribute respiratory resources. Fortunately, there are models for predicting clinical success in noninvasive ventilation for hypercapnia [6–8].

When assessing the success of NIV, it is important to assess relevant parameters over an appropriate time period. Elevated serum levels of carbon dioxide, pH, and level of consciousness all contribute to the decision to try noninvasive ventilation in the hypercapnic patient. Avoiding mechanical ventilation and survival while on NIV is a measure of success.

Most studies rely on arterial blood gas measurements and vital signs as measures of success. $PaCO_2$, PaO_2, pH, respiratory rate, and heart rate should also be followed closely. Serial measurements should be taken between 1 and 4 h after initiation of NIV. Delays beyond an hour may expose the patient to higher risk of aspiration from positive pressure ventilation with a diminished level of consciousness. It also exposes the patient to the risks of worsening acidosis and hypercarbia such as right ventricular failure, hypotension, and shock. An increase in pH and a decrease in $PaCO_2$ after 1 h were much more common in patients successfully treated than those who failed [9]. Improvements in pH and $PaCO_2$ can continue for hours; however, a lack of improvement at 1 h is associated with treatment failure. Increases in pH of 0.04–0.07 are predictors of success along with reductions in pCO_2 by 8–13 mmHg. A reduction of respiratory rate was not consistently found to be a predictor of success. Lower initial respiratory rate and $PaCO_2$, higher starting pH, and fewer comorbidities were associated with higher rates of success.

There are standardized methods of assessing level of consciousness in critically ill patients. One such method, the Kelly–Matthay score, can be used to judge patient's success with NIV [10, 11]. A score of 1 indicates an awake patient following commands, while a score of 6 indicates coma with signs of brainstem dysfunction. Patients with lower scores have more success with noninvasive ventilation. Patients with a Kelly score greater than 3 (lethargic but arousable and follows simple commands) had a 45% chance of failure with NIV for hypercapnic respiratory failure [12]. More than half of patients with very altered levels of consciousness still had success with NIV: close monitoring of success and improvement in neurologic function over hours can allow continued successful NIV in patients with an altered level of consciousness while identifying those who would benefit from intubation and mechanical ventilation.

Another indicator of likely success is the patient's previous functional status. Ability to complete activities of daily living was a strong predictor of NIV success in an Indian study [8, 13]. Inability to complete two or more ADLs was associated with a hazard ratio of 60 for NIV failure compared to independent patients.

Noninvasive ventilation requires patient compliance with the tight-fitting mask and adequate consciousness to manage secretions and avoid aspiration. Patients with hypercapnic respiratory failure due to obstructive airway disease benefit from noninvasive ventilation by improving ventilation and acidosis and avoiding mechanical ventilation and its myriad complications. Improvements in pH, pCO_2, and level of consciousness should be apparent at 1 h of therapy. Failure to improve at 1 h is strongly associated in multiple studies with treatment failure and should lead the clinician to alternate therapy including mechanical ventilation.

30.3 NIV for Patients with Respiratory Failure Due to Cardiogenic Pulmonary Edema

- Look for improvement early.
- Achieving normal SpO_2 and pH above 7.20 is an indicator of success.

Noninvasive ventilation is a safe and effective treatment for cardiogenic pulmonary edema [14]. It provides positive pressure, favorably affecting the relationship between pulmonary capillary and alveolar pressures while reducing cardiac preload and afterload. Both bi-level noninvasive ventilation and continuous positive airway pressure are effective in treating cardiogenic pulmonary edema [15, 16].

While the principles through which NIV works in obstructive airway disease and cardiogenic pulmonary edema are different, their predictors of success are not. Initial patient selection is important, with decreased level of consciousness associated with poor outcomes [17]. Ability to maintain normal oxygen saturation while using NIV is also a predictor of success [18].

Patients with cardiogenic shock leading to pulmonary edema, severely reduced left ventricular ejection fraction (less than 30%), and severe acidosis (pH < 7.20) have lower rates of success with NIV than patients without such severe disease [19]. It may be difficult or undesirable to do repeat arterial blood gas sampling. Venous blood gases can sometimes be drawn from an existing venous access and are generally easier to draw and less painful for the patient. Venous gases processed in a timely manner can approximate arterial pH, $PaCO_2$, and bicarbonate in patients with acute heart failure [13].

Selecting appropriate patients for NIV and monitoring for clinical and laboratory improvements are equally important. Patients on the extreme ends of the spectrum of illness may not be appropriate for NIV because they are too well (not hypoxemic despite pulmonary edema) or too ill (hypotensive, dyspneic, and hypoxemic). Inappropriate use of NIV in these patients and failure to monitor for improvement may lead to worse clinical outcomes as more invasive, but more effective therapies are delayed or avoided.

30.4 Noninvasive Positive Pressure Ventilation for Respiratory Failure Due to Pneumonia

- Improvement in oxygenation
- Improved symptoms in work of breathing
- Caution with secretions

In patients with a clinical diagnosis of pneumonia with dyspnea, pulmonary infiltrates, fever, and a deterioration in pulmonary gas exchange can be considered for NIV if they do not have hemodynamic instability, a deterioration in neurological status, more than two new organ failures, or facial deformities. These patients should be monitored in a continuous pulse oximetry setting. They should also have a baseline arterial blood gas and a follow-up blood gas after an hour on the NIV. Mental status should also be closely monitored, and any deterioration in mental status should be a relative contraindication for continuation of NIV [20]. The rate of administration of oxygen should be adjusted to achieve a level of arterial oxygen saturation above 90%. The head of the bed should be kept elevated at a 45-degree angle to prevent aspiration. Ventilator settings should be adjusted on the basis of continuous monitoring of arterial oxygen saturation, clinical data, and measurements of arterial blood gases. Pressure support should be incrementally increased to achieve an exhaled tidal volume of 8–10 mL/kg. Continuous positive airway pressure should be increased by 2–3 cm of H_2O repeatedly, up to 10 cm of H_2O, until the FiO_2 requirement is 0.6 or less.

Indicators of improvement in terms of gas exchange can be defined on the basis of the ability to increase the PaO_2/FiO_2 to more than 200 or to a value that is more than 100 above the baseline value [21]. Gas exchange should be evaluated prior to initiating NIV support and an hour or 2 after starting NIV. This will allow evaluation of any ini-

tial improvement and over time to detect sustained improvement. A sustained improvement in gas exchange is the ability to maintain the improvement in PaO_2/FiO_2 until ventilation is discontinued [22]. Other indicators are a respiratory rate of fewer than 25 breaths/min, the disappearance of accessory muscle activity, and patient comfort. Noninvasive support should be discontinued if the patient can maintain a respiratory rate lower than 30 breaths/min and a PaO_2 greater than 75 mmHg with a FiO_2 of 0.5, without ventilatory support [23].

In patients needing NIV, noninvasive support for pneumonia intubation should be considered when there is a failure to maintain a PaO_2/FiO_2 of more than 85, the development of severe encephalopathy with a score on the Glasgow Coma Scale of 8 or less; the development of copious tracheal secretions requiring frequent suctioning; an increase in the partial pressure of arterial carbon dioxide accompanied by a pH of 7.30 or less; agitation requiring increasing sedation; 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; and an inability to tolerate the face mask [24].

30.5 Conclusions

NIV ventilation is a respiratory treatment that can successfully be used to treat acute respiratory failure from hypercapnia, heart failure, and pneumonia successfully if used in the appropriate patient using the appropriate precautions (Table 30.1). If left unmonitored it places the patient at high risk for failure, aspiration, and worsening hypercapnia. NIV ventilation should not be used with static settings; frequent ABG monitoring should be done with titration of settings. Caution should be taken with patients who have copious secretions or alteration of mental status. Monitoring oxygen saturation, pH, and PCO_2 are the hallmarks of success in all of these patients. NIV is well tolerated and can save patients from intubation in many circumstances.

Table 30.1 NIV ventilation in respiratory failure treatment

Type of respiratory failure	Time period to monitor	Measures of success
Hypercapnic respiratory failure	1–4 h after initiation	$PaCO_2$, PaO_2, pH, respiratory rate, and heart rate. Increases in pH of 0.04–0.07 are predictors of success along with reductions in pCO_2 by 8–13 mmHg
Cardiogenic pulmonary edema	Within 1 h of initiation	Achieving normal SpO_2 and pH above 7.20
Respiratory failure from pneumonia	Monitor in continuous pulse oximetry settings and get a baseline arterial blood gas and a follow-up blood gas after an hour	Ability to increase the PaO_2/FiO_2 to more than 200 or to a value that is more than 100 above the baseline value. Other indicators are a respiratory rate of fewer than 25 breaths/min, the disappearance of accessory muscle activity, and patient comfort

References

1. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817–22.
2. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med. 2008;359:142–51.
3. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med. 2001;344:481–7.
4. Ferrer M, Sellares J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet. 2009;374:1082–8.
5. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004;350:2452–60.
6. Singh VK, Khanna P, Rao BK, Sharma SC, Gupta R. Outcome predictors for non-invasive positive pressure ventilation in acute respiratory failure. J Assoc Physicians India. 2006;54:361–5.

7. Antón A, Güell R, Gómez J, et al. Predicting the result of noninvasive ventilation in severe acute exacerbations of patients with chronic airflow limitation. Chest. 2000;117(3):828–33.
8. Bhattacharyya D, Prasad B, Tampi PS, Ramprasad R. Early predictors of success of non-invasive positive pressure ventilation in hypercapnic respiratory failure. Med J Armed Forces India. 2011;67(4):315–9.
9. Salahuddin N, Irfan M, Khan S, et al. Variables predictive of outcome in patients with acute hypercapneic respiratory failure treated with noninvasive ventilation. J Pak Med Assoc. 2010;60(1):13–7.
10. Ergan B, Nasiłowski J, Winck JC. How should we monitor patients with acute respiratory failure treated with noninvasive ventilation? Eur Respir Rev. 2018;27(148):170101.
11. Kelly BJ, Matthay MA. Prevalence and severity of neurologic dysfunction in critically ill patients. Influence on need for continued mechanical ventilation. Chest. 1993;104(6):1818–24.
12. Scala R, Naldi M, Archinucci I, Coniglio G, Nava S. Noninvasive positive pressure ventilation in patients with acute exacerbations of COPD and varying levels of consciousness. Chest. 2005;128(3):1657–66.
13. Masip J, De Mendoza D, Planas K, Paez J, Sanchez B, Cancio B. Peripheral venous blood gases and pulse-oximetry in acute cardiogenic pulmonary oedema. Eur Heart J Acute Cardiovasc Care. 2012;1(4):275–80.
14. Vital FM, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database Syst Rev. 2013;(5):CD005351.
15. Mehta S, Jay GD, Woolard RH, et al. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. Crit Care Med. 1997;25(4):620–8.
16. Moritz F, Brousse B, Gellée B, et al. Continuous positive airway pressure versus bilevel noninvasive ventilation in acute cardiogenic pulmonary edema: a randomized multicenter trial. Ann Emerg Med. 2007;50(6):666–75. 675.e1.
17. Shirakabe A, Hata N, Yokoyama S, et al. Predicting the success of noninvasive positive pressure ventilation in emergency room for patients with acute heart failure. J Cardiol. 2011;57(1):107–14.
18. Passarini JN, Zambon L, Morcillo AM, Kosour C, Saad IA. Use of non-invasive ventilation in acute pulmonary edema and chronic obstructive pulmonary disease exacerbation in emergency medicine: predictors of failure. Rev Bras Ter Intensiva. 2012;24(3):278–83.
19. Luo Z, Han F, Li Y, et al. Risk factors for noninvasive ventilation failure in patients with acute cardiogenic pulmonary edema: a prospective, observational cohort study. J Crit Care. 2017;39:238–47.
20. Kelly CR, Higgins AR, Chandra S. Videos in clinical medicine. Noninvasive positive-pressure ventilation. N Engl J Med. 2015;372:e30. https://doi.org/10.1056/NEJMvcm1313336.
21. Meduri GU, Turner RE, Abou-Shala N, Wunderink R, Tolley E. Noninvasive positive pressure ventilation via face mask: first-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. Chest. 1996;109:179–93.
22. Guerin C, Girard R, Chemorin C, De Varax R, Fournier G. Facial mask noninvasive mechanical ventilation reduces the incidence of nosocomial pneumonia: a prospective epidemiological survey from a single ICU. Intensive Care Med. 1997;23:1024–32.
23. Wysocki M, Tric L, Wolff MA, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure: a randomized comparison with conventional therapy. Chest. 1995;107:761–8.
24. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med. 1998;339:429–35.

Escalation of Therapy from NIV

31

Martin Scharffenberg

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Abbreviations

ARF	Acute respiratory failure
ATS	American Thoracic Society
CPAP	Continuous positive airway pressure
ECMO	Extracorporeal membrane oxygenation
ERS	European Respiratory Society
F_IO_2	Inspired fraction of oxygen
GCS	Glasgow Coma Scale
HFNC	High-flow nasal cannula
ICU	Intensive care unit
MV	Mechanical ventilation
NIPPV	Noninvasive positive pressure ventilation
NIV	Noninvasive ventilation
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PEEP	Positive end-expiratory pressure

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31.1 Introduction

Noninvasive ventilation (NIV) is an effective and safe method to support lung function in case of acute or chronic respiratory impairment as well as in perioperative care. It may prevent intubation or re-intubation and reduce the risks associated with invasive mechanical ventilation. In contrast, NIV may also hide a respiratory deterioration and delay a necessary therapy escalation. Although it is evident that this deterioration should be diagnosed

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and treated immediately, there is no clear evidence about the time point and steps of therapy escalation. This chapter aims to summarize the recent clinical trials on NIV escalation.

31.2 Methodology

NIV can be performed successfully to treat respiratory impairment of different causes, unless contraindications or signs of NIV failure become present. Indicators of NIV failure are summarized in Chap. 35. In case of respiratory deterioration or absent improvement under NIV, the ventilatory therapy should be escalated. To evaluate the current scientific evidence of options and steps that represent an escalation of NIV, a systematic literature search was conducted focusing on clinical trials published between January 2017 and March 2019 in the English and Spanish language using combinations and synonyms of the following key words: "noninvasive ventilation," "escalation," "therapy escalation," "re-intubation," "respiratory failure," and "withdrawal." As a result of the review of literature published in this time frame, no clinical trial about the therapy escalation of NIV could be identified. In contrast, eight studies [1–8] which address different related research questions were found (see Table 31.1). Although some of them focus on the implementation of NIV protocols, escalation strategies have not been described in detail. However, some facts of these trials can be highlighted in this chapter.

31.3 Steps of Escalation

NIV describes a wide range of methods of ventilatory support. The term includes every ventilation therapy without using an invasive airway, e.g., from the simple application of continuous positive airway pressure (CPAP) with varying pressures and fractions of inspired oxygen (F_iO_2), to oxygen delivered via high-flow nasal cannula (HFNC) with gas flows of up to 70 L/min, and to the application of noninvasive intermittent positive pressure ventilation (NIPPV), e.g., noninvasive bilevel ventilation. Therewith, possible steps of escalation may theoretically include increasing F_iO_2, CPAP, positive end-expiratory airway pressure (PEEP), inspiratory pressure support, and the time on NIV when used intermittently. Along with adjusting sedation to decrease the oxygen consumption and to reduce a possible subject ventilator asynchrony, exchanging the patient ventilator interface may represent some of the possible steps of NIV escalation, e.g., from an oronasal mask to a helmet. Finally, endotracheal intubation and initiation of invasive mechanical ventilation represent the most important steps of NIV escalation. As an ultima ratio, extracorporeal lung assist techniques may be applied in case of further cardiorespiratory deterioration. Interestingly, case reports of successful awake extracorporeal membrane oxygenation (ECMO) in non-intubated patients being have been reported years ago [9].

If intensification of NIV in terms of changing the NIV mode represents a useful step of escalation, it may be indirectly answered by one of the clinical trials identified in the literature search which compared CPAP to NIPPV in 114 patients with cardiopulmonary edema admitted to the ICU [5]. Patients were randomized to receive CPAP or noninvasive bilevel ventilation via an oronasal mask, and end-expiratory pressures were increased until respiratory improvement was noticed in both modes. Patients treated with NIPPV showed a faster improvement of oxygenation within the first 60 min. However, effects were similar afterwards, and neither the intubation rate as the primary endpoint nor secondary outcomes, e.g. length of ICU and hospital stay, length of ventilation, and mortality, differed between CPAP and NIPPV. The number of recorded complications was similar between both groups. In conclusion, there was no clinical benefit from the use of NIPPV over CPAP. Applied to the escalation of NIV, switching from CPAP to NIPPV can be considered but may not be beneficial and may delay a necessary intubation.

Oxygen insufflation via HFNC is a relatively new mode of NIV, and since its clinical implementation, the question about its significance was risen. One post hoc analysis of a former randomized controlled trial [10] published in the relevant period was performed to test the hypothesis that

Table 31.1 Summary of clinical trials in alphabetic order

First author	Published in	Ref.	Population	Intervention	Comparator	Outcome
Baillard	2018	[8]	Adult ICU patients with acute hypoxemic respiratory failure	NIV for preoxygenation	Standard preoxygenation with bag-valve-mask	Sequential Organ Failure Assessment within 7 days after intubation
Belenguer-Muncharaz	2017	[5]	Adult patients with cardiogenic pulmonary edema	NIV	CPAP	Intubation rate
Duan	2019	[3]	Mechanically ventilated patients ≥65 years	NIV after extubation	Conventional oxygen therapy	Intubation rate within 72 h after extubation
Hongisto	2017	[6]	Patients with cardiogenic shock	n/a	n/a	Assessment of real-life use of different ventilatory support
Jalil	2017	[7]	Children with acute respiratory failure due to acute lower respiratory infection	Protocolized NIV management	NIV management according to clinical criteria	Duration of NIV, hospital stay, and supplemental oxygen after discontinuation of NIV
Kudela	2019	[4]	Mechanically ventilated patients with unplanned extubation (deliberately or accidentally)	Prophylactic NIV and rescue NIV	No NIV	Re-intubation rate within 72 h after unplanned extubation
Stéphan	2017	[1]	Obese patients after cardiothoracic surgery	Continuous HFNC after extubation	Intermittent NIV after extubation	Treatment failure rate, switch to the other study treatment, and premature discontinuation of treatment
Vargas	2017	[2]	Mechanically ventilated patients with chronic respiratory disorders	Intermittent NIV after extubation	Conventional oxygen therapy after extubation	Respiratory failure rate within 48 h after extubation

NIV noninvasive ventilation, *CPAP* continuous airway pressure, *n/a* not applicable, *HFNC* high-flow nasal cannula

postoperative HFNC is superior compared to NIV in obese cardiothoracic surgery patients [1]. In this trial, patients were randomized to receive either continuous HFNC or intermittent noninvasive pressure ventilation. This analysis revealed no difference regarding the rate of treatment failure and time to treatment failure, as well as similar re-intubation rates. In this specific population, there was no major clinical benefit of HFNC. Therewith, the value of HFNC regarding escalation of NIV cannot be judged. For further studies about HFNC, see Chap. 10.

Initiation of invasive mechanical ventilation with endotracheal intubation is the most relevant major step of therapy escalation. It provides patent airways, gas exchange, and unloading of respiratory muscles. The literature search revealed an observational, multicentered clinical trial on 219 patients with cardiogenic shock, which was aimed to analyze the real-life use of different ventilatory therapies in this specific patient population. Patients were classified according to the following types of respiratory support: room air, supplementary oxygen, NIV, or invasive ventilation. The different ventilation strategies were chosen by the attending physician according to "common indications and contraindications" [6]. As the primary endpoint, all-cause 90-day mortality did not differ between patients ventilated noninvasively and invasively after adjustment for severity of disease. Further results included a higher blood pressure in the NIV group, higher utilization of vasoactive medication in the invasive ventilation group, and a shorter duration of ventilation with NIV. However, the length of stay in ICU and hospital did not differ. Despite the finding that patients with less severe diseases can be handled safely with NIV while those with more severe impairments need invasive ventilation, unfortunately, no conclusion about escalation from NIV to invasive ventilation can be drawn from this trial. However, the authors emphasize in the discussion that an indicated intubation should not be delayed by NIV.

In preparation for endotracheal intubation, sufficient preoxygenation is necessary. Years ago, a clinical trial revealed that using NIV for preoxygenation is superior in preventing desaturation compared to the standard method with bag-valve-mask in hypoxemic patients [11]. Now, the same author aimed to investigate if preoxygenation with NIV affects organ failure in critically ill patients who need endotracheal intubation [8]. In a prospective, multicentered trial, 201 patients were randomized to receive either pressure support ventilation or ventilation with a bag-valve-mask prior to intubation. As the primary endpoint, the median Sequential Organ Failure Assessment values did not differ between the groups. The type of preoxygenation did not affect the length of ICU stay, number of ventilation free-days, and mortality. However, only in the standard preoxygenation group, preoxygenation failure requiring immediate intubation occurred in five patients. Interestingly, the number of adverse events was similar on both groups, but adverse events were more frequent in patients who have been treated with NIV before but who have been randomized to standard preoxygenation. In conclusion, the preoxygenation strategy did not affect organ function, but this trial emphasizes that NIV should not be stopped prior to endotracheal intubation. In already noninvasively ventilated patients requiring therapy escalation, NIV should be continued with 100% inspired fraction of oxygen for preoxygenation.

If escalation to invasive ventilation was necessary and the critical phase has been overcome, the invasiveness of ventilation should be decreased as soon as possible, and weaning should be started early. This aims to reduce the need of deep sedation and vasopressors, as well as to reduce the risk of nosocomial infections, ventilator-induced diaphragmatic dysfunction, and prolonged ventilator dependence. Prophylactic use of NIV after planned extubation can decrease the risk of post-extubation respiratory failure and prevent re-intubation. Especially patients with chronic respiratory diseases are at risk. One prospective, multicentered clinical trial, which was published in the relevant time frame, investigated the effects of early NIV after extubation in this specific cohort [2]. In this study, 144 patients were randomized to receive intermittent noninvasive pressure support with PEEP (or bilevel ventilation) or standard oxygen

insufflation after their extubation. Early prophylactic NIV via face mask for 1 h every 3 h/day reduced the frequency of post-extubation respiratory failure and re-intubations compared to the control group. There was no difference regarding mortality. In contrast, a propensity-matched analysis of an observational clinical trial about the effects of prophylactic NIV after planned extubation in 176 elderly patients revealed lower rates of re-intubation and lower in-hospital mortality when patients received NIV after extubation [3]. Therewith, prophylactic NIV after extubation should be considered, especially in patients at high risk of post-extubation respiratory failure. This is in line with the current ERS/ATS guideline for NIV [12]. For further information about NIV after planned extubation, see Chap. 48.

Usual extubations allow careful anticipatory planning of the procedure itself and the following steps. However, unplanned extubations on ICUs have an incidence of up to 35% and represent an emergency. Kudela and colleagues performed a single-center retrospective analysis of clinical records of 121 patients with 131 unplanned extubations, to test the effect of NIV in these situations [4]. Due to the retrospective design, NIV was not protocolized but performed by the physician's individual choice. The trial revealed re-intubation rates of 64.3% when NIV was performed as rescue strategy due to symptoms of acute respiratory distress, 10% when NIV was used prophylactically in absence of such clinical signs, and 25.8% when NIV was not instituted after unplanned extubation. Patients who received NIV after unplanned extubation but have been subsequently intubated had a significantly longer time to intubation than those who were not ventilated noninvasively. Interestingly, the application of NIV after unplanned extubation did not reduce the intubation rate; in contrast, their time on ventilation and length of ICU stay were significantly longer. There was no difference regarding mortality. This small retrospective study suggests that after unplanned extubation, quick escalation is necessary, because both prophylactic and rescue NIV did not reduce the intubation rate but may delay an indicated intubation. According to this trial, especially rescue NIV in case of symptoms of respiratory distress should be avoided.

31.4 NIV Protocols

Using NIV according to the physician's discretion may be unstructured, and procedures may differ due to the fluctuating personnel on duty. Structured NIV protocols should include standard operating procedures including specified criteria for initiation and withdrawal, as well as steps for escalation of NIV. The literature search did not identify any clinical trials comparing different NIV protocols. In one observational trial, NIV was performed at the physician's discretion, and no certain protocol was described [6].

A very small prospective randomized controlled trial investigated the effects of implementing a protocol to standardize NIV initiation and discontinuation [7]. Forty-seven children with acute respiratory failure caused by acute lower respiratory infection were randomized to be treated with either NIV according to usual medical criteria or to a protocol-based NIV treatment. The protocol, in brief, included repeated assessments at intervals to record the Modified Wood Scale [13, 14] and respiratory variables. In case of respiratory deterioration, e.g., increasing Modified Wood Scale values, NIV was adjusted. However, steps of escalation were not described. In this trial, the protocol was successfully implemented, but it did not improve outcomes. There were no differences in the duration of hospital stay, the duration of NIV, and the duration of oxygen after NIV discontinuation. Furthermore, intubation rates were similar in both groups.

In one clinical trial emphasizing the usefulness of structured NIV protocols [2], 144 patients with chronic respiratory disorders were randomized to receive NIV or standard care after extubation. In this trial, prespecified criteria for therapy escalation, i.e., re-intubation, were used. Criteria were classified as major and minor criteria. Re-intubation was indicated if one of the major criteria or at least two of the minor criteria were met. Similarly, in two other clinical trials, major and minor criteria were specified to guide

Table 31.2 Major and minor criteria for re-intubation in patients with NIV

	Stéphan et al. [1]	Vargas et al. [2]	Duan et al. [3]
Major criteria (at least one positive)	Respiratory arrest	Respiratory arrest	Respiratory arrest
	Respiratory pauses with loss of consciousness or gasping respiration	Cardiac arrest	Loss of consciousness
	Encephalopathy	Persistent severe hypoxemia (PaO_2/F_IO_2 < 130 mmHg) despite NIV	Inability to correct dyspnea
	Cardiovascular instability	Hemodynamic instability with systolic blood pressure ≤85 mmHg despite adequate vascular filling	Conditions necessitating intubation to protect the airway (coma or seizure disorders)
	–	Severe cardiac arrhythmia	Copious tracheal secretions requiring management
	–	–	PaO_2/F_IO_2 < 100 mmHg
Minor criteria (at least two positive)	>20% increase in respiratory rate or $PaCO_2$	Ineffective ventilation due to agitation and/or major air leaks under NIV	Respiratory rate ≥35 breaths/min
	>20% decrease in PaO_2 compared with baseline	Clinical signs of severe ARF with tachypnea <35/min and/or pH < 7.20	pH < 7.35 for hypoxemic patients and <7.30 for hypercapnic patients
	Unmanageable secretions	Occurrence, persistence, or worsening of ARF under NIV (tachypnea, sweats, cyanosis, involvement of accessory respiratory muscles, paradoxical abdominal motion, and/or respiratory acidosis impairment)	Persistent tachycardia
	Clinical signs of exhaustion	Consciousness deterioration or respiratory encephalopathy score worsening (>3) under NIV	Persistent activation of accessory respiratory muscles
	Refractory hypoxemia	Bronchial hypersecretion under NIV	PaO_2/F_IO_2 < 150 mmHg
	Respiratory acidosis	Development of other organ failure	–

According to [1–3]
NIV noninvasive ventilation, $PaCO_2$ arterial partial pressure of carbon dioxide, PaO_2 arterial partial pressure of oxygen, F_IO_2, inspired fraction of oxygen, *ARF* acute respiratory failure

escalation of NIV to invasive ventilation [1, 3]. Major and minor criteria for intubation in these two trials are summarized in Table 31.2. A different approach was described in another clinical trial about the comparison of NIV with CPAP in 110 patients with cardiopulmonary edema, where criteria for intubation were not classified into major and minor [5]. These criteria included absence of improvement in gas exchange or dyspnea, intolerance of CPAP or NIV, onset of ventricular arrhythmias, deteriorating level of consciousness (Glasgow Coma Scale, GCS < 10), respiratory or cardiac arrest, or evolution toward cardiogenic shock. However, it was not described how many of the stated criteria have to be met by the patient.

Although all of these criteria stated above have not been evaluated in these trials as endpoints, they have been used successfully and may be adopted to clinical use. As an expert opinion, these criteria appear reasonable to guide escalation of NIV. However, it would be interesting to conduct a clinical trial to compare different NIV escalation protocols and criteria.

31.5 Time Point of Escalation

As it is clear that an indicated intubation should not be delayed by trying NIV, the time point of therapy escalation is crucial. Unfortunately, the literature search did not reveal clinical studies

published in the last 2 years about the time point if NIV escalation. Despite this, respiratory conditions, e.g., arterial carbon dioxide tension as well as ratio of arterial tension and inspired fraction of oxygen, showed the largest increase within the first 60 min after initiation of NIV and CPAP in one of the aforementioned trials [5]. This time frame may represent a threshold where escalation may be considered if no improvement or even deterioration is recognized. However, in another study, 50% of NIV failures occurred within the first 24 h after admission [6]. In the discussion, the authors state that patients should be intubated promptly if there is no improvement, while there is no definition of time frames. Therewith, the time point of NIV escalation stays at the physician's discretion and depends on close monitoring of the patient's condition.

31.6 Final Conclusions

Within the reviewed timeframe of January 2017 to March 2019, no clinical trial focusing on the escalation of respiratory support has been published. However, the following key messages can be stated:

- The most relevant escalation of NIV is the endotracheal intubation with subsequent invasive ventilation.
- Prespecified clinical criteria and standardized NIV protocols may help to guide the initiation, withdrawal, and escalation of NIV.
- Clinical criteria for re-intubation as used in some larger trials appear to be reasonable and may be applied for clinical routine. However, their predictive value, safety, and efficacy may need further investigation.
- Early recognition of NIV failure is essential to prevent delayed escalation.

Possible steps of escalation are summarized in Fig. 31.1.

Due to the lack of evidence in the reviewed time frame, decisions for or against escalation of NIV are based on former trials, expert opinions, and/or personal experiences. Even the current ERS/ATS guideline on NIV does not provide certain information about escalation of NIV, despite the important information that NIV may delay a necessary intubation [12]. As a future perspective, randomized controlled clinical trials comparing different protocols and criteria for escalation of NIV are needed. Additionally, the possible escalation steps and their timing should be investigated regarding safety and efficacy.

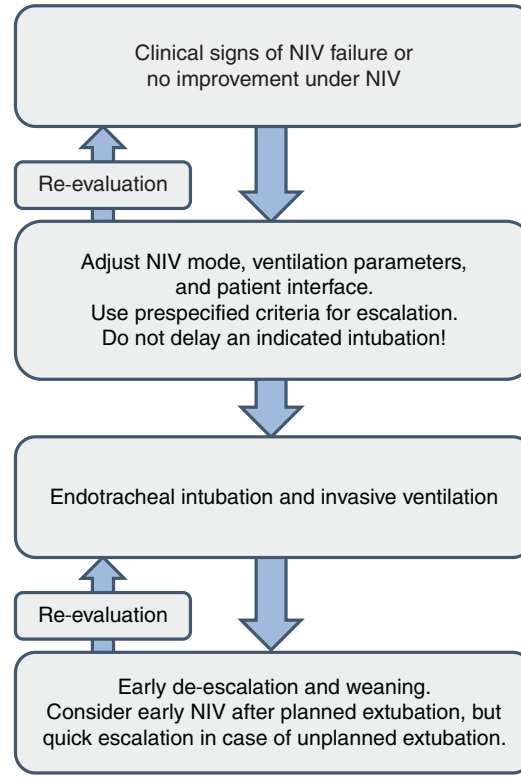

Fig. 31.1 Escalation of noninvasive ventilation (NIV)

References

1. Stéphan F, Bérard L, Rézaiguia-Delclaux S, Amaru P, BiPOP Study Group. High-flow nasal cannula therapy versus intermittent noninvasive ventilation in obese subjects after cardiothoracic surgery. Respir Care. 2017;62:1193–202.
2. Vargas F, Clavel M, Sanchez-Verlan P, Garnier S, Boyer A, Bui H-N, et al. Intermittent noninvasive ventilation after extubation in patients with chronic respiratory disorders: a multicenter randomized controlled trial (VHYPER). Intensive Care Med. 2017;43:1626–36.

3. Duan J, Bai L, Zhou L, Han X, Huang S. Decreasing re-intubation using prophylactic noninvasive ventilation in elderly patients: a propensity-matched study. J Crit Care. 2019;50:77–81.
4. Kudela A, Millereux M, Gouezel C, Prat D, Jacobs F, Hamzaoui O, et al. Effect of noninvasive ventilation after unplanned extubation. Respir Care. 2019;64:248–54.
5. Belenguer-Muncharaz A, Mateu-Campos L, González-Luís R, Vidal-Tegedor B, Ferrándiz-Sellés A, Árguedas-Cervera J, et al. Non-invasive mechanical ventilation versus continuous positive airway pressure relating to cardiogenic pulmonary edema in an intensive care unit. Arch Bronconeumol. 2017;53:561–7.
6. Hongisto M, Lassus J, Tarvasmaki T, Sionis A, Tolppanen H, Lindholm MG, et al. Use of noninvasive and invasive mechanical ventilation in cardiogenic shock: a prospective multicenter study. Int J Cardiol. 2017;230:191–7.
7. Jalil Y, Damiani F, Astudillo C, Villarroel G, Barañao P, Bustos E, et al. Impact of a noninvasive ventilation protocol in hospitalized children with acute respiratory failure. Respir Care. 2017;62:1533–9.
8. Baillard C, Prat G, Jung B, Futier E, Lefrant JY, Vincent F, et al. Effect of preoxygenation using noninvasive ventilation before intubation on subsequent organ failures in hypoxaemic patients: a randomised clinical trial. Br J Anaesth. 2018;120:361–7.
9. Yeo HJ, Cho WH, Kim D. Awake extracorporeal membrane oxygenation in patients with severe postoperative acute respiratory distress syndrome. J Thorac Dis. 2016;8:37–42.
10. Stéphan F, Barrucand B, Petit P, Rézaiguia-Delclaux S, Médard A, Delannoy B, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. JAMA. 2015;313:2331–9.
11. Baillard C, Fosse J-P, Sebbane M, Chanques G, Vincent F, Courouble P, et al. Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. Am J Respir Crit Care Med. 2006;174:171–7.
12. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1602426.
13. Wood DW, Downes JJ, Lecks HI. A clinical scoring system for the diagnosis of respiratory failure. Preliminary report on childhood status asthmaticus. Am J Dis Child. 1972;123:227–8.
14. Duarte-Dorado DM, Madero-Orostegui DS, Rodriguez-Martinez CE, Nino G. Validation of a scale to assess the severity of bronchiolitis in a population of hospitalized infants. J Asthma Off J Assoc Care Asthma. 2013;50:1056–61.

NPPV vs. HFNC for Acute Respiratory Failure

32

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32.1 Introduction

Acute respiratory failure (ARF) in adults is a common complication of many diseases frequently encountered in both the emergency room and critical care settings. It accounts for up to 30% of intensive care unit (ICU) admissions where approximately 60% of patients require endotracheal intubation with invasive mechanical ventilation (IMV) [1].

IMV doesn't come without risk; it is associated with a range of complications and mortality as high as 30% [1]. Early complications include esophageal intubation, vocal cord injury/paralysis, sedative side effects, and acute traumatic injury that can lead to laryngeal or tracheal injury. Prolonged IMV can result in delayed complications that arise as a sequela of sedation and ventilator-induced diaphragmatic dysfunction [2]. Infections, specifically ventilator-associated pneumonia, are the most common of the delayed complications and have been correlated with increased ICU length of stay (LOS), duration of ventilation, and mortality [3].

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As a result, there has been an increased interest in the utilization of noninvasive modalities for the prevention and management of ARF to avoid complications associated with IMV. Noninvasive positive pressure ventilation (NIPPV) includes noninvasive variable positive airway pressure or "bilevel" devices (BiPAP) which consist of a higher inspiratory positive airway pressure and a lower expiratory pressure applied through an arguably comfortable facial interface, i.e., helmet, facial mask, nasal prongs, etc. [4]. Historically NIPPV has been shown to be beneficial in select set of disease processes, specifically acute COPD exacerbation [5], acute cardiogenic pulmonary edema [6], hypoxic ARF in the immunocompromised [7], and post-extubation of high-risk patients with prior cardiac and/or pulmonary disease [8]. In these patients, there was a significant reduction in the need for airway intubation [9] avoiding the well-known complications of IMV. Furthermore, use of NIPPV leads to additional benefits. NIPPV utilizes more cautious use of sedation as the patient has to maintain cooperativeness requiring relative consciousness for appropriate use, and often no sedation is needed at all as the patient interface is more tolerable than an endotracheal tube. NIPPV is also associated with lower risk of nosocomial infections [10–12] and allows patients to speak as well as eat during NIPPV breaks. Unfortunately, outside of the immunocompromised patient population, NIPPV has shown little benefit in hypoxic ARF and even has been associated with higher rates of failure leading to increased mortality [13]. Additionally, NIPPV comes with its own set of drawbacks including skin damage at the interface site, eye irritation, interface intolerance, and diet and expectoration interruption [14].

Consequently, high-flow nasal cannula (HFNC) has grown in popularity as yet another noninvasive option and a possible alternative to NIPPV. HFNC allows the clinician to set an oxygen flow rate of up to 60 liters per minute (L/min) in which the heated and humidified air is delivered at a designated inspired oxygen (FiO_2) from 21% up to 100% [15]. In addition to improving oxygenation, HFNC has been noted to help decrease dead space by continuously washing out upper airway carbon dioxide (CO_2) as well as decrease ventilation-perfusion mismatch by recruiting atelectatic lung via pressurizing the oropharynx and hypopharynx with each spontaneous breath [16]. This positive end-expiratory pressure (PEEP) effect is estimated to be as high as 1 cm H_2O for every 10 L/min of flow when the patient's mouth is closed [17]. Although HFNC possesses innate physiological benefits, most of the data to support its use are from observational studies or randomized trials studying heterogenous populations with multiple arms for comparison, leading to mixed results when pooling the data in regard to intubation rate and mortality benefit [1, 18]. Despite these limitations, HFNC is frequently used in patients with severe hypoxic respiratory failure [19]. As a result, the purpose of this review is to explore and compare noninvasive ventilation (NIV) modalities, mainly HFNC and NIPPV, and their application in different types of ARF in adults.

32.2 NIV in Hypercapnic ARF

Hypercapnia results from the inability of the respiratory muscles to achieve adequate alveolar ventilation to remove CO_2, the byproduct of oxidative metabolism. Hypoventilation etiologies range from central nervous system diseases ("won't breathe") such as ischemic strokes to pulmonary diseases ("can't breathe") such as chronic obstructive pulmonary disease (COPD).

32.2.1 NIV in COPD Hypercapnic ARF

During COPD exacerbations, approximately 20% of patients develop hypercapnia [20]. This is a result of poor alveolar function with hyperinflation leading to a rapid shallow breathing pattern characterized by increased respiratory rate with small tidal volumes consequently causing respiratory muscle fatigue and increase in CO_2 with acute respiratory acidosis. If left untreated, this pathophysiologic process can lead to respiratory

failure, arrest, and death. NIPPV has been considered in COPD patients with exacerbations in three main clinical settings: prevention of acute respiratory acidosis, prevention of endotracheal intubation with IMV, and as an alternative to IMV.

Most recent ATS/ERS 2017 guidelines recommend against using NIPPV in preventing acute respiratory acidosis in COPD patients with an exacerbation. This specifically refers to COPD patients without an acute elevation in CO_2, thus having a normal pH range of 7.35–7.45 including patients who may have a chronic compensated hypercapnia. In this patient population, there is no evidence showing a reduction in mortality or need for intubation; therefore, the anticipated undesirable effects of NIPPV should be avoided [4]. On the contrary, in patients with acute elevation in CO_2 levels resulting in a pH $\leq$ 7.35 during an acute or acute on chronic COPD exacerbation (i.e., hypercapnic ARF), there is a strong recommendation for the application of NIPPV, including those patients who are being considered for endotracheal intubation and IMV. Multiple studies have confirmed that in patients with a COPD exacerbation in hypercapnic ARF, NIPPV decreases mortality, the need for intubation, as well as nosocomial pneumonia. This effect is most prominent in patients considered as mild to moderate COPD exacerbation defined by a pH of 7.25–7.35 in the absence of metabolic causes for the acidosis. In severe disease where the pH <7.25 the evidence for utilization is less compelling. In these patients NIPPV can be tried, however, with very close monitoring. A good predictor of successful outcomes with NIPPV is an improvement in either pH or respiratory rate, or preferably both, within the first 1–4 h of treatment [4].

32.2.2 NIV Post-extubation ARF

NIPPV was also considered in patients undergoing IMV weaning and planned extubation as a possible strategy to prevent recurrent ARF and need for reintubation. Patients defined as high risk, by age over 65 and prior underlying cardiac or respiratory diseases, seemed to benefit most, especially those who developed hypercapnia during spontaneous breathing trials (SBT) [4]. These patients had decreased mortality as well as lower need for reintubation. On the other hand, patients who failed planned extubation by developing overt respiratory distress or ARF did worse overall when NIPPV was attempted as treatment. It was found that NIPPV in these patients often leads to delay in reintubation. Thus, ERS/ATS does not recommend NIPPV use as rescue therapy after ARF post-extubation. It is important to note that the studies investigating NIPPV implementation as treatment of ARF after planned extubation had a number of limitations. Firstly, the studies included very few COPD patients who often benefit the most. Some centers also had limited overall enrollment as well as possible lack of experience with NIPPV. Furthermore, NIPPV did have higher success rates in ARF post-planned extubation in those patients who received it as an initial treatment prior to intubation [4].

Theoretically, HFNC may be able to wash out CO_2 filling the nasopharyngeal cavity as well as provide some clearance through gaseous mixing in more distal airways, especially with high flow rates [21]; however, to date, clinical data for its application specifically in hypercapnic ARF as prevention or treatment is limited. Most studies concentrate on the application of HFNC in patients with hypoxic ARF [22] reviewed later.

A small single-center retrospective pilot study by Kim et al. looked at the application of HFNC in patients admitted to MICU with ARF and concurrent hypercapnia. In the 33 patients enrolled, 33% with history of COPD in acute exacerbation, HFNC reduced CO_2 while maintaining adequate oxygenation [23] irrespective of whether chronic hypercapnia was present or not. Most beneficial effects were seen within the first hour of HFNC use. This data is quite interesting; however, clearly larger studies are needed before more definitive recommendations can be concluded. Another study is currently investigating the application of HFNC to reduce the duration of NIPPV therapy in hypercapnic ARF [24]. Its results can be useful in optimizing this patient population management.

32.3 NIV in Hypoxic ARF

There are five main mechanisms that can cause hypoxic ARF. The first is simply decreased inspired oxygen pressure as occurs in high altitudes. The remaining four are usually the end result of advanced disease processes which include alveolar hypoventilation (i.e., drug overdose, neuromuscular disorders, chest wall restriction, airway obstruction), impaired diffusion (i.e., interstitial lung disease, acute respiratory distress syndrome), ventilation-perfusion mismatch (i.e., asthma, COPD, pulmonary embolism, pulmonary edema), and shunting (i.e., pulmonary arteriovenous malformations, hepatopulmonary syndrome, atelectasis, pneumonia, intracardiac communications). These disease processes result in hypoxia by interfering with more than one of these mechanisms simultaneously.

32.3.1 NIV in Cardiac Disease Hypoxic ARF

Hypoxic ARF is often the initial presentation of cardiac disease. Due to its prevalence, numerous studies have investigated the benefits of NIPPV in ARF due to cardiogenic pulmonary edema. Hypoxic ARF in pulmonary edema is a result of decreased respiratory system compliance and alveolar flooding in the setting of high capillary pressures. In these patients, NIPPV (both BiPAP and CPAP) decreases the negative pressure swings during spontaneous breathing improving respiratory mechanics and optimizing left ventricular work by decreasing afterload. NIPPV application in this patient population has shown a reduction in mortality as well as the need for intubation. Comparable benefits were observed in studies performed on similar groups of patients pre-hospitalization. Due to the heterogeneity of trial designs, the supporting evidence is less strong here. It is important to note that patients with cardiogenic shock were excluded from most of these studies. Although a concern for increased myocardial infarction was raised with use of NIPPV, given the low certainty of evidence, the desirable effects offset this apprehension [4].

There is some evidence that suggests improved cardiovascular dynamics with the application of HFNC in patients with stable chronic heart failure (CHF), but we did not find any clinically applicable data to support the use of HFNC in decompensated CHF with pulmonary edema [25].

32.3.2 NIV in Asthma Hypoxic ARF

Asthma is another commonly encountered disease process that often causes hypoxic ARF. The main feature of an acute asthma exacerbation is the sudden episode of bronchoconstriction. This leads to increased airway resistance and mechanical load generating hyperinflation requiring additional respiratory muscle effort with reduced efficiency, leading to fatigue and culminating in hypercapnia. In addition to conventional pharmacological treatment, NIPPV was investigated with the aim to off-load respiratory muscle work to improve ventilation and reduce the sensation of dyspnea, with the hope to avoid intubation and IMV. Unfortunately, no consensus can be reached on recommendations regarding the application of NIPPV in acute asthma exacerbations with ARF as studies have not shown any significant beneficial effect on clinically relevant outcomes compared to conventional treatment including intubation with IMV [4]. Part of the reason for this recommendation is the lack of evidence because episodes of severe acute asthma exacerbations requiring ICU admission are uncommon [4]. Additionally, a subset of asthmatics with COPD overlap (i.e., fixed airway obstruction) may show benefit from NIPPV.

The application of HFNC in asthma exacerbations is limited; however, optimistic data is found mainly in children. A pilot clinical trial by Ballestero et al. randomly allocated 62 children with moderate to severe asthma exacerbation refractory to first-line treatment to receive either HFNC or standard oxygen therapy. HFNC resulted in a notable improvement in pulmonary scores after 2 h of therapy. There were no differences in disposition, LOS, or need for additional therapies. Importantly, there was no side effects reported [26].

32.3.3 NIV in Immunocompromised Hypoxic ARF

NIPPV has also been successfully implemented in the immunosuppressed patients of various etiologies with mild to moderate hypoxemic ARF. Compared to conventional treatment, i.e., nasal cannula oxygen supplementation and intubation with IMV, NIPPV was found to decrease mortality, the need for intubation, as well as rates of nosocomial pneumonia [4].

Due to the notable positive promising outcomes in the application of HFNC in hypoxic ARF, Lemiale et al. performed a post hoc analysis of a randomized controlled trial of noninvasive ventilation in critically ill immunocompromised patients with hypoxic ARF to assess treatment outcomes in 29 ICUs in France and Belgium. HFNC when compared to standard oxygen did not reduce intubation or survival rates [27].

32.3.4 NIV in De Novo ARF

De novo ARF refers to respiratory failure occurring in patients without prior chronic respiratory disease. Most of these patients had hypoxic ARF in the setting of pneumonia and/or ARDS. Thus, patients with COPD, cardiogenic pulmonary edema, or postoperative respiratory distress were not considered. NIPPV was applied in attempt to improve oxygenation and augment ventilation to decrease the work of breathing as well as the need for intubation with all its complications.

One of the limitations of NIPPV in hypoxemic de novo ARF is the need for higher pressures to achieve adequate work of breathing reduction. These high pressures often lead to high tidal volumes which both of which have been shown to increase lung injury, thus perpetuating ARF especially in ARDS. Some of the other undue consequences of NIPPV high inspiratory pressures include increased air leaks, gastric insufflation, and patient intolerance. Decisively the main risk of NIPPV in de novo ARF is the potential delay in intubation. In fact, patients with hypoxic de novo ARF who fail NIPPV requiring intubation had more complications and higher risk for mortality [4]. ERS/ATS guidelines note that a trial of NIPPV can be considered in this patient population under direct supervision of experienced clinical team, care patient selection, as well as close ICU monitoring with reassessment for intubation need early after NIPPV initiation.

One of the first randomized controlled trials that investigated the utility of HFNC in the de novo ARF patient population compared HFNC to standard oxygen therapy and NIPPV. The primary outcome of endotracheal intubation was not statistically different between the groups [19]. When a post hoc adjusted analysis was done using a lower PaO_2/FiO_2 ratio $\leq$200 mmHg instead of the original $\leq$300 mmHg, a significant reduction in the need for intubation rates was found in the HFNC group. Furthermore, HFNC increased ventilator-free days, reduced 90-day mortality, and was associated with improved comfort as well as dyspnea severity [21]. It is important to note that this was a very specific group of patients that excluded COPD exacerbations, other hypercapnia causes, acute cardiac pulmonary edema, severe neutropenia, other organ failures, hemodynamic instability, or those on vasopressors. Other critiques of this study are the short NIPPV use time during treatment, high NIPPV tidal volumes (i.e., inspiratory pressures) with low expiratory pressures perpetuating lung injury, and lack of NIPPV facial interface options which could have contributed to higher discomfort levels.

32.3.5 NIV Use in Post-extubation Hypoxic ARF

Physicians who care for critically ill patients on IMV often have to balance the benefits of prolonging IMV to allow for further recovery against the well-known risks of the treatment. Failure occurs in approximately 20% of planned extubations and is associated with increased morbidity and mortality. Identifying the appropriate patients for weaning and investigating measures to augment or supplement safe and successful IMV weaning to extubation are vital to improve patient care and outcomes.

As mentioned previously regarding post-extubation patients, NIPPV seemed to help prevent reintubation only in older patients with prior history of cardiac and/or pulmonary disease. A randomized control trial by Maggiore et al. looked at patients with ARF due to pneumonia and trauma, who required IMV more than 5 days. After planned extubation, patients were randomized for 48 h of either HFNC or convention oxygen supplementation via Venturi mask. HFNC was associated with significantly better comfort, oxygenation, and more importantly lower reintubation rates, 4% compared to 21% [21]. Patient characteristics suggested no prior cardiovascular and/or pulmonary disease; less than 6% of patients in this study had cardiogenic pulmonary edema, and all had normal carbon dioxide levels upon inclusion [28]. Thus one can deduce that HFNC is a reasonable if not preferred choice for oxygen supplementation post-extubation in low-risk patients. These results were reinforced by Hernandez et al. in a multicenter randomized trial which fortified the use of HFNC to prevent reintubation after planned extubation for low-risk patients [21].

Moreover, NIPPV has benefits in preventing reintubation post-planned extubation of high-risk patients with previously known cardiac and/or pulmonary disease especially those with hypercapnia. NIPPV has not been shown to help prevent reintubation or treat post-extubation hypoxic ARF. Fernandez et al. randomized non-hypercapnic patients considered high risk of extubation failure to HFNC and conventional oxygen therapy. The investigators stopped the trial after 18 months due to low recruitment. Of the 155 patients included, there were no significant differences in outcomes [29].

32.3.6 NIV in Post-op ARF

Surgery, including the associated anesthesia and postoperative pain, can often have unfavorable effects on the respiratory system. Sedatives and pain contribute to diminished breaths resulting in decreased lung volumes as well as atelectasis often leading to hypoxia. This effect has been found to be exaggerated as the surgical site approaches the diaphragm. Studies have found benefits of NIPPV implementation in patients after lung resection surgery, cardiothoracic surgery, abdominal surgery, solid organ transplant (mainly liver), and even chest trauma patients. Overall NIPPV demonstrated a decrease in mortality, need for intubation and IMV, and incidence of nosocomial pneumonia [4]. ERS/ATS 2017 guidelines suggest NIPPV use in patients with ARF postoperatively; however, this recommendation is conditional on the fact that surgical complications such as anastomotic leak or intra-abdominal sepsis are appropriately addressed, and there are no other contraindications to NIPPV such as patients' uncooperativeness or inability to protect their airway [4].

Investigations in nonobese post-cardiothoracic surgery patients that are considered low risk for extubation failure have found similar HFNC benefits compared to conventional oxygen therapy.

32.4 Conclusions

NIV ventilation (i.e., HFNC or NIPPV) is being utilized in different clinical settings that cause ARF, and Table 32.1 summarizes the positive and negative connotations of these noninvasive modalities based on the current literature review. Understanding predictors of outcome of NIV ventilation, as seen in Table 32.2, risks and benefits are important in order to optimize therapy and avoid catastrophe in ARF patients. Between the two modalities, there is clear evidence to support the use of NIPPV for the treatment of ARF in COPD, cardiogenic pulmonary edema, and immunocompromised patients, postoperatively, and has also shown benefits in preventing ARF after planned extubation of high-risk patients. On the other hand, HFNC has shown clear benefits in the treatment of de novo ARF where NIPPV has fallen short. Similar to NIPPV, HFNC can be used to treat ARF in postoperative patients and is also the preferred preventative measure for low-risk patients after planned extubation. There is promising data in the use of HFNC in asthmatics

Table 32.1 NIPPV vs. HFNC in ARF of varying etiologies

	Decreased mortality	Decreased intubation	Decreased pneumonia	Notes
Hypercapnic ARF				
Chronic obstructive pulmonary disease (COPD)				
NIPPV	+	+	+	Most studied with clear benefits
HFNC	IC	IC	0	Small studies that mainly show $PaCO_2$ decrease
Prevent reintubation in low-risk patient				
NIPPV	–	0	0	Low risk: age < 65, no underlying cardiac and/or pulmonary disease, not obese
HFNC	0	+	0	Increased comfort and better oxygenation
Prevent reintubation in high-risk patients				
NIPPV	+	+	0	High-risk patient: age > 65 with underlying cardiac and/or lung disease
HFNC	0	IC	0	Low recruitment number of patients High-risk patients: age > 65, CHF, non-hypercapnic COPD, APACHE II > 12, BMI > 30, weak cough, copious secretions, >1SBT failure, IMV > 7 days
Hypoxic ARF				
Cardiogenic pulmonary edema				
NIPPV	+	+	0	Excluded ACS and cardiogenic shock
HFNC	0	0	0	No data
Asthma				
NIPPV	IC	IC	0	May benefit COPD/asthma overlap syndrome
HFNC	*	*	0	Small studies mainly in children
Immunocompromised				
NIPPV	+	+	+	
HFNC	/	/	0	Minimal data
De novo (without prior chronic respiratory disease)—excluding COPD, cardiac pulmonary edema, neutropenia, MOSF, shock				
NIPPV	–	–	0	Negative outcomes attributed to delay in intubation; if NIPPV started should be monitored closely with low threshold for intubation
HFNC	+	+	0	Other benefits: increased VFD and comfort
Post-op—cardiothoracic, thoracic, and abdominal surgeries including solid organ transplant				
NIPPV	+	+	+	Treat post-op complications appropriately
HFNC	+	+	+	Good alternative
Key			**Abbreviations**	
0	data lacking		ARF	Acute respiratory failure
*	possible benefit		NIPPV	Noninvasive positive pressure ventilation
+	definite benefit/ recommended use		HFNC	High-flow nasal cannula
/	no added benefit		MOSF	Multiorgan system failure
–	negative effect/not recommended use		VFD	Ventilator-free days
IC	inconclusive		LOS	Length of stay
			SBT	Spontaneous breathing trial
			IMV	Invasive mechanical ventilation

and highly anticipated upcoming trial of combining the use of HFNC with NIPPV in patients with COPD. It is difficult to definitely segregate hypercapnic ARF from hypoxic ARF as many disease processes have overlapping mechanisms; however, more and more data seems to favor the use of NIPPV in hypercapnia while supporting the use if HFNC in hypoxia (Table 32.3).

Table 32.2 Predictors of outcome in NIV modalities

Predictors of outcome	Predictors of success	Predictors of failure
NIPPV	Improved pH and/or RR within first hour	Worsening mental status Inability to cooperate or tolerate interface Worsening pH especially <7.25 Copious secretions De novo ARF/ARDS
HFNC	ROX index (SpO_2/FiO_2:RR) >4.88 after 12 h	Thoraco-abdominal asynchrony within 30 min Lack of improved RR and PaO_2/FiO_2 after 1 h Nonpulmonary organ failure Shock

Table 32.3 Summary points

• Acute respiratory failure (ARF) is a common complication leading to 30% intensive care unit (ICU) admissions and 60% of patients requiring endotracheal intubation also associated with a higher mortality rate
• For ARF, literature favors the use of NIPPV in hypercapnia, while HFNC is more supported in the setting of hypoxia
• Future trials are underway using HFNC and NIPPV in combination

References

1. Ni YN, Luo J, Yu H, et al. Can high-flow nasal cannula reduce the rate of endotracheal intubation in adult patients with acute respiratory failure compared with conventional oxygen therapy and noninvasive positive pressure ventilation: as systematic review and meta-analysis. Chest. 2017;151(4):764–75.
2. Goligher EC, Dres M, Fan E, et al. Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. AJRCCM. 2018;197(2):204.
3. Melsen WG, Rovers MM, Groenwold RH, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomized prevention studies. Lancet Infect Dis. 2013;13:665–71.
4. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi P, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof S. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1602426.
5. Keenan SP, Sinuff T, Cook DJ, et al. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. Ann Intern Med. 2003;138(11):861.
6. Vital FM, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary edema. Cochrane Database Syst Rev. 2013;(5):CD005351.
7. Wang T, Zhang L, Luo K, et al. Noninvasive versus invasive mechanical ventilation for immunocompromised patients with acute respiratory failure: a systematic review and meta-analysis. BMC Pulm Med. 2016;16(1):129.
8. Burns KE, Meade MO, Premji A, et al. Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure. Cochrane Database Syst Rev. 2013;(12):CD004127.
9. Liesching T, Kwok H, Hill NS. Acute applications of noninvasive positive pressure ventilation. Chest. 2003;124(2):699.
10. Guerin C, Girard R, Chemorin C. Facial mask noninvasive mechanical ventilation reduces the incidence of nosocomial pneumonia. A prospective epidemiological survey from a single ICU. Intensive Care Med. 1997;23(10):1024.
11. Hess DR. Noninvasive positive-pressure ventilation and ventilator-associated pneumonia. Respir Care. 2005;50(7):924.
12. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med. 1998;339(7):429.
13. Demoule A, Girou E, Richard JC, et al. Benefits and risks of success or failure of noninvasive ventilation. Intensive Care Med. 2006;32:1756–65.
14. Hill NS. Complications of noninvasive ventilation. Respir Care. 2000;45(5):480–1.
15. Roca O, Riera J, Torres F, et al. High-flow oxygen therapy in acute respiratory failure. Respir Care. 2010;55:408–13.
16. Nishimura M. High-flow nasal cannula oxygen therapy in adults. J Intensive Care. 2015;3:15.
17. Parke RL, McGuinness SP. Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. Respir Care. 2013;58:1621–4.
18. Monro-Somerville T, Sim M, Ruddy J, et al. The effect of High-flow nasal cannula oxygen therapy on mortality and intubation rate in acute respiratory failure: a systematic review and meta-analysis. Crit Care Med. 2017;45(4):e449.
19. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185–96.
20. Plant PK, Owen J, Elliott MW. One year period prevalence study of respiratory acidosis in acute exac-

erbation of COPD; implications for the provision of non-invasive ventilation and oxygen administration. Thorax. 2000;55:550–4.
21. Hernández G, et al. HFNC support therapy: new insights and improving performance. Crit Care. 2017;21:62.
22. Leong LB, Ming NW, Feng LW. HFNC oxygen vs NIV in adult ARF: a systemic review of randomized-controlled trials. Eur J Emerg Med. 2019;26(1):9–18.
23. Kim ES, et al. Effectiveness of HFNC oxygen therapy for ARF with hypercapnia. J Thorac Dis. 2018;10(2):882–8.
24. Ricard J-D, Dib F, Esposito-Farese M, et al. Comparison of HFNC oxygen & conventional oxygen therapy on ventilatory support duration during acute-on-chronic respiratory failure: study protocol of a multicenter, randomised, controlled trial. The 'HIGH-FLOW ACRF' study. BMJ Open. 2018;8:e022983.
25. Chua MR, Kuan WS. The use of HFNC in acute decompensated heart failure: ready for prime time yet? J Emerg Crit Care Med. 2017;1:22.
26. Ballerstero Y, et al. Pilot clinical trial of high flow oxygen therapy in children with asthma in the emergency service. J Pediatr. 2018;194:204–10.
27. Lemiale V, et al. HFNC oxygenation in immunocompromised patients with acute hypoxemic respiratory failure: a groupe de recherche respiratoire en reanimation onco-hematologique study. Crit Care Med. 2017;45:e274–80.
28. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med. 2014;190:282–8.
29. Fernandez R, et al. HFNC to prevent postextubation respiratory failure in high-risk non-hypercapnic patients: a randomized multicenter trial. Ann Intensive Care. 2017;7:47.

Noninvasive Ventilation in Hypoxemic Respiratory Failure

33

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Abbreviations

AMI	Acute myocardial infarction
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ATS	American Thoracic Society
BiPAP	Bi-level positive airway pressure
cm H_2O	Centimeters of water
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
COT	Conventional oxygen therapy
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary edema
EPAP	Expiratory positive airway pressure
ERS	European Respiratory Society
F_IO_2	Fraction of inspired oxygen
HFNC	High-flow nasal cannula
HRF	Hypoxemic respiratory failure
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
IPAP	Inspiratory positive airway pressure
L	Liters
LOS	Length of stay
min	Minute
mL	Milliliters
NIV	Noninvasive ventilation

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PaO_2	Partial pressure of oxygen
PEEP	Positive end expiratory pressure
RCTs	Randomized control trials
SOFA	Sequential organ failure assessment

33.1 Introduction

HRF is a leading cause of intensive care admissions and contributes to significant acute and late mortality [1, 2]. Common causes include ARDS, pneumonia, asthma, pulmonary edema, and immunosuppression. While NIV has been increasingly used in HRF, evidence for its use is still somewhat controversial. In this chapter, we review literature pertaining to the use of NIV in HRF, as well as growing data for HFNC in HRF within the last 2 years.

33.2 Methods

Electronic database PubMed was searched with index words "noninvasive ventilation" and "acute respiratory failure" including articles published between January 2017 to March 2019 in the field of Title/Abstract. An initial screening of the title, abstract, and keywords of every record identified was performed. The next step was to retrieve the full text of potentially relevant studies. Only studies in English and those addressing adult age groups were considered.

33.3 Results

After applying the above search terms, we got 102 articles, out of which 89 were excluded due to various reasons (Fig. 33.1). The remaining 13 articles were analyzed for the preparation of this chapter (Table 33.1).

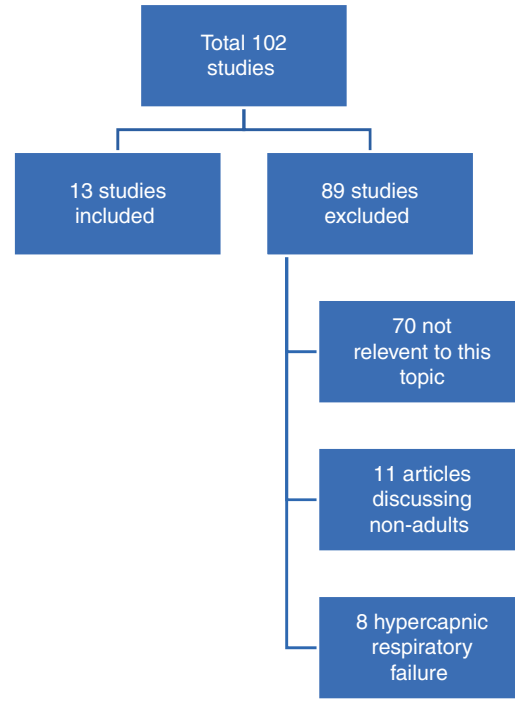

Fig. 33.1 Summary of searched articles from PubMed

33.4 Discussion

HRF is typically treated by an escalation therapy that starts with supplemental oxygen and etiological treatment. Patients in severe respiratory distress may require intubation, mechanical ventilation, and even extracorporeal membrane oxygenation in extreme cases. Between the two extremes lies the use of NIV. The rationale for its use lies in its ability to supplement oxygen and reduce the work of breathing among other physiological effects. However, because there is a large variation in the etiology and thus pathophysiology of hypoxemic respiratory failure, recommendation for NIV use largely depends on the underlying disease. This is illustrated in recent guidelines such as the 2017 European Respiratory Society (ERS)/American Thoracic Society (ATS) clinical practice guidelines [3]. To understand which NIV method is optimal for which scenario, we must first discuss the physiology associated with each modality.

Noninvasive positive pressure ventilation supplies positive pressure air with up to 100% inspired oxygen via a range of applicators including helmets and facial or nasal masks. Pressure can be supplied by continuous positive airway pressure (CPAP) where the pressure remains the same throughout the respiratory cycle, via inspiratory pressure support alone, or by bi-level

Table 33.1 Summary of articles discussed in this chapter

Authors, year	Summarization
Rochwerg et al., 2017 [3]	ERS/ATS recommendations for use of NIV based on pooled data from multiple studies
Bello et al., 2018 [7]	Discussion of NIPPV interfaces, modes of delivery, recent studies, and overview of indications
David-João et al., 2019 [9]	Systematic review of NIV for HRF. NIV showed protective effect for immunocompromised patients and patients with acute pulmonary edema/community-acquired pneumonia
Dumas et al., 2018 [10]	Investigated how initial oxygen management influenced the need for intubation for immunocompromised patients. Ventilation/oxygenation management had no impact on the probability of intubation on the coming day
Sklar et al., 2018 [13]	Systematic review and meta-analysis for HFNC use in immunocompromised patients. HFNC decreased mortality and IMV compared to controls
Belenguer-Muncharaz et al., 2017 [15]	Prospective RTC comparing CPAP to BiPAP for ARF from CPE. No significant difference was seen for duration of ventilation, ICU, and hospital LOS
Bellani et al., 2017 [18]	NIV use with ARDS patients with severity based on Berlin criteria. NIV is associated with higher ICU mortality in patients with PaO_2/FiO_2 lower than 150 mmHg
Xu et al. 2018 [20]	Systematic review and meta-analysis for HFNC used in adults with ARF and after extubation. HFNC was superior to COT in reducing treatment failure, HFNC reduced intubation rate compared to NIV when used as initial support
García-de-Acilu et al., 2019 [21]	Discussion of recent studies for NIV and HFNC for patients with de novo respiratory failure and strategies for treatment
Stéphan et al., 2017 [23]	Compared HFNC to NIV in obese subjects after cardiothoracic surgery. HFNC did not result in a worse rate of treatment failure
Beng et al., 2019 [25]	Systematic review of RTCs for NIV vs. HFNC in ARF. Results varied by study, but ICU mortality and patient tolerability favored HFNC
Tu et al., 2017 [28]	Compared HFNC vs. NIV for patients with ARF who received renal transplants. HFNC was associated with increased number of ventilator-free days and fewer complications

positive airway pressure (BiPAP) where different levels are set for inspiratory and expiratory pressures.

CPAP delivers continuous positive pressure throughout the respiratory cycle and does not assist with inspiration. Due to this, it can only be tolerated by patients that initiate spontaneous inspiration. During the expiratory phase of respiration, the continuous pressure applied by CPAP is physiologically analogous to the expiratory positive airway pressure (EPAP) supplied by BiPAP in that it supplies a positive end expiratory pressure (PEEP). This pressure helps to open or "recruit" alveoli that have collapsed or are filled with fluid and maintain their patency throughout the respiratory cycle. When the alveoli are collapsed, blood with low oxygen content from the right heart passes to the left heart without oxygen diffusion occurring, resulting in a shunt. Increasing the EPAP/CPAP pressure recruits more alveoli and decreases this intrapulmonary shunt. The positive pressure also has the effect of increasing lung compliance and functional residual capacity (FRC) while decreasing hypoxemia and the work of breathing [4].

BiPAP provides in increased inspiratory positive airway pressure (IPAP). The higher pressures supplied during inspiration help to overcome the difference in pressures during inspiration and expiration. It creates a larger change in the size of the alveoli throughout the ventilatory cycle reflecting an increase in the tidal volume. Increasing the difference of the IPAP and the EPAP will increase ventilation and thus helps to decrease hypercarbia. The increased pressures during inspiration with BiPAP also reduce the work of breathing to a greater extent than is achieved with CPAP [4].

Positive airway pressures also have significant effects on the hemodynamics of the heart. Positive pressures applied to the thoracic cavity increase the pressure within the thoracic cavity, placing higher pressures on the venous return to the heart and decreasing ventricular preload. The

positive pressure also increases intrathoracic pressure which decreases transmural pressures. This lowers the pressure that is needed to be generated by the ventricle during systole to achieve forward flow, resulting in a reduction in afterload. The combined reduction in preload and afterload helps to decrease myocardial oxygen demand without augmenting cardiac output for this population [5].

High-flow nasal cannula (HFNC) works via a different mechanism than NIPPV. HFNC supplies heated and humidified oxygen and air via wide bore nasal prongs. Rates can be achieved of up to 60 liters (L)/minute (min) of inspired air with up to 100% oxygen, though the percentage of oxygen that enters the patient's airway is widely variable due to the open system by which it is supplied resulting in oxygen dilution. The high rate of flow associated with HFNC helps to wash out carbon dioxide (CO_2) from anatomic dead space or the portion of the upper airways where inspired air does not take part in gas exchange. This high flow also increases ventilation of the alveoli independent of minute ventilation. It also facilitates a reduction in the resistance of the upper airways, improves lung compliance, and decreases work of breathing. Additionally, when the mouth is closed, a PEEP of 7.4 centimeters of water (cm H_2O) can be achieved [6], but these pressures are generally less than 4 cm H_2O [7]. This allows for alveolar recruitment and prevention of atelectasis similar to the mechanism of CPAP/EPAP. This positive pressure effect additionally augments cardiac function by modulating preload and afterload as discussed above. Finally, the effect of humidified and heated air is not only much better tolerated, it also helps to facilitate mucociliary clearance of secretions, avoid bronchospasm, and decrease irritation that can occur with administration of non-humidified air [6].

There are four main types of interfaces used to apply positive pressure support. The first is via a nasal mask which is a conical device that rests over the nose on a soft cushion that is held in place by a strap that fits around the head. The nasal mask is often used by individuals who require chronic noninvasive ventilation such as those with obstructive sleep apnea or obesity hypoventilation syndrome. This option is usually better tolerated than the oronasal mask but can still cause skin breakdown, irritation, erythema, ulceration, and even necrosis with prolonged use. Additionally, major air leaks can occur if the mouth is opened [7].

The second interface is the oronasal mask which is currently the most commonly used interface in the setting of acute respiratory failure. The mask is larger than the nasal mask and fits over both the nose and the mouth, thus preventing air leak from mouth opening. This is preferred in acute settings as individuals with respiratory distress instinctually open their mouths to assist with air flow. This interface has a high risk of air leaks due to improperly sized masks or due to variability in facial structures. It also prevents the wearer from talking, eating, or taking medication by mouth and has a risk of aspiration in the event of emesis. It can cause anxiety in individuals who have claustrophobia and causes the skin symptoms mentioned above with prolonged use. The third interface is the full facial mask. This is a larger mask that encompasses the entire face and is designed to be more comfortable to wear to increase compliance [7].

The fourth interface is the helmet. This is made of a transparent hood that fits over the entire head and rests on a soft collar at the neck and shoulders that creates a seal. Pressure is maintained by straps that wrap under the axilla. This interface is more comfortable to wear, is better tolerated, and allows individuals to talk while receiving pressure support. The pressure from the helmet is transferred around the neck and produces less skin lesions and irritation, as well as reduced air leak. The helmet, as well as all of the aforementioned interfaces, can also accommodate nasogastric tubes [7]. Due to its size, one of the largest concerns with helmet use is that the added volume increases dead space and can potentially increase rebreathing of CO_2 and exacerbate hypercapnic respiratory failure. Helmet volumes can range widely from 110 to 10,000 milliliters (mL), but computational flow models suggest the actual dead space is only increased by 110–370 mL. The washout of CO_2

from the helmet is also affected by ventilator settings. The pressure generated by CPAP does not proportionally change the partial pressure of CO_2 within the helmet. The difference in pressure achieved with BiPAP is more effective at clearing CO_2 than CPAP and can reduce it to insignificant levels. Additionally, when flow rate is increased to between 45 and 60 L/min, CO_2 is effectively washed out and has little effect [7].

33.4.1 Noninvasive Ventilation Modes and Settings

There are multiple modes that can be used to administer positive pressure ventilation. Pressure support ventilation provides a preset pressure when triggered by the patient. The pressure will continue to be applied until the flow rate decreases to a preset limit. This mode does not offer any expiratory support, and the respiration rate as well as inspiratory time and expiratory times are set by the patient. Proportional assist ventilation senses and adjusts flow and pressure needs to match that of the patient. Since the patient is triggering the start and duration of inspiration and expiration for both of these modes, greater synchrony with the ventilator is achieved [8].

Pressure control ventilation can be administered either by CPAP or BiPAP. As described before, CPAP applies continuous pressure and does not assist with inspiration and therefore has no inspiration triggers or settings. BiPAP applies separate preset pressures for inspiration and expiration. Additionally, it supplies inspiratory pressure over a preset inspiratory time. The patient can trigger the inspiration, but after the preset time, it will trigger the expiratory pressure. This is the most commonly used mode in the acute setting as it supplies a PEEP, and the IPAP allows augmentation of ventilation [8]. Volume control mode also exists, but this is used much less commonly. It applies pressure until a preset volume is reached. This can be useful in settings of obesity or chest wall restrictions when high pressures may be needed to achieve desired tidal volumes [7].

Initial ventilatory settings for pressure control ventilation are started at lower pressures and uptitrated as needed and as tolerated by the patient. CPAP or EPAP should be set between 3 and 5 cm H_2O, and IPAP should be set 8–12 cm H_2O above the EPAP. These values should be uptitrated to improve symptoms of dyspnea, decrease respiratory rate, and achieve adequate exhaled tidal volumes of 6–8 mL/kg for predicted body weight. Fraction of inspired oxygen (F_IO_2) should be titrated to oxygen saturation above 92% or between 85% and 90% for patients at risk for hypercapnic respiratory failure [7]. EPAP can be increased by small increments as needed to help recruit alveoli and increase oxygen saturation to the desired level, along with a proportional increase in IPAP. Higher differences between EPAP and IPAP can assist with ventilation of CO_2 if patients have hypercapnic respiratory failure [4].

33.4.2 Etiologies

33.4.2.1 Immunocompromised

For the immunocompromised population, acute hypoxemic respiratory failure is the most common cause of critical illness and admission to the intensive care unit (ICU) [1]. NIPPV offers several advantages to immunocompromised patients as it can potentially avoid complications associated with invasive mechanical ventilation (IMV) such as heavy sedation, the need for vasopressors, airway trauma, and ventilator-associated pneumonias. The current ERS/ATS guidelines advise NIV, both BiPAP and CPAP, for immunocompromised patients with mild to moderate acute respiratory failure to prevent intubation and decrease mortality with a moderate certainty of evidence [3], though recent studies continue to show mixed result. The majority of patients included in recent studies had a diagnosis of hematological malignancies, solid tumors, systemic diseases, and transplantation, with the most common cause of AHRF being pneumonia [9–14].

A recent systematic review of nine randomized control trials (RTCs) from 1995 to 2018 found that NIPPV had a protective effect for intubation for immunocompromised patients with AHRF. A decreased risk for intubation was seen in 23% of

cases with relatively low heterogeneity ($I^2 = 47.5\%$, $p = 0.168$), though they note that the RTC that showed significantly better results was conducted nearly 20 years ago. This study did not show a protection for mortality [9]. Conversely, a large multicenter post hoc analysis by Dumas et al. compared the effect of NIV vs. conventional oxygen therapy (COT) administered via nasal cannula or Venturi mask, on the probability of next day intubation in immunocompromised patients with AHRF. This study found that there was no significant difference in cumulative incidence of IMV between the two study groups observed ($p = 0.44$) nor was there a difference in the mortality rates in mechanically vented patients. These results suggest NIV vs. COT had no impact on the probability of intubation the following day [10].

A recent single-center retrospective cohort with a large patient population ($n = 1614$) compared the outcomes in immunocompromised individuals who received NIPPV vs. IMV for first-line therapy. The severity of illness for each individual was assessed with the sequential organ failure assessment (SOFA) score. The median and mean SOFA scores were highest in the IMV-only group (10; 10.8 ± 4.5), followed by the NIPPV failure group (9; 9.7 ± 4.5), and the NIPPV success group (7; 7.5 ± 3.5; $p < 0.0001$). Those who failed NIPPV had the greatest hospital length of stay (LOS), ICU LOS, ICU mortality (71.3%), and hospital mortality (79.5%) compared to those who did not fail NIPPV or received first-line IMV ($p < 0.0001$). This means that despite having lower SOFA scores, the NIPPV failure group fared worse than the first-line IMV group. The factors associated with NIPPV failure were younger age (OR, 0.99; 95% CI 0.98–0.99; $p = 0.031$), non-Caucasian race (OR, 1.61; 95% CI 1.14–2.26; $p = 0.006$), presence of a hematologic malignancy (OR, 1.87; 95% CI 1.33–2.64; $p = 0.0003$), and higher sequential organ failure assessment score (OR, 1.12; 95% CI 1.08–1.17; $p < 0.0001$). An important finding was that there was no significant difference in those who received early versus (vs.) late intubation (less than or greater than 24 or 48 h) for the NIPPV failure group [11].

Recent studies have additionally sought to compare HFNC vs. NIV and COT to determine its efficacy in preventing IMV and mortality. A large multinational observational prospective cohort published in 2017 by Azoulay et al. with more than 1600 patients found that HFNC, but not NIV, had an effect on decreasing the rate of IMV (HR = 0.77, 95% CI 0.59–1.00, $p = 0.05$). The factors associated with IMV were age (HR = 0.92/year, 95% CI 0.86–0.99), day-1 SOFA score (1.09/point, 1.06–1.13), day-1 partial pressure of oxygen (PaO_2)/FiO_2 (1.47, 1.05–2.07), and respiratory failure etiology including *Pneumocystis jirovecii* pneumonia (2.11, 1.42–3.14), invasive pulmonary aspergillosis (1.85, 1.21–2.85), and undetermined cause (1.46, 1.09–1.98). The factors that were associated with mortality were age (OR = 1.18/year, 1.09–1.27), direct admission to ICU (0.69, 0.54–0.87), day-1 SOFA excluding respiratory score (1.12/point, 1.08–1.16), $PaO_2/FiO_2 < 100$ (1.60, 1.03–2.48), and undetermined ARF etiology (1.43, 1.04–1.97). The highest risk for mortality with IMV was seen in the groups who failed HFNC, followed by COT and NIV. This study also found that the initial oxygen strategy used did not have an impact on decreasing mortality rates. It stressed the need in determining the underlying etiology of the ARF as patients with an undetermined cause were at increased risk for IMV and mortality [12].

A recent systematic review with nearly 2000 subjects and including multiple RCTs showed that mortality at the longest available follow-up was lower with HFNC compared to NIV or COT in seven out of 13 studies (1429 subjects; relative risk 0.72, 95% CI 0.56–0.93, $p = 0.01$). Additionally, eight out of the 13 studies showed a lower rate of IMV with HFNC vs. NIV or COT (1529 subjects, relative risk 0.81, 95% CI 0.67–0.96, $p = 0.02$) [13]. Although HFNC may be a promising treatment of choice to prevent both IMV and mortality, the heterogeneity of study results as well as the ERS/ATS current guidelines state that more high-quality studies are required to make any recommendations [3].

33.4.2.2 Cardiogenic Pulmonary Edema

Cardiac dysfunction from multiple etiologies can lead to cardiogenic pulmonary edema (CPE) and HRF. A drastic increase in pulmonary capillary hydrostatic pressure and trans-vascular fluid filtration forces fluid into the alveoli and interstitial space. This results in rapid accumulation and impairment of alveolar gas exchange, decrease in pulmonary compliance, decrease in lung volume, and ultimately cases a transpulmonary shunt. These combined factors cause an increased WOB and, if allowed to progress, can cause AHRF and cardiorespiratory collapse. As described above, the positive pressure from NIV can help clear alveolar and interstitial edema, recruit alveoli to mitigate the right-to-left intrapulmonary shunt, and decrease WOB. It also decreases LV preload and afterload without significantly altering cardiac output [5].

The use of NIV for the treatment of ARF in the setting of CPE has been extensively studied in several trials over the last 30 years. The ERS/ATS guidelines strongly recommend either BiPAP or CPAP for patients with ARF due to CPE with a moderate certainty of evidence. This was based on a pooled analysis of multiple studies that showed NIV decreased mortality (RR 0.80, 95% CI 0.66–0.96) and the need for intubation (RR 0.60, 95% CI 0.44–0.80) in this population. This recommendation excludes patients with acute cardiac syndrome and cardiogenic shock as these conditions were excluded from most trials and there was insufficient evidence to make a recommendation. The largest multicenter trial was published in 2008 and included 1069 patients with ARF due to CPE who were randomized into receiving COT, CPAP, or BiPAP. This study showed that groups treated with NIV had earlier resolution of dyspnea, respiratory distress, and metabolic alterations than COT but noted no difference in rates of mortality or ETI. The guidelines also recommend CPAP or BiPAP prior to hospitalization to prevent deterioration in this patient population. This recommendation is based off of six single-center RCTs whose pooled analysis showed a decrease in mortality and need for intubation but noted this recommendation has a low certainty of evidence due to heterogeneity of data [3].

The ERS/ATS guidelines make no recommendations between using CPAP and BiPAP for CPE-induced ARF. It does note that in some studies, BiPAP was associated with a possible increase in the rates of acute myocardial infarction (AMI) but stated this was based on a very low level of evidence (OR 1.18, 95% CI 0.95–1.48) [3]. This finding was initially based on two studies. The first study compared BiPAP to CPAP for ARF from CPE and was stopped after recruiting only 27 patients because the rate of AMI was significantly higher in the BiPAP group. It is noted that this may have been caused by a recruitment bias as the majority of patients had chest pain at presentation. The second study compared treatment with BiPAP to treatment with nitrates and found that the BiPAP group had significantly higher rates of AMI (55% vs. 10%) and IMV (80% vs. 20%) [5]. The reason for this may have been that the BiPAP group received less IV treatment and had very strict ventilation parameters that may have limited treatment efficacy. Further trials did not reproduce this effect [3].

Two recent studies have been published comparing treatment of ARF from CPE with COT or CPAP vs. BiPAP. One large multicenter prospective observational study conducted in Italy included over 1200 patients. The causes for acute CPE were hypertensive crisis, acute cardiac syndrome, arrhythmia, and valvular disease. The initial treatment groups were COT (n = 273, 21%), CPAP (n = 788, 61%), and BiPAP (n = 232, 18%). There was no significant difference in rates of mortality within 24 h (3%, 3%, and 3%, respectively; $p = 0.760$) or mortality during hospitalization (10%, 8%, and 10%, respectively; $p = 0.330$). There was a significant difference in IMV rates which were 1% for COT, 2% for CPAP, and 6% for BiPAP ($p < 0.05$), though the authors note that the higher rate of IMV for BiPAP may be due to a higher severity of illness in this group. This study also noted that 25% of patients initially treated with COT failed initial treatment and were changed to BiPAP without treatment failure. The odds ratio for COT failure was 3.365 (95% CI 2.55–5.23, $p < 0.001$) [14].

Another single-center RCT compared treatment with BiPAP to CPAP for this population. This study found that both groups had similar clinical improvement but noted the BiPAP group had a higher PaO_2/FiO_2 ratio (205 ± 112 in NIV vs. 150 ± 84 in CPAP, $p = 0.02$). There was no difference in the rate of IMV (9% in NIV vs. 9% in CPAP, $p = 1.0$). There were also no significant differences in duration of ventilation or ICU and hospital LOS. There was also no difference in ICU, hospital, and 28-day mortality [15]. These findings suggest that the choice between using CPAP and BiPAP for this patient population can be made based on provider experience and patient comfort, though BiPAP will provide more ventilation support to assist with CO_2 clearance [4].

Few studies have been published that compare HFNC to NIV for treatment of ARF from CPE. Only one RCT has been published by Makdee et al. that was conducted in a single-center emergency department in Thailand. This study randomized patients with CPE to treatment with COT or HFNC with a flow rate of 35–60 L/min. The results showed that HFNC decreased respiratory rate at 15-, 30-, and 60-min intervals compared to COT, but the decrease was too small to have clinical significance as the mean difference at the 60-min interval was a reduction in 3.3 breaths/min (95% CI 1.9–4.6). No significant differences were found in the admission rate, ED and hospital lengths of stay, rate of intubation, or mortality [16]. Finally, a retrospective analysis for treatment of AHRF with HFNC was published in 2015 by Hyun et al. This study found that for the CPE population, IMV was prevented for 81.3% of patients, which was significantly higher than patients with other conditions (OR 13.33; 95% CI 1.746–101.882, $p = 0.013$) [17]. Though the data appears promising, more large RTCs are needed to make conclusive evidence regarding using HFNC for ARF in CPE [3].

33.4.2.3 De Novo

De novo respiratory failure is defined as respiratory failure that occurs without underlying chronic cardiopulmonary disease. De novo respiratory failure usually results in HRF and is defined as significant hypoxemia ($PaO_2/FiO_2 \leq 200$), tachypnea (RR > 30–35 breaths/min), and a diagnosis that does not include chronic obstructive pulmonary disease (COPD). The most common etiologies are pneumonia and ARDS. This definition does not include patients with CPE or postsurgical respiratory failure as the underlying mechanism and efficacy of treatments are different [3].

The goal for utilizing NIV for de novo respiratory failure is to improve oxygenation and ventilation, decrease WOB, and prevent IMV to minimize its associated complications. The ERS/ATS 2017 guidelines pooled data on patients with ARF from ARDS and pneumonia was unable to provide a recommendation based on the uncertainty of evidence. The pooled data showed that NIV decreased mortality (RR 0.83, 95% CI 0.65–1.05) and the need for intubation (RR 0.75, 95% CI 0.63–0.89), though this is based on a low certainty of evidence [3].

There are many aspects of NIV that potentially limit its efficacy in this patient population. One issue is that the positive pressure needed to reduce inspiratory effort may result in large transpulmonary pressures and tidal volumes that can cause damage to the lung over time in a manner similar to ventilator-associated lung injury. These high pressures can also cause air leaks and gastric insufflation, resulting in patient intolerance. Additionally, interruptions in NIV cause a loss of alveolar recruitment and an immediate return in hypoxia and increased WOB, though this effect can be augmented by the application of HFNC. Furthermore, NIPPV could potentially improve a patient's respiratory symptoms and mask progression of the underlying pathology, thus delaying intubation and increasing mortality risk [3].

A recent publication by Bellani et al. called the LUNG SAFE study applied NIV to patients with ARDS regardless of the degree of hypoxemia. This study showed that as patients' severity of ARDS increased based on PaO_2/FiO_2 ratio, the rate of NIV failure increased (22.2%, 45.4%, and 47.1% for mild, moderate, and severe ARDS, respectively). NIV use was independently associated with increased ICU mortality (HR, 1.446; 95% CI 1.159–1.805) and was associated with a

higher mortality compared to those treated with IMV for patients with PaO_2/FiO_2 ratio lower than 150 mmHg. No difference was seen in hospital mortality [18].

Two recent systematic reviews and meta-analyses published in 2017 showed promising results for NIV in this population. Both of these reviews compared NIV to COT for treatment of AHRF, excluding those caused by CPE and COPD. The first involved 1691 patients and found that NIV lowered both the short-term mortality and rate of IMV compared with COT [19]. The second by Xu et al. included 1480 patients and found that NIV significantly reduced the rate of IMV (risk ratio, 0.59; 95% CI 0.44–0.79; $p = 0.0004$) and hospital mortality (risk ratio, 0.46; 95% CI 0.24–0.87; $p = 0.02$). A subgroup analysis showed that BiPAP was associated with a reduction in ICU mortality ($p = 0.007$) and the helmet interface could reduce hospital mortality ($p = 0.0004$), whereas the face/nasal mask could not [20]. This last study illustrates the limitations of the oronasal and face mask interface for NIV. Compared to the helmet, these interfaces are associated with substantial mask leak, patient discomfort, and asynchronies and can generate potentially high tidal volumes that can cause lung injury [7].

Multiple recent studies sought to see the effect different interfaces had on NIV success in this population. These studies have shown that the helmet offered enhanced PEEP titration with reduced air leaks, lower respiratory rates, lower rate of IMV, fewer ventilator-free days, lower hospital and 90-day mortality and found a low incidence of adverse events when compared to NIPPV via face mask. One follow-up study also showed the patients were more likely to be discharged home, be functionally independent at discharge, and had lower 1-year mortality. Because there are only a small number of studies available for use in these analyses, more large rigorous RTCs are needed before these findings can be confirmed [22].

Defining the role of HFNC in the treatment of de novo respiratory failure can be difficult to assess. According to the Berlin criteria, ARDS is defined as hypoxemia that persists after the application of a PEEP of 5 cm H_2O or more, and this level of PEEP may not be attained with HFNC. A recent study comparing lung inflammatory biomarkers found similar patterns in ARDS patients treated with ETI and similar patients treated with HFNC. This suggests that these patients would have met the Berlin criteria and can be considered similar to ARDS patients. In the last 2 years, ten meta-analyses evaluated the use of HFNC in ARDS. These reviews showed mixed results with five studies showing HFNC reduces rates of ETI compared with COT, two studies showing no difference in rates of ETI from NIV, one showing a reduction in short-term mortality and another showing reduction in ICU mortality. The other studies showed HFNC had no different outcomes from COT in these measures, and one study reported the data was too heterogenous to make any conclusions. The majority of these studies agree that more larger RTCs are needed to make any recommendations for the use of HFNC in ARDS [21].

33.4.2.4 Postsurgical

Surgical procedures, especially those that encroach upon the diaphragm, can cause AHRF. Anesthesia can suppress the respiratory drive and diaphragmatic dysfunction, and pain with inspiration can lead to atelectasis, all of which can lead to hypoxia and cause respiratory failure that can potentially last up to 7 days. Both CPAP and BiPAP are frequently used in these situations and have been shown to decrease atelectasis and increase lung aeration and arterial oxygenation without having adverse hemodynamic effects during the post-op period following extubation [3].

The ERS/ATS 2017 guidelines recommend using NIV for patients who develop postoperative ARF with a moderate certainty of evidence. Pooled analysis shows NIV reduces mortality (RR 0.28, 95% CI 0.09–0.84), the need for intubation (RR 0.27, 95% CI 0.12–0.61), and the incidence of nosocomial pneumonia (RR 0.20, 95% CI 0.04–0.88) in this postoperative population but states the last two effects have low and very low certainty of evidence respectively. This recommendation applies to both sub- and supra-

diaphragmatic surgeries. It states that before initiating NIV, patients should be assessed for surgical complications and intra-abdominal sepsis, as well as their ability to protect their airway [3].

Two recent studies have been published regarding the use of HFNC in this population. One study is a meta-analysis comparing HFNC to COT for patients following cardiothoracic surgery. Over 600 patients were included, and compared to COT, a significant reduction was found for the patients treated with HFNC in escalation of respiratory support (OR = 0.44, 95% CI 0.29–0.66, $p < 0.001$) and pulmonary complications (OR = 0.28, 95% CI 0.13–0.6, $p = 0.001$). No significant difference was seen in the re-intubation rate and ICU or hospital LOS [22]. The second is a post hoc analysis of RTC for obese patients undergoing cardiothoracic surgery who developed ARF in the post-op period. In this study, no significant difference was found for treatment with HFNC vs. NIV for treatment failure (15.4% vs. 13.3%, $p = 0.62$) or ICU mortality (2.2% vs. 5.9%, $p = 0.22$) [23]. Although no official recommendations were made for HNFC in the ERS/ATS guidelines, the data appears promising that it may be more efficacious that it may present a more comfortable and tolerable alternative to NIV for this population.

33.4.3 HFNC vs. Noninvasive Positive Pressure Ventilation

Literature comparing traditional modalities of NIPPV (BiPAP/CPAP) and HFNC are still being published. Within the last 2 years, publications have been limited to meta-analyses, systematic reviews, and retrospective reviews for specific patient populations. While clinical applicability is limited by the lack of prospective randomized trials, it is worth reviewing these to serve as a framework for how we utilize each modality in practice.

Leeies et al. published a systematic review and meta-analysis in October of 2017 to compare the efficacy and safety of HFNC compared to NIV [24]. They reviewed recent RCTs from 2014 to 2016, with the primary outcome measure of mortality incidence at longest duration of follow-up. Endotracheal intubation, patient tolerability, and dyspnea rating, as well as physiologic variables (PaO_2:FiO_2 ratio, $PaCO_2$, pH), were measured as secondary outcomes. Safety was measured by rates of cardiorespiratory arrest, delirium, and skin breakdown. Each outcome was measured at the longest duration of study follow-up. They identified seven studies that were included in the analysis, of which five were conducted in European centers, one in Thailand, and one in New Zealand. All included trials were designed as parallel group RCTs, with one designed as a non-inferiority trial. One limitation of these studies, as is with most studies that compare NIPPV and HFNC, is the lack of ability to blind the studiers and patients. Settings included the emergency department, medical, surgical, and cardiac surgical ICUs. This encompassed patients who had HRF of various etiologies.

While the group concluded that mortality between HFNC and NIV or standard nasal cannula oxygen was not different, they graded the evidence as low. Examining the studies that were discussed, there is marked heterogeneity in the modality of ventilation and oxygenation used within each study. This combined with the low number of studies included severely limits our applicability of this information to our practice. This also applies to the reported secondary outcomes as well, where the group concluded that it cannot be systematically concluded based on the examined studies. A similar review was done recently by Beng et al., which concluded similar results of limited applicability after they had examined five randomized trials [25].

One particular topic that has been compared between HFNC and NIPPV is their ability to prevent re-intubations. Within the last 2 years, this has also been examined primarily by meta-analyses and systematic reviews. In 2017, Yue-Nan Ni et al. examined eight trials from 2013 to 2017 to compare re-intubation rates, ICU mortality, and ICU LOS, between conventional oxygen therapy, NIPPV, and HFNC [26]. Notably of the eight, only two studies that were included directly compared NIPPV and HFNC. One of these two studies was also included in the Leeies

article discussed above. Yue-Nan Ni's group concluded that re-intubation rates were comparable between NIPPV and HFNC. However, this was statistically not significant owing to the lack of included studies and can only be seen as a trend. Secondary outcomes of ICU LOS and ICU mortality were also not different between these groups.

In a larger more recent study, Zhihen Xu et al. analyzed 18 RCTs and concluded that HFNC statistically significantly reduced intubation rates compared to NIV, when used as an initial modality of respiratory support [27]. However, this study was limited by the heterogeneity and reportability of the degree of hypoxia for the patients included. Thus we cannot apply their conclusion to HRF patients.

Non-systematic reviews and meta-analyses comparing HFNC and NIPPV remain limited to specific patient populations such as post-renal transplant patients and after cardiothoracic surgery [23, 28]. While these studies support the non-inferiority of HFNC compared to NIPPV, the retrospective and post hoc nature of the study with the specificity of patient population also limit its generalizability.

33.5 Conclusion

NIPPV and HFNC continue to be a popular method of oxygenation support for patients in HRF who do not improve with conventional oxygen supplementation. Its benefits for particular conditions mentioned within this chapter have been shown by prospective data and explained physiologically. However, its applicability outside of these indications and data on mortality and failure rate/intubation rate remain limited. Part of this can be attributed by the patient-to-patient variability that we clinically encounter. To further guide the appropriateness of patients for NIPPV or HFNC, there have been proposed bedside scoring systems. One such system is the HACOR score, which is based off of vital signs and laboratory studies readily available at bedside [29]. While clinical judgment based off of these parameters is already being used to tailor NIV therapy, systems like HACOR will add another objective criterion to properly select patients. In concert with more prospective studies on NIPPV and HFNC, we hope to see an even more refined use of NIV for hypoxemic respiratory failure.

References

1. Vincent J-L, Akça S, De Mendonça A, Haji-Michael P, Sprung C, Moreno R, Antonelli M, Suter PM, SOFA Working Group. Sequential organ failure assessment. "The Epidemiology of Acute Respiratory Failure in Critically Ill Patients(∗)". Chest. 2002;121(5):1602–9.
2. Prescott HC, Sjoding MW, Langa KM, Iwashyna TJ, McAuley DF. Late mortality after acute hypoxic respiratory failure. Thorax. 2018;73(7):618–25.
3. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1602426.
4. Kallet RH, Diaz JV. The physiologic effects of noninvasive ventilation. Respir Care. 2009;54(1):102–15.
5. Masip J, Peacock WF, Price S, et al. Indications and practical approach to non-invasive ventilation in acute heart failure. Eur Heart J. 2017;39(1):17–25. https://doi.org/10.1093/eurheartj/ehx580.
6. Chua M, Kuan W. The use of high-flow nasal cannula in acute decompensated heart failure: ready for prime time yet? J Emerg Crit Care Med. 2017;1(9):22.
7. Bello G, Ionescu Maddalena A, Giammatteo V, Antonelli M. Noninvasive options. Crit Care Clin. 2018;34(3):395–412. https://doi.org/10.1016/j.ccc.2018.03.007.
8. Nava S, Hill N. Lancet. 2009;374(9685):250–9. https://doi.org/10.1016/S0140-6736(09)60496-7.
9. David-João PG, Guedes MH, Réa-Neto Á, Chaiben VBO, Baena CP. Noninvasive ventilation in acute hypoxemic respiratory failure: a systematic review and meta-analysis. J Crit Care. 2019;49:84–91. https://doi.org/10.1016/j.jcrc.2018.10.012.
10. Dumas G, Chevret S, Lemiale V, et al. Oxygenation/non-invasive ventilation strategy and risk for intubation in immunocompromised patients with hypoxemic acute respiratory failure. Oncotarget. 2018;9(72):33682–93. https://doi.org/10.18632/oncotarget.26069.
11. Rathi NK, Haque SA, Nates R, Kosturakis A, Wang H, Dong W, Feng L, Erfe RJ, Guajardo C, Withers L, et al. Noninvasive positive pressure ventilation vs invasive mechanical ventilation as first-line therapy for acute hypoxemic respiratory failure in cancer patients. J Crit Care. 2017;39:56–61. https://doi.org/10.1016/j.jcrc.2017.01.007.
12. Azoulay E, Pickkers P, Soares M, Perner A, Rello J, Bauer PR, van de Louw A, Hemelaar P, Lemiale

V, Taccone FS, et al. Acute hypoxemic respiratory failure in immunocompromised patients: the Efraim multinational prospective cohort study. Intensive Care Med. 2017;43:1808. https://doi.org/10.1007/s00134-017-4947-1.
13. Sklar MC, Mohammed A, Orchanian-Cheff A, Del Sorbo L, Mehta S, Munshi L. The impact of high-flow nasal oxygen in the immunocompromised critically ill: a systematic review and meta-analysis. Respir Care. 2018;63(12):1555–66. https://doi.org/10.4187/respcare.05962.
14. Aliberti S, Rosti VD, Travierso C, et al. A real life evaluation of non invasive ventilation in acute cardiogenic pulmonary edema: a multicenter, perspective, observational study for the ACPE SIMEU study group. BMC Emerg Med. 2018;18(1):61. https://doi.org/10.1186/s12873-018-0216-z.
15. Belenguer-Muncharaz A, Mateu-Campos L, González-Luís R, Vidal-Tegedor B, Ferrándiz-Sellés A, Árguedas-Cervera J, Altaba-Tena S, Casero-Roig P, Moreno-Clarí E. Non-invasive mechanical ventilation versus continuous positive airway pressure relating to cardiogenic pulmonary edema in an intensive care unit. Arch Bronconeumol. 2017;53:561. https://doi.org/10.1016/j.arbres.2017.02.005.
16. Makdee O, Monsomboon A, Surabenjawong U, et al. High-flow nasal cannula versus conventional oxygen therapy in emergency department patients with cardiogenic pulmonary edema: a randomized controlled trial. Ann Emerg Med. 2017;70:465.
17. Cho WH, Yeo HJ, Yoon SH, Lee SE, SooJeon D, Kim YS, Kim KU, Lee K, Park HK, Lee MK. High-flow nasal cannula therapy for acute hypoxemic respiratory failure in adults: a retrospective analysis. Intern Med. 2015;54(18):2307–13. https://doi.org/10.2169/internalmedicine.54.4266.
18. Bellani G, Laffey JG, Pham T, et al. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. Am J Respir Crit Care Med. 2017;195:67–77.
19. Kondo Y, Kumasawa J, Kawaguchi A, Seo R, Nango E, Hashimoto S. Effects of non-invasive ventilation in patients with acute respiratory failure excluding post-extubation respiratory failure, cardiogenic pulmonary edema and exacerbation of COPD: a systematic review and meta-analysis. J Anesth. 2017;31(5):714–25. https://doi.org/10.1007/s00540-017-2389-0.
20. Xu XP, Zhang XC, Hu SL, et al. Noninvasive ventilation in acute hypoxemic nonhypercapnic respiratory failure: a systematic review and meta-analysis. Crit Care Med. 2017;45(7):e727–33. https://doi.org/10.1097/CCM.0000000000002361.
21. García-de-Acilu M, Patel BK, Roca O. Noninvasive approach for de novo acute hypoxemic respiratory failure: noninvasive ventilation, high-flow nasal cannula, both or none? Curr Opin Crit Care. 2019;25(1):54–62. https://doi.org/10.1097/MCC.0000000000000570.
22. Wu X, Cao W, Zhang B, Wang S. Effect of high-flow nasal cannula oxygen therapy vs conventional oxygen therapy on adult postcardiothoracic operation: a meta-analysis. Medicine (Baltimore). 2018;97(41):e12783. https://doi.org/10.1097/MD.0000000000012783.
23. Stéphan F, Bérard L, Rézaiguia-Delclaux S, Amaru P, BiPOP Study Group. High-flow nasal cannula therapy versus intermittent noninvasive ventilation in obese subjects after cardiothoracic surgery. Respir Care. 2017;62:1193. https://doi.org/10.4187/respcare.05473.
24. Leeies M, Flynn E, Turgeon AF, et al. High-flow oxygen via nasal cannulae in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. Syst Rev. 2017;6(1):202. https://doi.org/10.1186/s13643-017-0593-5.
25. Beng Leong L, Wei Ming N, Wei Feng L. High flow nasal cannula oxygen versus noninvasive ventilation in adult acute respiratory failure: a systematic review of randomized-controlled trials. Eur J Emerg Med. 2019;26(1):9–18. https://doi.org/10.1097/MEJ.0000000000000557.
26. Ni YN, Luo J, Yu H, et al. Can high-flow nasal cannula reduce the rate of reintubation in adult patients after extubation? A meta-analysis. BMC Pulm Med. 2017;17(1):142. https://doi.org/10.1186/s12890-017-0491-6.
27. Haywood ST, Whittle JS, Volakis LI. HVNI vs NIPPV in the treatment of acute decompensated heart failure: subgroup analysis of a multi-center trial in the ED. Am J Emerg Med. 2019;37:2084. https://doi.org/10.1016/j.ajem.2019.03.002. pii: S0735-6757(19)30151-2.
28. Tu G, He H, Yin K, Ju M. High-flow nasal cannula versus noninvasive ventilation for treatment of acute hypoxemic respiratory failure in renal transplant recipients. Transplant Proc. 2017;49(6):1325–30. https://doi.org/10.1016/j.transproceed.2017.03.088.
29. Duan J, Han X, Bai L, Zhou L, Huang S. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. Intensive Care Med. 2017;43:192. https://doi.org/10.1007/s00134-016-4601-3.

34 Noninvasive Positive Pressure Ventilation (NIPPV) in Hypercapnic Respiratory Failure

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Abbreviations

APACHE-II scoring system	Acute Physiology and Chronic Health Evaluation II scoring system
BiPAP	Bi-level positive airway pressure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
FiO_2	Fraction of inspired oxygen
HFNC	High-flow nasal cannula
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
NIPPV	Noninvasive positive pressure ventilation
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
$PaCO_2$	Partial pressure of carbon dioxide
PAV	proportional assist ventilation
PEEP	Positive end expiratory pressure
SAPS	Simplified Acute Physiology Score
VCV	Volume-control ventilation

34.1 Etiology and Morbidity/Mortality of Hypercapnic Respiratory Failure

Acute respiratory failure can present as acute-on-chronic respiratory failure in patients with preexisting pulmonary or cardiac disease or de novo respiratory failure secondary to acute disease states [1]. Patients with underlying lung disease are at risk of acute exacerbations that may require endotracheal intubation and mechanical ventilation. Hypercapnia in acute respiratory failure results from factors that increase the partial pressure of arterial carbon dioxide in the bloodstream. These factors include pathologies that increase carbon dioxide production, increase lung dead space, or decrease minute ventilation as determined by tidal volume and respiratory rate. Hypercapnic respiratory failure is associated with significant mortality and morbidity, including increased need for ICU admission, endotracheal intubations, and increased length of hospitalization [2]. In-hospital mortality due to acute hypercapnic respiratory failure varies widely and has been reported between 15% and 68% [3, 4]. The use of noninvasive ventilation is therefore of interest to decrease the risks associated with mechanical ventilation and improve patient outcomes.

34.2 Traditional Standard Medical Treatment for Hypercapnic Respiratory Failure

Standard medical therapy for acute hypercapnic respiratory failure has traditionally ranged from oxygen delivery by nasal cannula to maintain SpO_2 between 90% and 92% to the use of endotracheal intubation and mechanical ventilation. Therapy for suspected underlying causes, such as the use of bronchodilators and steroids for suspected COPD exacerbations and the use of antibiotics and fluids for suspected pneumonia, is the standard of care [5]. In the past, atropine and aminophylline have also been used, though these have not shown evidence for efficacy and are no longer considered as standard therapy. Standard medical care also includes reversal of sedatives in patients suspected of sedative overdose and correction of coexisting hypoxemia through oxygen administration. To avoid the morbidity and mortality associated with endotracheal intubation, NIPPV has been utilized with increasing evidence in the treatment of acute hypercapnic respiratory failure [6].

34.3 Physiology of NIPPV Use

Carbon dioxide (CO_2) is a product of oxidative metabolism and is eliminated from the body with exhalation. Hypercapnia is defined as CO_2 retention due to hypoventilation or an increase in dead space. The term dead space is used to describe an area of the lung that is receiving ventilation but no perfusion to allow for gas exchange [7]. If either of these processes occurs, the amount of CO_2 in the body builds as it is continually produced but unable to be exhaled. An increase in CO_2 leads to acidemia and has important pathophysiological and clinical significance. Exposure of the lung to hypercapnia can lead to impaired alveolar fluid resorption, impaired alveolar epithelial cellular repair, and depressed innate cellular immunity [8]. Clinically, hypercapnia leads to dyspnea, confusion, and, ultimately, respiratory failure and cardiac arrest due to CO_2 narcosis. The use of noninvasive ventilation in the treatment of hypercapnic respiratory failure has been studied numerous times over the last three decades. The aim of these studies has been to treat hypercapnia with a resultant decrease in CO_2, increase in pH, and decrease the work of breathing in order to prevent the need for invasive mechanical ventilation [9, 10]. A variety of noninvasive pressure support systems have been studied, including continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP), proportional assist ventilation (PAV), and volume-control ventilation (VCV). Depending on the method used, NIV reduces inspiratory respiratory effort (as measured by esophageal pressures or transdiaphragmatic pressures) by more than 50% representing a significantly decreased work of breathing [10]. While pressure support of 5 cm H_2O (CPAP) causes only about 5% reduction in work of breathing, stepwise increments pressure support up to 15–20 cm H_2O with constant PEEP has the greatest reduction in inspiratory muscle oxygen consumption [10]. This is due to both the supply of transpulmonary pressure during positive pressure inhalation with inspiratory pressure support and counteracting the intrinsic PEEP with the application of external PEEP allowing a lower threshold for inspiration to take place [9]. In fact, in one study by Diaz et al., after just 15 min of NIPPV with a mean pressure support and PEEP of 12 and 3, respectively, there was a statistically significant decrease in respiratory rate; increase in tidal volume, minute ventilation, and alveolar ventilation; an increase in arterial PO_2 by 7 mmHg; and a decrease in PCO_2 by 7 mmHg [10]. It is important to remember that while increasing pressure support will continue to improve respiratory mechanics in a linear pattern, patients were found to have the most discomfort of the highest and lowest ends of pressure support, and this must be taken into account when adjusting settings [10].

34.3.1 Evidence for Use of NIPPV

The use of NIPPV has shown a significant in-hospital mortality reduction compared with endotracheal intubation. Pooled meta-analysis data suggests a mortality reduction of 46% with a risk ratio of 0.54 and a decreased endotracheal intubation rate of 65% with a relative risk of 0.36 of NIPPV compared with standard therapy [11]. Another meta-analysis reported a statistically significant mortality of 23% in NIPPV compared with 39% in endotracheal intubation and a statistically significant decreased ICU length of stay [12]. Success of NIPPV in this patient population independently predicts survival, and it has become the first-line therapy for COPD and post-extubation from endotracheal intubation [1]. NIPPV leads to improvement in breathing patterns, decreases respiratory rate, and improves tidal volume per inspiratory time [5].

34.3.2 Physiology of Different Interfaces: NIPPV vs. HFNC

NIPPV is a noninvasive modality of ventilation that provides external support for the spontaneous movement of the respiratory system by providing positive pressure. This method assists critical patients with ventilation without requiring invasive and artificial ventilation. NIPVV

includes CPAP, which simply provides continuous positive airway pressure. It also includes pressure support modalities that can also provide positive end expiratory pressure (PEEP). Pressure support NIPPV provides assistance to the respiratory muscles during ventilation, decreasing the respiratory muscle work load. In critically ill patients, this allows for increased inspiration volumes and improvement in ventilation and perfusion as reflected in arterial blood gas levels. In comparison, high-flow nasal cannula provides humidified oxygen at high rates of gas flow at a rate that matches the patient's inspiratory flow rate, which also provides positive pressure [13]. However, HFNC is not associated with the same discomfort and potential complications as noninvasive ventilation [13]. HFNC cannot provide PEEP and cannot provide a gas flow rate above 60 L/min [13].

34.4 Conditions with Evidence Supporting NIPPV Use

34.4.1 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic inflammatory lung disease characterized by airflow limitation that is not fully reversible. The use of NIPPV for management of chronic hypercapnic secondary to COPD as well as acute hypercapnic respiratory failure due to COPD has been well established, and NIPPV has become the gold standard for first-line treatment. In general, BiPAP has been recommended in COPD patients to prevent acute respiratory acidosis and to prevent endotracheal intubation in patients with up to moderate acidosis and as an alternative to invasive ventilation in patients with severe acidosis and severe respiratory distress [1]. NIPPV in this patient population often replaces endotracheal intubation successfully [10]. In patients with mild or moderate acute respiratory failure, pH between 7.25 and 7.35, and $PaCO_2$ greater than 45 mmHg, NIPPV is recommended in addition to standard medical therapy [6]. The use of NIPPV in these patients with acidotic hypercapnic respiratory failure and COPD reduces mortality, length of hospitalization, and intubation rates [1, 6, 14]. In addition, though traditionally hypercapnic coma in the setting of acute respiratory failure has been considered a contraindication to NIPPV, patients with hypercapnic coma caused by underlying COPD and Glasgow Coma Scale less than or equal to 8 still had an 80% success rate in avoiding intubation and ICU discharge with NIPPV use for a mean duration of 2 days. The patients most likely to fail were those with higher acuity of illness or organ failure scores. While no specific parameters upon admission were able to predict success, improvements in pH, $PaCO_2$, Glasgow Coma Score, and PaO_2/FiO_2 ratio within the first hour of NIPPV correlated with a response to therapy. In a 2017 meta-analysis of 17 randomized controlled trials using parallel-group design, NIPPV in addition to standard medical therapy was beneficial as first-line treatment and reduced mortality and endotracheal intubation [11]. Studies mostly delivered NIPPV via pressure-cycled ventilation, and most studies uptitrated IPAP based on patient tolerance and targeted respiratory rate. The mean EPAP for these studies was 4 cm H_2O. In addition to the aforementioned 46% mortality benefit with NIPPV, this study found a 64% risk reduction of intubation in patients treated with NIPPV compared with usual care and a NNTB of 5 [11]. Length of hospitalization was also decreased. Patients with coma due to COPD have the highest rate of success. Hypercapnic coma patients should be monitored closely in an ICU setting, but the use of NIPPV can prevent intubation rand is also a useful option for COPD patients with a do not intubate order. In general, BiPAP has been recommended in COPD patients to prevent acute respiratory acidosis and to prevent endotracheal intubation in patients with up to moderate acidosis and as an alternative to invasive ventilation in patients with severe acidosis and severe respiratory distress [1].

34.4.2 Post-extubation Weaning

Reintubation after endotracheal exudation is estimated to occur in as high as 48% of patients

and is associated with increased morbidity and mortality [15]. Risk increases with age above 65 years, cardiac failure as the cause of intubation, and APACHE-II scores above 12 on extubation day [15]. In this population, early use of NIPPV decreases risk of respiratory failure and ICU mortality [15]. In patients with hypercapnia and chronic respiratory disorders, early use of NIPPV decreased the risk of respiratory failure by 75% and led to decreased mortality at 90 days [16]. While two separate randomized control trials did not show a reduction in reintubation rates, and in one trial a higher mortality, only 10% of these patients had COPD [17], suggesting the patients with the most benefit of weaning to NIPPV are those with underlying COPD. Current guidelines recommend the use of NIPPV to facilitate early liberation from mechanical ventilation in patients with COPD but do not make any recommendation about the use of NIPPV in other patient populations because of insufficient evidence [18]. However, more recently, another randomized control trial assessing NIPPV as a weaning facility strategy in patients with various etiologies for respiratory failure requiring intubation for at least 3 days compared to oxygen face mask found a significantly lower reintubation rate (5% compared to 28%). This difference was maintained even after exclusion of patients with COPD [19]. The weaning protocol included uptitrating the IPAP if $PaCO_2$ is greater than 50 mmHg to prevent progression of hypercapnic respiratory failure. The patients in the NIPPV had a higher PaO_2, lower $PaCO_2$, respiratory rate, and mean blood pressure compared with the oxygen face mask group [19]. Although less data exists, recently high-flow oxygen therapy has been compared with NIPPV for weaning high-risk patients from mechanical ventilation and was proven to be noninferior. The data remains inconsistent on various etiologies of respiratory failure, but extubation to NIV should be applied to the correct patient population, most commonly those with hypercapnic respiratory failure.

34.4.3 Neuromuscular Diseases and Chest Wall Disorders

Neuromuscular diseases are a group of diseases with varying pathophysiology but are characterized by muscle impairment, including respiratory muscle impairment. Chest wall disorders, such as scoliosis and kyphosis, and neuromuscular diseases are both groups of diseases that are associated with decreased chest wall compliance and restrictive lung disease. NIPPV can be used in chronic and acute respiratory failure associated with these diseases, though evidence for this is based on care reports and few randomized controlled trials [6]. In patients with these disorders, hypercapnia actually correlates with worse clinical outcomes, as this points to a decreased respiratory reserve. If patients have neuromuscular diseases with no skeletal abnormalities, a low degree of pressure support is effective. Although no trials exist for NIPPV, it is reasonable and even good practice to use NIPPV in patients with neuromuscular diseases or chest wall disorders who present with acute hypercapnic respiratory distress. The BTS provides grade D guideline recommendations to use controlled oxygen therapy, to trial acutely ill patients on NIPPV even if there is no evidence of acidosis yet, and considering controlled ventilation instead of patient triggered methods may be effective. NIPPV is actually the ventilation mode of choice in neuromuscular disorders because; although ventilation is improved in endotracheal intubation, extubating is often difficult [20]. Chronic nocturnal NIPPV use in these patients results in short-term improvement of hypoventilation symptoms [21]. NIPPV is recommended in slowly progressive or nonprogressive neuromuscular disorders in patients with nighttime hypoxia or daytime hypercapnia. In acute respiratory failure associated with these conditions, combination of NIPPV with traditional airway clearance techniques reduces intubation rate and shortens weaning time in patients post-extubation [21].

34.4.4 Obstructive Sleep Apnea (OSA) and Obesity Hypoventilation Syndrome (OHS)

Obstructive sleep apnea is a sleep-associated respiratory disorder characterized by partial or complete airflow obstruction, usually in the setting of soft tissue collapse and upper airway blockage. Obesity hypoventilation syndrome is a syndrome of obesity and arterial hypercapnia in the absence of other causes of hypoventilation [22]. In patients with OHS and chronic hypercapnia, BiPAP or CPAP use is beneficial [22]. This is especially significant given that both morbidity and mortality of ICU patients with obesity are increased compared to patients with normal BMI [22]. Furthermore, patients with OHS have worse mortality outcomes compared with simply obese patients, especially within 3 months of hospital discharge. Long-term use of NIPPV, particularly PAP therapy, led to a significantly improved mortality rate of less than 10%. In patients with OHS or OSA and acute hypercapnic respiratory failure, mixed evidence exists for the use of NIPPV [22]. Evidence suggests that OHS is the second most frequently documented indication for the use of NIPPV, second only to COPD. NIPPV use in acute respiratory failure in OHS may decrease subjective sleepiness, dyspnea, need for intubation, mortality and 1-year survival, and endotracheal intubation rate [22]. Acutely, oronasal BiPAP is recommended to increase tidal volumes. Since patients with OHS may have increased constriction from abdominal tissue on their thoracic muscles, they may require increased levels of IPAP and EPAP to avoid both upper airway collapse and atelectasis. Studies have also found benefit of pressure support-tidal volume modes to be more effective in ventilation as measured by transcutaneous PCO_2, though quality of sleep was not significantly improved [22]. Nonetheless, it is clear that NIPPV use in OHS patients at home provides subjective improvement in quality of life and decreases the number of hospitalization, especially when it is started after an acute-on-chronic respiratory failure episode [22].

34.4.5 Cardiogenic Pulmonary Edema

Cardiogenic pulmonary edema results from increased cardiac and pulmonary artery pressures in the setting of heart failure resulting in fluid accumulation within the lungs. Mixed evidence exists for the use of NIPPV in this population. One study found that CPAP use in these patients decreases intubation rates and led to a trend toward decreased mortality [23]. A randomized prospective study found no difference between noninvasive pressure support ventilation and CPAP in resulting endotracheal intubations, mortality, or resolution time [24]. A multicenter, randomized trial showed that early use of NIPPV was associated with quicker improvement in $PaCO_2$ and a lower intubation rate compared with oxygen therapy in patients with hypercapnic cardiopulmonary edema but not in patients with hypoxemia [25]. Another multicenter trial in 2008 randomized patients with cardiogenic pulmonary edema to CPAP, BiPAP, or standard oxygen therapy and found that NIPPV had improvement in physiology but no changes in mortality or intubation rates. NIPPV does decrease the need for intubation and reduce hospital mortality, and there is a potential role for use of NIPPV in the subgroup of cardiogenic pulmonary edema patients presenting with hypercapnia alone [1]. The ERS/ATS guidelines in 2017 do recommend the use of BiPAP or CPAP for patients with acute respiratory failure and cardiogenic pulmonary edema as a strong recommendation with a moderate level of evidence [1].

34.4.6 Asthma

Asthma is a respiratory condition characterized by reversible airway obstruction and bronchospasm. Low levels of evidence suggest some role for NIPPV use in acute respiratory failure secondary to asthma [2]. NIPPV may correct gas exchange abnormalities and reduce intubation rate, decrease hospitalization rate, improve lung function, and shorten exacerbation dura-

tion [20]. Compared with COPD exacerbations, asthma exacerbations are less likely to respond to PEEP, and there is a more limited window to successful NIPPV use [6]. Severe asthma exacerbations associated with respiratory muscle fatigue and hyperdynamic and reactive airways require endotracheal intubation [6]. In general, NIPPV is not indicated in status asthmaticus, as trialing NIPPV is associated with risk and invasive ventilation for asthma is associated with a very low mortality rate [20]. In patients with acute or chronic hypercapnia and an underlying diagnosis of asthma, hypercapnia may lead to a clinical picture similar to that found in COPD, which may benefit from NIPPV use [20]. The prevalence of NIPPV for asthma has been reported as 4% compared with a 5% rate of invasive ventilation. In 4.7% of NIPPV, endotracheal intubation was required. However, pooled analysis does not show a clear benefit for NIPPV on mortality, ICU length of stay, or intubation rates [1]. At this time, there does not exist a good body of evidence to provide recommendations on the use of NIPPV for acute respiratory failure secondary to asthma.

34.4.7 Pneumonia

NIPPV use in hypercapnic pneumonia is poorly studied. Most studies of NIPPV use in pneumonia include hypoxemic patients. In a study of both hypercapnic and hypoxemic acute respiratory failure secondary to pneumonia, NIPPV use decreased endotracheal intubation but had no effect on survival. A prospective observational study of patients with severe community-acquired pneumonia showed a 66% intubation rate after failed NIPPV [26]. In general, de novo forms of acute respiratory failure, which includes pneumonias, do not have evidence to support the use of NIPPV successfully. Use of NIPPV may hide a clinically worsening patient, which would lead to delayed diagnosis and delayed intubation, potentially worsening outcomes. NIPPV in acute respiratory failure secondary to pneumonia is generally not indicated.

34.4.8 Bronchiectasis

Bronchiectasis is a chronic respiratory condition resulting from chronic inflammation or infection leading to widening of lung bronchi. The use of NIPPV in bronchiectasis is most supported in patients with cystic fibrosis to support chest wall muscles, decrease work of breathing, and improve gas exchange and oxygenation. Use of NIPPV as a bridge therapy to transplantation in patients who fail medical management has mixed evidence, but nocturnal NIPPV in chronic cystic fibrosis improves symptoms, exercise capacity, and exertional dyspnea [27]. NIPPV during acute exacerbations is associated with improved outcomes compared with endotracheal intubation when the precipitating cause of acute respiratory failure is infection [20]. In patients with bronchiectasis resulting from other disorders, no randomized controlled trials exist assessing the outcomes of NIPPV compared with intubation. In general, patients with chronic bronchiectasis who present with respiratory acidosis may be trialed on NIPPV, as with patients with COPD. In acute respiratory failure, NIPPV may decrease respiratory rates, decrease FiO_2 requirements, increase oxygen saturations, and resolve atelectasis [27].

34.5 Optimal NIPPV Settings

No specific set of guidelines exists for optimal NIPPV settings in acute hypercapnic respiratory failure. Assist control modes are generally preferable to pressure support modes if appropriate due to increased patient comfort, and both assist control and pressure support decrease inspiratory effort [5]. Initial pressure support with EPAP of 3 and IPAP of 15 in COPD, OHS, and kyphosis is recommended [20]. In patients with neuromuscular disorder, initial IPAP of 10 is recommended. Increasing IPAP up to 30 with a goal of slowing respiratory rate can be performed within the first 10–30 min [22]. In patients with OSA, EPAP can be increased to 8 [20].

34.6 Failure of NIPPV and Future Directions

34.6.1 Predictors of NIPPV Failure

Several independent risk factors have been established for NIPPV failure, and predictors of failure are patient and disease specific. Patients with de novo acute respiratory failure had increased rates of failure compared with patients with acute-on-chronic respiratory failure [12]. Patients with acute respiratory failure secondary to pneumonia are at increased risk of failure [28], and a diagnosis other than COPD in itself is a risk factor for NIPPV failure [12]. NIPPV failure is also associated with worse Simplified Acute Physiology Score (SAPS) scores, high APACHE II scores, tachycardia, and elevated $PaCO_2$ 1 h after beginning NIPPV [12]. Tachypnea over 30 breaths/min, etiology of failure, severe hypoxemia with PaO_2/FiO_2 < 200 mmHg, and severe acidosis with pH of less than 7.30 are independently associated with NIPPV failure [28].

34.6.2 Recognizing NIPPV Failure

NIPPV is absolutely contraindicated in severe facial deformities, facial burns, and fixed upper airway obstructions, and it is relatively contraindicated in agitated patients and patients with cardiopulmonary arrest or hemodynamic instability [20]. NIPPV failure can be categorized as immediate (within 1 h), early (within the first 48 h), and late (beyond 48 h) [29]. Weak cough reflexes, excessive secretions, encephalopathy and coma in the setting of hypercapnia, psychomotor agitation, and patient-ventilator asynchrony are all signs that alert clinicians to a higher likelihood of NIPPV failure [29]. Increasing tachypnea within the first hour of NIPPV use (>25 breaths/min) and pH less than 7.25 are highly suggestive of failure and need for endotracheal intubation.

34.6.3 Future Directions

Although strong evidence supports the use of NIPPV in acute hypercapnic respiratory failure secondary to COPD and post-extubation, other conditions like bronchiectasis and OHS/OSA have weaker and oftentimes conflicting evidence supporting their use [6]. Further strong evidence such as randomized controlled trials for the use of NIPPV in other conditions are required to make specific recommendations on NIPPV use. Newer modalities beyond mechanical ventilation are also being investigated, including extracorporeal carbon dioxide removal, a new technique that removes carbon dioxide without affecting oxygenation and may be promising in the treatment of acute hypercapnic respiratory failure.

34.7 Conclusion

Endotracheal intubation is associated with morbidity and mortality. The use of NIPPV successfully to avoid endotracheal intubation has demonstrated a mortality benefit in certain patient populations. In acute hypercapnic respiratory failure secondary to COPD exacerbations and in patients who are being weaned from mechanical ventilation after endotracheal intubation, NIPPV use is recommended with strong evidence. In other patient populations such as cardiogenic pulmonary edema and OHS/OSA, moderate levels of evidence exist with some randomized controlled trials suggesting mortality benefit. Neuromuscular diseases and chest wall disorders may also benefit from NIPPV, though the level of evidence for these diseases is limited due to lack of randomized trials. In patients with de novo acute hypercapnic respiratory failure, such as in patients with pneumonia, NIPPV is not recommended. There are conditions in which NIPPV use still remains of unclear benefits, such as in asthma, and no recommendations can be established. Use of outcomes from existing trials and meta-analysis in combination with clinical acumen may provide the highest level of success, but a larger amount of strong trials is necessary to establish strong guidelines for management of these populations.

References

1. Rochwerg B, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2): 1602426.
2. Hess DR. The evidence for noninvasive positive-pressure ventilation in the care of patients in acute respiratory failure: a systematic review of the literature. Respir Care. 2004;49(7):810–29.
3. El-Solh AA, et al. Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients. Eur Respir J. 2006;28(3):588–95.
4. Moretti M, et al. Incidence and causes of non-invasive mechanical ventilation failure after initial success. Thorax. 2000;55(10):819–25.
5. Girault C, et al. Comparative physiologic effects of noninvasive assist-control and pressure support ventilation in acute hypercapnic respiratory failure. Chest. 1997;111(6):1639–48.
6. Scala R, Pisani L. Noninvasive ventilation in acute respiratory failure: which recipe for success? Eur Respir Rev. 2018;27(149):180029.
7. Patel S, Majmundar SH. Physiology, carbon dioxide retention. In: StatPearls. Treasure Island, FL: StatPearls Publishing LLC; 2019.
8. Schreiber A, et al. Noninvasive ventilation in hypercapnic respiratory failure: from rocking beds to fancy masks. Breathe. 2018;14(3): 235–7.
9. Sydow M, et al. Effect of low-level PEEP on inspiratory work of breathing in intubated patients, both with healthy lungs and with COPD. Intensive Care Med. 1995;21(11):887–95.
10. Diaz O, et al. Effects of noninvasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;156(6):1840–5.
11. Osadnik CR, et al. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;(7):CD004104.
12. Demoule A, et al. Benefits and risks of success or failure of noninvasive ventilation. Intensive Care Med. 2006;32(11):1756–65.
13. Zhao H, et al. High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to noninvasive mechanical ventilation on intubation rate: a systematic review and meta-analysis. Crit Care. 2017;21(1):184.
14. Lightowler JV, et al. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ. 2003;326(7382):185.
15. American Thoracic Society, et al. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med. 2001;163(1):283–91.
16. Ferrer M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet. 2009;374(9695):1082–8.
17. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet. 2009;374(9685):250–9.
18. Keenan SP, et al. Clinical practice guidelines for the use of noninvasive positive pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ. 2011;183(3):E195–214.
19. Ornico SR, et al. Noninvasive ventilation immediately after extubation improves weaning outcome after acute respiratory failure: a randomized controlled trial. Crit Care. 2013;17(2):R39.
20. Davidson AC, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl 2):ii1–35.
21. Annane D, Orlikowski D, Chevret S. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database Syst Rev. 2014;(12):CD001941.
22. Sequeira TCA, BaHammam AS, Esquinas AM. Noninvasive ventilation in the critically ill patient with obesity hypoventilation syndrome: a review. J Intensive Care Med. 2017;32(7):421–8.
23. Pang D, et al. The effect of positive pressure airway support on mortality and the need for intubation in cardiogenic pulmonary edema: a systematic review. Chest. 1998;114(4):1185–92.
24. Bellone A, et al. Noninvasive pressure support ventilation vs. continuous positive airway pressure in acute hypercapnic pulmonary edema. Intensive Care Med. 2005;31(6):807–11.
25. Nava S, et al. Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter randomized trial. Am J Respir Crit Care Med. 2003;168(12):1432–7.
26. Jolliet P, et al. Non-invasive pressure support ventilation in severe community-acquired pneumonia. Intensive Care Med. 2001;27(5):812–21.
27. Young AC, et al. Randomised placebo controlled trial of non-invasive ventilation for hypercapnia in cystic fibrosis. Thorax. 2008;63(1):72–7.
28. Contou D, et al. Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit. Respir Care. 2013;58(12):2045–52.
29. Ozyilmaz E, Ugurlu AO, Nava S. Timing of noninvasive ventilation failure: causes, risk factors, and potential remedies. BMC Pulm Med. 2014;14:19.

35 Noninvasive Ventilation for Patients with Obesity Hypoventilation and Acute Hypercapnic Respiratory Failure

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35.1 Introduction

Mortality in patients with severe obesity hypoventilation syndrome (OHS) is higher than that in those with obstructive sleep apnea (OSA; 15.5% vs. 4.5%) [1]. OHS may present with acute hypercapnic respiratory failure (AHRF), and there are increasing numbers of patients with OHS being admitted to intensive care units (ICUs) with hypercapnic respiratory failure [2]. Patients with OHS are more likely to develop AHRF requiring ICU admission than their counterparts obese subjects without OHS (40% vs. 26%) and to require more long-term care after discharge (19% vs. 2%) [3, 4].

OHS remains under-recognized as a cause of AHRF. It has been shown that 40% of patients with OHS present for the first time with AHRF [5], but few are correctly diagnosed [6]. In a prospective study of 173 patients with OHS and AHRF over 13 years in Spain, causes of exacerbation included respiratory infection (68%), cardiac disease (13%), respiratory depressant medication (5%), trauma (3%), and surgery (3%) [7].

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It is within this context that we review the updates on use of noninvasive ventilation (NIV) in patients with OHS and respiratory failure.

35.2 Review Method

The literature search started on March 1, 2019, with keyword searches of "obesity hypoventilation syndrome," "acute hypercapnic respiratory failure," and "noninvasive ventilation," using PubMed, Clarivate, and Google Scholar. Additionally, the reference lists of identified articles were also searched for further references. The following inclusion criteria for human studies were used: men and women were accepted as participants, and both randomized controlled trials and nonrandomized trials were accepted.

35.3 Management of Acute-on-Chronic Exacerbation in Patients with OHS

35.3.1 Oxygen Therapy

The possibility of OHS should be considered in all obese patients with AHRF. The aims of NIV are to improve upper airway patency via expiratory positive airway pressure (EPAP), augment alveolar ventilation via inspiratory positive airway pressure (IPAP), and reduce the extent of hypoxemia. Oxygen therapy alone is an insufficient treatment for OHS and can be detrimental in high concentrations [8–10]. Administering oxygen at a high concentration may increase the $PaCO_2$ in patients with stable OHS [11]. A double-blind, crossover randomized controlled trial (RCT) in patients with newly diagnosed OHS demonstrated that administration of 100% oxygen for 20 min increased transcutaneous carbon dioxide by 5 mmHg and reduced minute ventilation by 13% [12]. Another recent crossover RCT assessed the effects of high-concentration titrated oxygen therapy in morbidly obese medical in-patients who were not selected for a preexisting diagnosis of OHS [13]. The study included 22 morbidly obese adults (body mass index >40) who were randomized to receive two 60-min interventions with a minimum 30-min washout period between the following two treatments: (1) titrated oxygen therapy via nasal prongs to attain an oxygen saturation (SpO_2) of 88–92% and (2) high-concentration oxygen therapy via a Hudson mask at 8 L/min, irrespective of SpO_2. Transcutaneous CO_2 ($PtCO_2$) and SpO_2 were recorded at 10-min intervals [13]. The mean difference in $PtCO_2$ between high-concentration and titrated oxygen therapy at 60 min was 3.2 mmHg (95% confidence interval 1.3–5.2; $p = 0.002$), indicating that high-concentration oxygen therapy increases $PtCO_2$ in morbidly obese patients [13].

35.3.2 Positive Airway Pressure Therapy

In stable ambulatory patients with OHS and severe OSA, NIV and continuous positive airway pressure (CPAP) have similar long-term effectiveness [14–18]; however, patients with OHS and AHRF require therapeutic strategies that simultaneously keep the upper airway open and augment alveolar ventilation. Therefore, NIV is the mainstay of therapy in patients with OHS and AHRF.

Invasive mechanical ventilation is occasionally required in patients with OHS and AHRF. Indications for invasive ventilation include hemodynamic instability and multiorgan failure. Moreover, NIV is generally not considered in uncooperative patients or those with uncontrolled arrhythmias, acute myocardial infarction, refractory hypoxemia, acute stroke, orofacial deformities, upper gastrointestinal bleeding, inability to clear secretions, or severe abdominal distension [19]. Coma may constitute a relative contraindication, although in a study of 76 patients with hypercapnic coma, 80% responded to NIV [20].

NIV must be delivered promptly in obese patients with AHRF. There is no need to perform sleep studies during the acute stage because early stabilization may prevent progression to invasive ventilation [21]. The lack of an available ICU bed

should not delay the start of NIV in this group of patients [22–24].

NIV therapy should be explained carefully to the patient before applying it [25]. The acceptance and success of NIV therapy depends to a large extent on appropriate selection of the interface. Given that mouth breathing is common in patients with acute respiratory failure, the full-face mask is considered to be the most effective interface in the acute setting, followed by the nasal mask, helmet, and mouthpiece [26]. In general, full-face masks are preferred in the acute setting because they have less air leak and maintain the higher tidal volumes needed to augment alveolar ventilation [26]. Nevertheless, patients may be shifted to a nasal mask when their clinical condition is stable and mouth leak is not present [27].

35.3.2.1 Noninvasive Ventilation in Acute-on-Chronic Exacerbation of OHS

There has been no prospective RCT assessing the efficacy of NIV in the management of AHRF in patients with OHS. However, recently developed practice guidelines have included NIV in this clinical setting [28].

Although CPAP can be effective in ambulatory patients with stable OHS [18], it is not recommended in the acute setting because it is unlikely to resolve alveolar hypoventilation problems in patients with OHS who are acutely sick and present with AHRF [8, 9, 14, 15, 29–32]. Positive airway pressure modes that augment minute ventilation are preferred in this category of patients. However, when the patient is stable and acid-base derangement is corrected, he/she may be shifted to CPAP with titration under polysomnographic monitoring [1, 17]. This can be done within 3 months of the acute event.

NIV therapy usually yields better results in patients with OHS and AHRF than in those with other causes of AHRF, such as chronic obstructive pulmonary disease (COPD) [33]. NIV ameliorates respiratory problems in patients with OHS by reducing the respiratory load, increasing minute volume for a given breathing effort, and providing ventilation during central apneic events [19]. There are no data to support the superiority of one mode of NIV over another in patients with OHS and AHRF [34]. Pressure-limited and volume-limited ventilation have been reported in patients with AHRF; however, most studies have recommended initiating treatment with bi-level positive airway pressure (BPAP) ventilation because there is no evidence indicating that other ventilatory modes are superior to BPAP [19, 28].

BPAP devices have two modes, i.e., a spontaneous mode and a spontaneous/timed (S/T) mode. In the spontaneous mode, the patient triggers cycling from the expiratory phase to the inspiratory phase, whereas the S/T mode has a backup respiratory rate set by the clinician to deliver machine breaths when the rate of patient-triggered breaths is lower than the set rate. Both modes are effective in the treatment of patients with OHS and AHRF; however, in an RCT that included ambulatory patients with stable OHS, the spontaneous mode was associated with a highly significant increase in abnormal respiratory events, mainly of central and mixed origin, when compared with S/T mode, and there was a significant difference between the two modes in measured transcutaneous PCO_2 [35]. Therefore, BPAP with S/T mode is recommended in patients with OHS and acute-on-chronic exacerbation. Figure 35.1 outlines the proposed scheme for titration of BPAP in patients with OHS and AHRF.

Continuous monitoring of level of consciousness, vital signs, respiratory pattern, oxygen saturation, and arterial blood gases is necessary during NIV therapy (Table 35.1) [8, 9, 36–38]. OHS is invariably accompanied by obstructive sleep-disordered breathing [39], so EPAP should be gradually built up until snoring, witnessed apneas, paradoxical chest wall movement, and dips in oxygen saturation are eliminated. To augment ventilation, pressure support (IPAP-EPAP) should be maintained at >4 cm H_2O and preferably at 8–10 cm H_2O [19]. Maximum IPAP should not exceed 30 cm H_2O [40]. In general, pressure support should be increased to ensure optimal ventilation and unloading of the respiratory muscles. However, tidal volume should always be calculated based on ideal body weight rather than

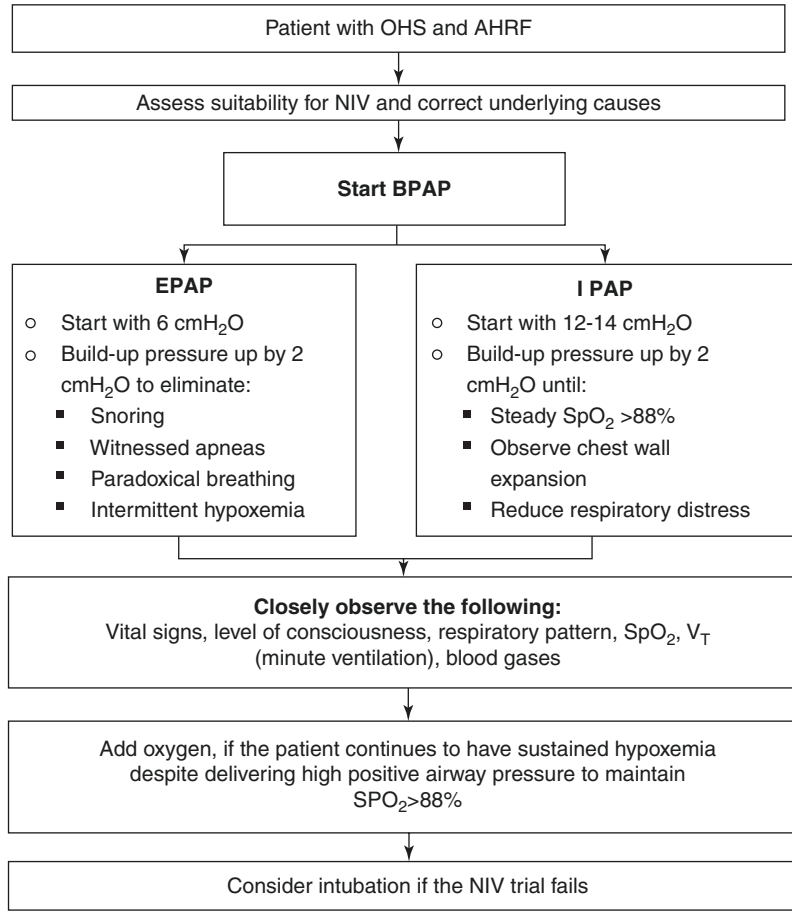

Fig. 35.1 Proposed algorithm for the management of acute hypercapnic respiratory failure in patients with OHS. *BPAP* bi-level positive expiratory pressure, *EPAP* expiratory positive airway pressure, *IPAP* inspiratory positive airway pressure, *OHS* obesity hypoventilation, *PAP* positive airway pressure, *SpO_2* arterial oxygen saturation

Table 35.1 Proposed monitoring during noninvasive ventilation therapy in the acute setting

Symptoms and signs	Respiratory discomfort
	Breathing pattern
	Snoring
	Chest wall expansion
	Paradoxical breathing
	Oxygen saturation
	Patient-ventilator dyssynchrony
	Use of accessory respiratory muscles
	Claustrophobia
	Air hunger
	Abdominal distension
	Blood pressure and pulse rate
	Obstructive respiratory events
	Level of consciousness (Glasgow Coma Scale or Kelly-Matthay score) [38]
Cardiorespiratory parameters	Arterial blood gases
	Transcutaneous CO_2
	Air leak
	Intrinsic positive end-expiratory pressure
	Flow and pressure wave forms
	Electrocardiography

actual body weight because the size of the lungs does not change significantly with increased weight.

Almost all patients with acute-on-chronic exacerbation of OHS require low levels of supplemental oxygen to maintain a saturation level between 88% and 92% [8, 9, 41]. Therefore, oxygen should be provided if the patient continues to have prolonged periods of hypoxemia despite elimination of obstructive events and hypoventilation. There have been no studies on how long NIV therapy should be applied in the acute setting. However, we recommend applying NIV continuously at night and for 6–8 h during the day so that patients can take medications and eat. When the level of consciousness is acceptable and arterial blood gases have improved with an acceptable pH (≥7.35), daytime NIV can be discontinued and replaced with low-flow supplemental oxygen [19, 21].

35.3.2.2 Other Ventilatory Modes

A new mode of NIV called volume-targeted pressure support (VtPS), which targets tidal volume and not pressure, has been used in patients with OHS [42]. The VtPS mode is a bi-level hybrid ventilatory mode that combines the advantages of pressure-limited and volume-limited ventilation modes into a ventilatory mode that aims to provide adequate minute ventilation in patients with hypoventilation while maintaining the comfort and advantages of pressure support ventilation [43, 44].

The VtPS monitors delivered tidal volume (or minute ventilation) through a built-in pneumotachograph, and when the delivered volume drops below a preset threshold, the algorithm automatically increases pressure support (IPAP) to augment tidal volume and achieve the target volume. In the newer VtPS models, EPAP is set automatically [19].

The initial studies that assessed the efficacy and utility of VtPS were conducted in ambulatory patients with stable OHS and found no clinically significant advantages over BPAP with S/T mode [42, 44–46]. A recent RCT compared BPAP in spontaneous mode and VtPS in patients with acute or acute-on-chronic hypercapnic respiratory failure [47]. There was no difference in the length of hospital stay or the course of $PaCO_2$, pH, and HCO_3 levels between the two modes. Furthermore, body mass index and body position had no notable effect in either mode [47].

35.3.2.3 Dedicated NIV Versus ICU Ventilators

Both ICU ventilators and dedicated portable devices can be used in the acute setting to apply NIV therapy. A randomized assessment of conventional ICU ventilators versus dedicated ventilators used for NIV therapy in 24 patients with AHRF and a body mass index of 29 [20–37] reported no differences in sleep quality according to the type of ventilator used [48]. However, ineffective efforts were more frequent in the dedicated noninvasive ventilator group ($p < 0.001$) [48]. Nevertheless, conventional ICU ventilators and dedicated NIV ventilators have important differences with regard to leak compensation [49]. A bench study of eight ICU ventilators featuring a noninvasive ventilation mode reported that in most of the tested ventilators, leaks led to an increase in trigger delay, a decrease in the ability to reach the pressure target, and delayed cycling [50]. In contrast, dedicated NIV ventilators allowed better synchronization than ICU ventilators when leak was present [51, 52]. Dedicated NIV ventilators provided more effective inspiratory triggering than the ICU ventilators [52, 53]. The above data support the use of dedicated NIV ventilators in preference to invasive ICU ventilators [54].

35.3.2.4 Predictors of Failure of NIV

A prospective study that assessed the factors associated with NIV failure in 76 patients with OHS and respiratory failure found that severe pneumonia and multiple organ failure often caused early NIV failure in morbidly obese patients with hypoxemic acute respiratory failure [55]. In one study, 84% of patients with OHS and AHRF reportedly had a successful response to NIV [55]. An important finding of that study was that more than half of the patients with OHS experienced a delayed response to NIV, with persistence of hypercapnic acidosis during the first

6 h [55]. Patients with a delayed response to NIV were more likely to have received diuretics or respiratory depressant drugs before admission.

Patients with OHS who had a good initial response to NIV but then developed a relapse of acute respiratory failure had a poor prognosis. All patients in this group (7/7) died in a study of 76 patients with NIV for AHRF [55].

Another large prospective multicenter study investigated patients who were admitted with acidosis (OHS, $n = 198$; COPD, $n = 540$; acute cardiogenic pulmonary edema, $n = 240$) and received NIV as an initial ventilatory support measure [56]. In that study, the time taken for pH to normalize was longer in patients with severe acidosis ($pH \geq 7.25$) than in those with less severe acidosis. Furthermore, the patients in the COPD group with severe acidosis had significantly longer ICU stays than their counterparts with less severe acidosis (5.1 ± 3 days vs. 3.6 ± 2.1 days, $p < 0.001$). Patients in the acute cardiogenic pulmonary edema group and the OHS group also had longer stays than those with less severe acidosis, but the differences were not statistically significant (4 ± 3.1 days vs. 3.6 ± 2.5 days and 4.3 ± 2.6 days vs. 3.7 ± 3.2 days). No difference in NIV failure rates was detected between the patients with severe acidosis and those with non-severe acidosis in the three disease groups. Moreover, no independent predictor of NIV failure was identified in the groups [56].

35.4 Conclusions

Intensivists and respirologists are very likely to encounter patients with OHS and AHRF. A high index of suspicion is needed to avoid misdiagnosis and delayed treatment that can only worsen morbidity and mortality and increase healthcare costs. Despite a lack of relevant RCTS, there is now a consensus that NIV is the first-line treatment for OHS presenting with acute-on-chronic hypercapnic respiratory failure. In this setting, NIV improves alveolar ventilation, hypercapnia, and hypoxemia, avoids invasive ventilation, and probably decreases the frequency of adverse outcomes.

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References

1. Castro-Anon O, Perez de Llano LA, De la Fuente Sanchez S, Golpe R, Mendez Marote L, Castro-Castro J, et al. Obesity-hypoventilation syndrome: increased risk of death over sleep apnea syndrome. PLoS One. 2015;10(2):e0117808.
2. Marik PE, Desai H. Characteristics of patients with the "malignant obesity hypoventilation syndrome" admitted to an ICU. J Intensive Care Med. 2013;28(2):124–30.
3. Lee WY, Mokhlesi B. Diagnosis and management of obesity hypoventilation syndrome in the ICU. Crit Care Clin. 2008;24(3):533–49. vii.
4. Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, et al. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. Am J Med. 2004;116(1):1–7.
5. BaHammam AS, Pandi-Perumal SR, Piper A, Bahammam SA, Almeneessier AS, Olaish AH, et al. Gender differences in patients with obesity hypoventilation syndrome. J Sleep Res. 2016;25(4):445–53.
6. Pepin JL, Borel JC, Janssens JP. Obesity hypoventilation syndrome: an underdiagnosed and undertreated condition. Am J Respir Crit Care Med. 2012;186(12):1205–7.
7. Carrillo A, Ferrer M, Gonzalez-Diaz G, Lopez-Martinez A, Llamas N, Alcazar M, et al. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186(12):1279–85.
8. BaHammam A, Syed S, Al-Mughairy A. Sleep-related breathing disorders in obese patients presenting with acute respiratory failure. Respir Med. 2005;99(6):718–25.
9. Perez de Llano LA, Golpe R, Ortiz Piquer M, Veres Racamonde A, Vazquez Caruncho M, Caballero Muinelos O, et al. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. Chest. 2005;128(2):587–94.
10. Masa JF, Corral J, Romero A, Caballero C, Teran-Santos J, Alonso-Alvarez ML, et al. The effect of supplemental oxygen in obesity hypoventilation syndrome. J Clin Sleep Med. 2016;12(10):1379–88.
11. Hollier CA, Harmer AR, Maxwell LJ, Menadue C, Willson GN, Unger G, et al. Moderate concentrations of supplemental oxygen worsen hypercapnia in obesity hypoventilation syndrome: a randomised crossover study. Thorax. 2014;69(4):346–53.
12. Wijesinghe M, Williams M, Perrin K, Weatherall M, Beasley R. The effect of supplemental oxygen

on hypercapnia in subjects with obesity-associated hypoventilation: a randomized, crossover, clinical study. Chest. 2011;139(5):1018–24.
13. Pilcher J, Richards M, Eastlake L, McKinstry SJ, Bardsley G, Jefferies S, et al. High flow or titrated oxygen for obese medical inpatients: a randomised crossover trial. Med J Aust. 2017;207(10):430–4.
14. Banerjee D, Yee BJ, Piper AJ, Zwillich CW, Grunstein RR. Obesity hypoventilation syndrome: hypoxemia during continuous positive airway pressure. Chest. 2007;131(6):1678–84.
15. Mokhlesi B. Positive airway pressure titration in obesity hypoventilation syndrome: continuous positive airway pressure or bilevel positive airway pressure. Chest. 2007;131(6):1624–6.
16. Mokhlesi B, Tulaimat A, Evans AT, Wang Y, Itani AA, Hassaballa HA, et al. Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. J Clin Sleep Med. 2006;2(1):57–62.
17. Howard ME, Piper AJ, Stevens B, Holland AE, Yee BJ, Dabscheck E, et al. A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax. 2017;72(5):437–44.
18. Masa JF, Mokhlesi B, Benitez I, Gomez de Terreros FJ, Sanchez-Quiroga MA, Romero A, et al. Long-term clinical effectiveness of continuous positive airway pressure therapy versus non-invasive ventilation therapy in patients with obesity hypoventilation syndrome: a multicentre, open-label, randomised controlled trial. Lancet. 2019;393:1721.
19. Piper AJ, BaHammam AS, Javaheri S. Obesity hypoventilation syndrome: choosing the appropriate treatment of a heterogeneous disorder. Sleep Med Clin. 2017;12(4):587–96.
20. Diaz GG, Alcaraz AC, Talavera JC, Perez PJ, Rodriguez AE, Cordoba FG, et al. Noninvasive positive-pressure ventilation to treat hypercapnic coma secondary to respiratory failure. Chest. 2005;127(3):952–60.
21. Bahammam AS, Al-Jawder SE. Managing acute respiratory decompensation in the morbidly obese. Respirology. 2012;17(5):759–71.
22. Ciledag A, Kaya A, Akdogan BB, Kabalak PA, Onen ZP, Sen E, et al. [Early use of noninvasive mechanical ventilation in patients with acute hypercapnic respiratory failure in a respiratory ward: a prospective study]. Arch Bronconeumol. 2010;46(10):538–542.
23. Corral-Gudino L, Jorge-Sanchez RJ, Garcia-Aparicio J, Herrero-Herrero JI, Lopez-Bernus A, Borao-Cengotita-Bengoa M, et al. Use of noninvasive ventilation on internal wards for elderly patients with limitations to respiratory care: a cohort study. Eur J Clin Investig. 2011;41(1):59–69.
24. Marik PE, Chen C. The clinical characteristics and hospital and post-hospital survival of patients with the obesity hypoventilation syndrome: analysis of a large cohort. Obes Sci Pract. 2016;2(1):40–7.
25. Nicolini A, Lemyze M, Esquinas A, Barlascini C, Cavalleri MA. Predictors of noninvasive ventilation failure in critically ill obese patients: a brief narrative review. Adv Respir Med. 2017;85(5):264–70.
26. BaHammam AS, Singh TD, Gupta R, Pandi-Perumal SR. Choosing the proper interface for positive airway pressure therapy in subjects with acute respiratory failure. Respir Care. 2018;63(2):227–37.
27. BaHammam AS, Singh T, George S, Acosta KL, Barataman K, Gacuan DE. Choosing the right interface for positive airway pressure therapy in patients with obstructive sleep apnea. Sleep Breath. 2017;21(3):569–75.
28. Davidson AC, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl 2):ii1–ii35.
29. Steier J, Jolley CJ, Seymour J, Roughton M, Polkey MI, Moxham J. Neural respiratory drive in obesity. Thorax. 2009;64(8):719–25.
30. Lee MY, Lin CC, Shen SY, Chiu CH, Liaw SF. Work of breathing in eucapnic and hypercapnic sleep apnea syndrome. Respiration. 2009;77(2):146–53.
31. Perez de Llano LA, Golpe R, Piquer MO, Racamonde AV, Caruncho MV, Lopez MJ, et al. Clinical heterogeneity among patients with obesity hypoventilation syndrome: therapeutic implications. Respiration. 2008;75(1):34–9.
32. Piper AJ, Wang D, Yee BJ, Barnes DJ, Grunstein RR. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. Thorax. 2008;63(5):395–401.
33. Qasrawi SO, BaHammam AS. NIV in type 2 (hypercapnic) acute respiratory failure. In: Esquinas A, Lemyze M, editors. Mechanical ventilation in the critically ill obese patient. 1st ed. Cham: Springer International Publishing; 2018. p. 229–38.
34. Sequeira TCA, BaHammam AS, Esquinas AM. Noninvasive ventilation in the critically ill patient with obesity hypoventilation syndrome: a review. J Intensive Care Med. 2017;32(7):421–8.
35. Contal O, Adler D, Borel JC, Espa F, Perrig S, Rodenstein D, et al. Impact of different backup respiratory rates on the efficacy of noninvasive positive pressure ventilation in obesity hypoventilation syndrome: a randomized trial. Chest. 2013;143(1):37–46.
36. Ergan B, Nasilowski J, Winck JC. How should we monitor patients with acute respiratory failure treated with noninvasive ventilation? Eur Respir Rev. 2018;27(148):170101.
37. Nava S, Ceriana P. Causes of failure of noninvasive mechanical ventilation. Respir Care. 2004;49(3):295–303.
38. Scala R. Hypercapnic encephalopathy syndrome: a new frontier for non-invasive ventilation? Respir Med. 2011;105(8):1109–17.
39. BaHammam AS, Alassiri SS, Al-Adab AH, Alsadhan IM, Altheyab AM, Alrayes AH, et al. Long-term com-

pliance with continuous positive airway pressure in Saudi patients with obstructive sleep apnea. A prospective cohort study. Saudi Med J. 2015;36(8):911–9.
40. Kushida CA, Chediak A, Berry RB, Brown LK, Gozal D, Iber C, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med. 2008;4(2):157–71.
41. Resta O, Guido P, Foschino Barbaro MP, Picca V, Talamo S, Lamorgese V. Sleep-related breathing disorders in acute respiratory failure assisted by non-invasive ventilatory treatment: utility of portable polysomnographic system. Respir Med. 2000;94(2):128–34.
42. Pluym M, Kabir AW, Gohar A. The use of volume-assured pressure support noninvasive ventilation in acute and chronic respiratory failure: a practical guide and literature review. Hosp Pract (1995). 2015;43(5):299–307.
43. Ambrogio C, Lowman X, Kuo M, Malo J, Prasad AR, Parthasarathy S. Sleep and non-invasive ventilation in patients with chronic respiratory insufficiency. Intensive Care Med. 2009;35(2):306–13.
44. Storre JH, Seuthe B, Fiechter R, Milioglou S, Dreher M, Sorichter S, et al. Average volume-assured pressure support in obesity hypoventilation: a randomized crossover trial. Chest. 2006;130(3):815–21.
45. Janssens JP, Metzger M, Sforza E. Impact of volume targeting on efficacy of bi-level non-invasive ventilation and sleep in obesity-hypoventilation. Respir Med. 2009;103(2):165–72.
46. Murphy PB, Davidson C, Hind MD, Simonds A, Williams AJ, Hopkinson NS, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax. 2012;67(8):727–34.
47. Turk M, Aydogdu M, Gursel G. Effects of modes, obesity, and body position on non-invasive positive pressure ventilation success in the intensive care unit: a randomized controlled study. Turk Thorac J. 2018;19(1):28–35.
48. Cordoba-Izquierdo A, Drouot X, Thille AW, Galia F, Roche-Campo F, Schortgen F, et al. Sleep in hypercapnic critical care patients under noninvasive ventilation: conventional versus dedicated ventilators. Crit Care Med. 2013;41(1):60–8.
49. Oto J, Chenelle CT, Marchese AD, Kacmarek RM. A comparison of leak compensation in acute care ventilators during noninvasive and invasive ventilation: a lung model study. Respir Care. 2013;58(12):2027–37.
50. Vignaux L, Vargas F, Roeseler J, Tassaux D, Thille AW, Kossowsky MP, et al. Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. Intensive Care Med. 2009;35(5):840–6.
51. Schettino GP, Tucci MR, Sousa R, Valente Barbas CS, Passos Amato MB, Carvalho CR. Mask mechanics and leak dynamics during noninvasive pressure support ventilation: a bench study. Intensive Care Med. 2001;27(12):1887–91.
52. Schonhofer B, Sortor-Leger S. Equipment needs for noninvasive mechanical ventilation. Eur Respir J. 2002;20(4):1029–36.
53. Schettino GP, Chatmongkolchart S, Hess DR, Kacmarek RM. Position of exhalation port and mask design affect CO2 rebreathing during noninvasive positive pressure ventilation. Crit Care Med. 2003;31(8):2178–82.
54. Miyoshi E, Fujino Y, Uchiyama A, Mashimo T, Nishimura M. Effects of gas leak on triggering function, humidification, and inspiratory oxygen fraction during noninvasive positive airway pressure ventilation. Chest. 2005;128(5):3691–8.
55. Lemyze M, Taufour P, Duhamel A, Temime J, Nigeon O, Vangrunderbeeck N, et al. Determinants of noninvasive ventilation success or failure in morbidly obese patients in acute respiratory failure. PLoS One. 2014;9(5):e97563.
56. Masa JF, Utrabo I, Gomez de Terreros J, Aburto M, Esteban C, Prats E, et al. Noninvasive ventilation for severely acidotic patients in respiratory intermediate care units: precision medicine in intermediate care units. BMC Pulm Med. 2016;16(1):97.

NIV in Acute Cardiac Diseases: Heart Failure and Acute Cardiogenic Pulmonary Edema

36

Roberto Cosentini, Andrea Duca, and Gerson Cipriano Junior

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36.1 Introduction

Acute heart failure (AHF) is defined by a constellation of symptoms (dyspnea, orthopnea, lower limb swelling) and signs (elevated jugular venous pressure, pulmonary congestion) often caused by a structural and/or functional cardiac abnormality resulting in reduced cardiac output and/or elevated intracardiac pressures [1]. Acute cardiogenic pulmonary edema (ACPE) is the most severe form of AHF, characterized by severe dyspnea at rest together with signs of lung congestion.

The prevalence of AHF ranges between 1% and 12% in the general population. Despite recent therapeutic advances, in-hospital mortality is still high as 10% [1, 2].

Noninvasive Ventilation (NIV) is one of the most relevant advances in the treatment of acute heart failure and acute cardiogenic pulmonary edema, and its use is recommended in this population by the most recent ATS/ERS guidelines [3].

This chapter reviews the most recent literature concerning the rationale and the clinical application of NIV in acute heart failure and acute cardiogenic pulmonary edema.

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36.2 Methods

We performed a comprehensive search of MEDLINE, EMBASE, and Web of Science and identified trials on NIV (either CPAP or PSV) in either acute heart failure or acute cardiogenic pulmonary edema.

The search strategy was defined according to the acronym PICO, population, intervention, comparison, outcomes (and context), to answer a clinical question within the best scientific evidence available.

- **Population:** "Heart Failure" [Mesh] or "Shock, Cardiogenic" [Mesh] or "Pulmonary Edema" [Mesh] not "Sleep Apnea, Obstructive" [Mesh] or "Sleep Apnea, Central" [Mesh] or "Sleep Apnea Syndromes" [Mesh]
- **Intervention:** "Noninvasive Ventilation" [Mesh] or "Intermittent Positive Pressure Ventilation" [Mesh] or "Continuous Positive Airway Pressure" [Mesh] or "Interactive Ventilatory Support" [Mesh] or "Positive Pressure Respiration" [Mesh] or "Respiration, Artificial" [Mesh] not "Exercise Therapy" [Mesh] or "Resistance Training" [Mesh] or "Exercise" [Mesh]
- **Comparison:** No restriction
- **Outcomes:** No restriction

36.3 Results

We included five observational studies including 1530 patients, one RCT on 110 patients, and two reviews (2664 patients).

36.4 Focus on Clinical Relevant Trials

36.4.1 NIV and Pathophysiology

PEEP application is physiologically useful in the course of acute heart failure on both respiratory and cardiac sides. (1) Alveolar recruitment leads to increased lung volume and compliance, improving both gas exchange and ventilation. (2) Reduced venous return and left ventricular (LV) afterload improves heart performance (Fig. 36.1).

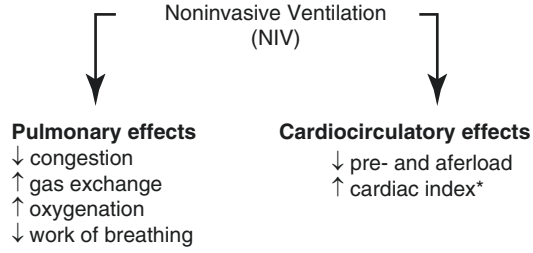

Fig. 36.1 Summary of pulmonary and circulatory effects of noninvasive mechanical ventilation

The recent literature has further delved into the cardiac effects of PEEP application.

In their elegant study [4] on 20 consecutive patients with acute cardiogenic pulmonary edema with LV dysfunction treated with PSV, Moret Iurilli et al. found that all four hemodynamic parameters (tricuspid annular plane systolic excursion, transpulmonary gradient, transaortic gradient, inferior vena cava diameter) measured at admission significantly improved after 3 and 6 h of treatment. These data confirm the efficacy of NIV in vivo on heart performance during PEEP application in the acute phase of the disease [4].

Another proof of concept of the efficacy of NIV on heart performance in HF comes from the study by T. Kato et al. on 20 stable patients with HF and LV systolic dysfunction (LVEF < 50%) with functional mitral regurgitation (fMR) [5]. The 20 patients underwent echocardiography during 10-min CPAP (4 and 8 cm H_2O) and adaptive servo-ventilation.

The authors found that positive airway pressure application reduced fMR by 20% and improved LV systolic dysfunction in patients with dilated LV.

36.4.2 Prehospital

In 2018, a prospective trial performed in the prehospital setting confirmed the efficacy of NIV in the treatment of presumed COPD exacerbation and acute cardiogenic pulmonary edema [6].

A cohort of 99 patients with presumed COPD exacerbation and ACPE was treated with incremental noninvasive ventilation (from CPAP to CPAP + PS) and compared with a historical group of 30 patients treated with medical therapy only. More than 50% of enrolled patients had presumed acute cardiogenic pulmonary edema.

Differences between baseline and hospital admission values of all endpoints showed improvement in NIV groups compared to the control group ($p > 0.001$). Patients were divided according to NIV duration (Group 1 ≤ 15 min; Group 2 > 15 min). All endpoints, i.e., heart rate, O_2 saturation, respiratory rate, SBP and dyspnea score, were significantly better in both groups as compared to controls. The authors conclude that prehospital NIV treatment should be performed in patients with COPD exacerbation and CPE, even if the distance between emergency scene and hospital is short.

36.4.3 In-hospital

Notwithstanding the efficacy of NIV in the treatment of acute cardiogenic pulmonary edema is proven, its use is still suboptimal. In a recently published real-life study, Aliberti et al. [2] showed that in Italy one out of five patients with acute cardiogenic pulmonary edema is still treated with standard oxygen. Among 1293 patients, 273 (21%) were initially treated with oxygen, 788 (61%) with CPAP, and 232 (18%) with PSV. One out of four patients who began with oxygen was subsequently switched to NIV, and initial treatment with oxygen therapy had an odds ratio for treatment failure of 3.65 (95% CI: 2.55–5.23, $p < 0.001$).

In 2017 the ERS/ATS issued their clinical practice guidelines on NIV in acute respiratory failure (ARF) [3]. They recommend either bi-level NIV or CPAP for patients with ARF due to cardiogenic pulmonary edema (strong recommendation, moderate certainty of evidence).

In the last 2 years, two papers addressed the question whether PSV is superior to CPAP in the treatment of acute cardiogenic pulmonary edema.

One prospective study [7] enrolled 153 patients in four Italian hospitals (CPAP = 88, PSV = 65) with comparable characteristics at enrolment. Primary outcome—mortality rate—did not differ in the two groups. NIV failures occurred more frequently in patients treated with CPAP (11.2% vs. 1.5%, $p = 0.02$), and five patients needed ETI. These observational data apparently show that PSV offer a benefit in terms of CO_2 reduction; however, (1) they included Boussignac as a method to deliver CPAP in an unspecified proportion of patient, which is not the standard; (2) CO_2 reduction was a secondary outcome; (3) this was not a randomized study; and (4) the authors did not stratify according to the presence/absence of COPD in the two groups.

More robust data come from the randomized trial conducted by Belenguer-Muncharaz et al. [8]. One hundred and ten patients were randomly assigned to either PSV ($n = 56$) or CPAP ($n = 54$). Whereas oxygenation was significantly better in the PSV group at 60 min, the primary outcome—intubation rate—was similar in both groups (9% in NIV vs. 9% in CPAP, $P = 1.0$). Interestingly, the author excluded from the analysis COPD patients. These last data confirm previous publication on comparable efficacy of PSV and CPAP in the treatment of acute cardiogenic pulmonary edema [9].

The 2018 clinical practice review by the ESC [10] confirms the equivalence of the two NIV modalities; the authors suggest that CPAP should be the first-line treatment, especially in the prehospital setting, whereas PSV is recommended in patients with significant hypercapnia.

Finally, in 2019 a Cochrane review [11] analyzed 24 studies with 2664 participants using NIV in the treatment of acute cardiogenic pulmonary edema. The authors state that (1) NIV may reduce hospital mortality (RR 0.65, 95% CI = 0.51–0.82) and has a NNT of 17 (12–32) and (2) NIV probably reduces ETI rates (RR 0.49, 95% CI = 0.38–0.62), with a NNT of 13 (11–18). They conclude that NIV is effective in the treatment of acute cardiogenic pulmonary edema, irrespective of the modality, either CPAP or PSV/bi-level positive pressure ventilation (Tables 36.1 and 36.2).

Table 36.1 The literature

Study	Patients	Treatment	What they found
T. Kato et al. Front Physiol. 2017	20 stable patients with HF and LVEF < 50%	10-min CPAP (4 and 8 cm H_2O) and adaptive servo-ventilation	1. Positive pressure application reduced fMR by 20% 2. Improved LV systolic dysfunction in patients with dilated LV
C. Moret Iurilli et al. J Intensive Care Med. 2018	20 consecutive patients with ACPE with LV dysfunction	PSV	Tricuspid anular plane systolic excursion, transpulmonary gradient, transaortic gradient, inferior vena cava diameter significantly improved after 3 and 6 h of PSV application
Prehospital			
M. Hensel et al. Am J Emerg Med. 2019	54 patients with presumed ACPE	2 groups according to NIV (CPAP ± PS) duration vs. historical controls without NIV: Group1 NIV ≤ 15 min, Group2 NIV > 15 min	All endpoints (HR, O_2 sat. RR, SBP, and dyspnea score) significantly improved in both NIV groups as compared to controls
In-hospital			
S. Aliberti et al. BMC Emerg Med. 2018	Observational study on ED treatment of ACPE	1293 patients with acute cardiogenic pulmonary edema. Initial treatment was O_2 in 273 (21%), CPAP in 788 (61%), and PSV in 232 (18%)	1. 5% of patients who began with O_2 were subsequently switched to NIV 2. Initial O_2 treatment had an OR for treatment failure of 3.65 (95% CI: 2.55–5.23, $p < 0.001$)
Pagano A et al. Respir Physiol Neurobiol. 2018	Observational study on 153 patients with ACPE	CPAP (88 patients) vs. PSV (55 patients)	1. No mortality difference. Patients treated with PSV had a significant lower rate of endotracheal intubation 2. Higher improvement of blood gas analyses parameters 3. However, no control for COPD was done
Belenguer-Muncharaz et al. Arch Bronconeumol. 2017	RCT on PSV vs. CPAP in ACPE	56 PSV vs. 54 CPAP	1. Oxygenation was significantly better in PSV group at 60 min 2. Primary outcome—intubation rate—was similar in both groups (9% in NIV vs. 9% in CPAP, $P = 1.0$). 3. Interestingly, the author excluded from the analysis COPD patients
Review and meta-analysis			
J. Masip et al. Indications and practical approach to noninvasive ventilation in acute heart failure. Our Heart J. 2018	ESC Clinical practice review on patients with AHF and ACPE	The review considers both CPAP and PSV	Authors suggest: 1. CPAP is a simpler technique that is recommended as first-line therapy, particularly in the prehospital setting/less well-equipped areas 2. PSV is equally effective in ACPE and may be preferable, by experienced teams, in patients with significant hypercapnia

Table 36.1 (continued)

Study	Patients	Treatment	What they found
N. Berbenetz et al. Noninvasive positive pressure ventilation (CPAP or bilevel NPPV) for Acute Cardiogenic Pulmonary Edema. Cochrane Systematic Review. 2019	24 studies with 2664 participants on NIV in the treatment of ACPE	Either CPAP or PSV	1. NPPV may reduce in-hospital mortality (RR 0.65, 95% CI = 0.51–0.82), NNT = 17 (12–32) 2. NPPV probably reduces ETI rates (RR 0.49, 95% CI = 0.38–0.6), NNT = 13 (11–18)

Table 36.2 Take-home points

1. NIV (CPAP or PSV) is highly effective in ACPE, starting from the prehospital setting
2. New devices and education will allow to apply NIV in every setting

36.5 Conclusion and Summary

1. **Learning Points**
   (a) New studies confirm the efficacy of NIV in ACPE. An early start of NIV in the prehospital setting can be beneficial to the patient.
   (b) There is no difference in using CPAP vs. PSV as modalities of NIV with regard to mortality.
2. **Critical Points**
   (a) NIV is highly effective in ACPE treatment (NNT for mortality is 17 and 13 for intubation).
   (b) Since its use in the ED is still suboptimal, effort should be made in order to increase NIV application to ED patients with acute cardiogenic pulmonary edema.
3. **Perspectives**
   (a) There is a need of education and device implementation in order to start NIV as early as possible, even in the prehospital setting.
   (b) Only one study has assessed the prehospital application of NIV in these patients. There is still lack of proof that PSV could be superior to CPAP for the treatment of ACPE.

References

1. Kurmani S, Squire I. Acute heart failure: definition, classification and epidemiology. Curr Heart Fail Rep. 2017;14(5):385–92. https://doi.org/10.1007/s11897-017-0351-y. PMID: 28785969.
2. Aliberti S, Rosti VD, Travierso C, Brambilla AM, Piffer F, Petrelli G, Minelli C, Camisa D, Voza A, Guiotto G, Cosentini R, SIMEU ACPE Study Group. A real life evaluation of non invasive ventilation in acute cardiogenic pulmonary edema: a multicenter, perspective, observational study for the ACPE SIMEU study group. BMC Emerg Med. 2018;18:61. https://doi.org/10.1186/s12873-018-0216-z.
3. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi P, Members of the Steering Committee, Antonelli M, Brozek I, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof S, Members of the Task Force. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2):1602426. https://doi.org/10.1183/13993003.02426-2016.
4. Moret Iurilli C, Brunetti ND, Di Corato PR, Salvemini G, Di Biase M, Ciccone MM, Procacci V. Hyperacute hemodynamic effects of BiPAP noninvasive ventilation in patients with acute heart failure and left ventricular systolic dysfunction in emergency department. J Intensive Care Med. 2018;33:128–33. https://doi.org/10.1177/0885066617740849. PMID: 29141525.
5. Kato T, Kasai T, Yatsu S, Murata A, Matsumoto H, Suda S, Hiki M, Shiroshita N, Kato M, Kawana F, Miyazaki S, Daida H. Acute effects of positive airway pressure on functional mitral regurgitation in patients with systolic heart failure. Front Physiol. 2017;8:921. https://doi.org/10.3389/fphys.2017.00921.
6. Hensel M, Hensel M, Strunden MS, Tank S, Gagelmann N, Wirtz S, Kerner T. Prehospital noninvasive ventilation in acute respiratory failure is justified even if the distance to hospital is short. Am J Emerg Med. 2019;37:651–6. https://doi.org/10.1016/j.ajem.2018.07.001. PMID: 30068489.

7. Pagano A, Numis FG, Rosato V, Russo T, Porta G, Bosso G, Serra C, Masarone M, Visone G, Paladino F. Pressure support ventilation vs Continuous positive airway pressure for treating of acute cardiogenic pulmonary edema: a pilot study. Respir Physiol Neurobiol. 2018;255:7–10. https://doi.org/10.1016/j.resp.2018.04.007.
8. Belenguer-Muncharaz A, Mateu-Campos L, González-Luís R, Vidal-Tegedor B, Ferrándiz-Sellés A, Árguedas-Cervera J, Altaba-Tena S, Casero-Roig P, Moreno-Clarí E. Non-invasive mechanical ventilation versus continuous positive airway pressure relating to cardiogenic pulmonary edema in an intensive care unit. Arch Bronconeumol. 2017;53(10):561–7. https://doi.org/10.1016/j.arbres.2017.02.005.
9. Li H, Hu C, Xia J, Li X, Wei H, Zeng X, Jing X. A comparison of bilevel and continuous positive airway pressure noninvasive ventilation in acute cardiogenic pulmonary edema. Am J Emerg Med. 2013;31(9):1322–7. https://doi.org/10.1016/j.ajem.2013.05.043.
10. Masip J, Peacock WF, Pric S, Cullen L, Martin-Sanchez JF, Seferovic P, Maisel AS, Miro O, Filippatos G, Vrints C, Christ M, Cowie M, Platz E, McMurray J, DiSomma S, Zeymer U, Bueno H, Gale CP, Lettino M, Tavares M, Ruschitzka F, Mebazaa A, Harjola VP, Mueller C, on Behalf of the AHF Study Group of the ACCA and the Committee on AHF of the HFA of the ESC. Indications and practical approach to non-invasive ventilation in acute heart failure. Eur Heart J. 2018;39:17–25. https://doi.org/10.1093/eurheartj/ehx580.
11. Berbenetz N, Wang Y, Brown J, Godfrey C, Ahmad M, Vital FM, Lambiase P, Banerjee A, Bakhai A, Chong M. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database Syst Rev. 2019;4:CD005351. https://doi.org/10.1002/14651858.CD005351.pub4. Review. PMID: 30950507.

Noninvasive Ventilation in Neurocritical Care

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The paper reviews the literature on the use of noninvasive ventilation (NIV) in neurocritical care.

37.1 Methodology

The author searched articles in PubMed using the terms "neurocritical care," "neurology," "neurosurgery," and "noninvasive ventilation." Abstracts were reviewed, and full texts of relevant articles were downloaded and summarized in this review.

37.2 NIV in Neurosurgery

37.2.1 Perioperative Use of NIV in Neurosurgery

Patients undergoing neurosurgical procedures are at a higher risk of postoperative respiratory failure compared to other surgical procedures. These complications occur more commonly with supratentorial than infratentorial procedures,

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presumably due to a higher degree of altered mental status seen in these patients [1].

NIV has been used preoperatively to ensure adequate preoxygenation. Respiratory failure in the postoperative period is most commonly due to lung atelectasis, and NIV has been used to recruit alveoli after extubation. Intraoperatively, NIV can be an alternative to endotracheal intubation in patients with COPD, where the risks of complications such as air trapping, barotrauma, bulla rupture, and prolonged mechanical ventilation are high.

One interesting case report [2] describes the use of NIV as a mode of ventilation during moderate to deep sedation in a frontal craniotomy for tumor excision in a patient with severe COPD. In this case report, NIV was delivered through a mechanical ventilator machine using a standard anesthesia mask. The patient had severe COPD with concerns for the risks of prolonged intubation postoperatively. The patient was offered that craniotomy be performed under moderate sedation without intubation, using NIV, with the option to resort to general anesthesia with endotracheal intubation if sedation was deemed inadequate.

The patient was fitted with a standard medium-sized adult mask with elastic straps. The anesthesia machine was set to pressure support ventilation, with a PEEP of 1–3 cm H_2O, adjusted to generate a tidal volume of 300 mL. Once settings were set to patient comfort, anesthesia was infused—dexmedetomidine at 0.1–0.3 μg/kg/h, remifentanil at 0.02–0.05 μg/kg/min, and propofol at 15–20 μg/kg/min. The patient was allowed to drift in and out of consciousness while still able to trigger pressure support. During the procedure, the patient was able to communicate periodically with the anesthesiologist to confirm proper placement of face mask or to alert the team of discomfort. During the procedure, end-tidal CO_2 was maintained at less than 40 mmHg, and arterial blood gas was checked periodically.

Several challenges were noted. Medications commonly used for awake craniotomies, such as dexmedetomidine, propofol, and remifentanil, can cause respiratory depression, increasing the risks of losing the airway with deepening sedation. Masks used in NIV may interfere with the surgical site or frame pins used to stabilize the skull. Also, the anesthesiologist needs to become familiar with a new machine that needs to be brought separately into the operating room.

Awake craniotomy was performed successfully using NIV, and authors suggested that this option may improve patient outcomes for patients with severe lung disease who require major surgery under moderate to deep sedation.

Whether routine or prophylactic NIV can prevent respiratory failure in neurosurgical patients is unknown. Currently, there is no evidence supporting the effectiveness of NIV in patients undergoing craniotomy. Applying positive pressure ventilation to patients with intracranial lesions should be weighed carefully against the risk of increasing intracranial pressure or the risk of cerebral vasospasm with decreased $PaCO_2$ from NIV.

37.2.2 Use of NIV in Chiari Malformation and Sleep Apnea

Chiari malformation is a structural defect of the cerebellum resulting in downward displacement of the cerebellar tonsils through the foramen magnum. Chiari malformations are associated with sleep-disordered breathing. The exact mechanism is unknown but may be related to abnormalities in central respiratory drive, resulting in central sleep apnea or to a dysfunction in the upper airway, resulting in obstructive sleep apnea (OSA). Cerebellar herniation could possibly mechanically disrupt the medullary respiratory center, resulting in apneic episodes.

A case report [3] describes the treatment of central sleep apnea in a patient with Chiari malformation using adaptive pressure support servo-ventilation. Adaptive servo-ventilation (ASV) treats complex abnormal breathing patterns by monitoring and reacting to changes in peak expiratory flow. This type of ventilation minimizes cyclical or ataxic breathing. A patient who was treated with sleep apnea was noted to be unresponsive to BPAP, CPAP, or ASV. Polysomnography revealed

central sleep apnea. An MRI revealed a Chiari Type 1 malformation and a syrinx in the spinal cord. The patient underwent craniocervical decompression, and a follow-up study with patient on ASV showed complete resolution of sleep apnea. Subsequent sleep study without ASV demonstrated that AHI increased to 22, which implies that the sleep apnea improved but was not cured by surgery. This case highlights that structural brain disorders can cause sleep-disordered breathing and should be considered in patients with poor response to initial NIV therapy. As in this case, surgical correction can result in just a partial treatment of sleep apnea, and ASV can provide additional benefit to patients with central sleep apnea following surgical correction.

37.2.3 Use of NIV in Transsphenoidal Surgery

OSA is common in patients presenting for pituitary surgery, affecting up to 70% of patients with acromegaly and 18–33% of patients with Cushing disease [4]. These patients are at risk for postoperative respiratory complications, and the risk is higher immediately after surgery as sedation leads to soft tissue obstruction, atelectasis, and decreased respiratory drive. Guidelines (on use of NIV for general surgery) state that patients who use NIV prior to surgery should have NIV applied soon after surgery unless contraindicated.

Several case reports have reported the development of pneumocephalus with NIV after transsphenoidal surgery, which often leads to additional surgery and prolonged hospital stay [5, 6]. Postoperative NIV should not be used in cases where positive airway pressure may result in breakdown of surgical site repair and introduction of air into potential spaces. These cases include surgery of the paranasal sinuses, skull base, pituitary fossa, middle ear, and retropharynx and reconstruction of large defects of head and neck. While NIV is contraindicated, patients should be closely monitored with continuous pulse oximetry, opiate use should be minimized, and early ambulation should be encouraged. The optimal time for resuming NIV in these patients is unknown and warrants further research. One case report recommends waiting 6 weeks after dural repair before restarting NIV [5]. Patients should be instructed to avoid the use of NIV after surgery until cleared by the surgeon.

37.2.4 NIV in the Treatment of Subarachnoid Pleural Fistula

Subarachnoid pleural fistula is a condition where an abnormal communication exists between the subarachnoid space and pleural space due to defects in both the dura mater and the parietal pleura. This fistula can develop spontaneously or more commonly after blunt or penetrating trauma or as a complication of thoracic and spinal surgery. Unlike most cerebrospinal fluid (CSF) leakages that heal spontaneously or after insertion of CSF drains, SAPF remains open despite conservative treatment.

Intrapleural pressure normally ranges from −5 to −7.5 cm H_2O, while pressure in the subarachnoid space ranges from 10 to 15 cm H_2O. Intrapleural pressure becomes most negative during inspiration. In the presence of the defects, the pressure gradient between the intrapleural and subarachnoid spaces produces a suction effect, and CSF flows along this gradient to accumulate in the pleural space and prevent spontaneous closure of the fistula. This assumes that only the parietal pleura contains a defect and the visceral pleura is intact. In the presence of a defective visceral pleura, intrapleural pressure overcomes CSF pressure and air leaks into the subarachnoid space, resulting in pneumocephalus [7].

Fluid collection in the pleural cavity eventually leads to symptoms of dyspnea, chest pain, and hypoxia. In time, the loss of CSF and subsequent intracranial hypotension also leads to symptoms of headaches, neck pain, stiffness, nausea, dizziness, photophobia, and impaired hearing.

The initial diagnostic work-up of subarachnoid pleural fistula includes chest imaging with a chest X-ray, ultrasound, or CT scan to confirm pleural effusion. Thoracentesis or chest tube

insertion may be necessary to aid in lung re-expansion. Pleural fluid can be tested for the presence of beta 2 transferrin, a biochemical marker for cerebrospinal fluid. Treatment includes conservative measures such as bed rest and lumbar drains which are typically ineffective. Surgical interventions include primary repair, patch grafts with muscle, fat or fascia, muscle flaps, and omental flaps, which may be effective but require a surgical operation.

Several reports have described the successful treatment of subarachnoid pleural fistulas with the use of NIV [8–10]. NIV is applied with full-face or nasal mask with pressure settings of 6–14 cm H_2O inspiratory pressure and 3–5 cm H_2O expiratory pressure. The positive airway pressure raises intrapleural pressure and stops the flow of CSF through the dura, enabling the dura to repair itself. The duration of treatment ranges from 5 to 14 days. The appropriate duration of NIV and optimal pressure settings are unknown. In contrast to surgical treatment, treatment with NIV is fully noninvasive, and restrictions to daily activities are minimal.

37.3 NIV and Stroke

The risk of stroke is higher in patients with OSA. The prevalence of OSA is as high as 60% in ischemic cerebrovascular disease. The prognosis of stroke is worse with OSA. OSA probably causes worse outcomes in stroke due to hypoxia which leads to sympathetic activation, release of free oxygen radicals, CRP, and other cytokines, increased thrombocyte activation, and aggregation and decreased fibrinolytic activity. OSA worsens the ischemia in brain tissue by periodic apneas and desaturations. Furthermore, excessive daytime sleepiness commonly seen in OSA also decreases motivation and cooperation of patients during rehabilitation and contributes to worse outcomes.

For this reason, a study [11] investigated the effects of early treatment of OSA on the prognosis of patients who suffered a stroke. Patients with stroke underwent whole-night polysomnography and titration study. The American Academy of Sleep Medicine (AASM) manual for scoring of sleep and associated events was used, and OSA was diagnosed if 15 or more respiratory events were noted per hour of sleep. Treatment with NIV was started within 48 h of stroke, and all patients were compliant for at least 5 h or more of NIV per night. MRI and MRA were performed on admission and during the second week and second month of stroke, and the size of infarction was determined by measuring the largest diameter of the lesion. The study showed that patients in the treatment group had significantly lower stroke severity scores (NIH Stroke Scale, Barthel Scale, Hamilton Depression Rating Scale, Epworth Sleepiness Scale, and PSQT) in the subacute (second week) and chronic (second month) stages. Furthermore, patients who were treated with NIV also showed a decrease in the lesion size more often compared to those who were not treated. Forty percent in the treatment group versus 20% in the control group showed a decrease in infarction size at the subacute stage, while 36.4% vs. 28.5% showed a decrease in the chronic stage. The difference was not statistically significant.

Another study [12] explored the effects of CPAP treatment on patients with OSA and stroke. Sleep study was performed, and treatment was started thereafter on the second week after stroke, and this continued for a total of 8 weeks. Compliance was poor, averaging 1.4 h a night. No improvements were noted after CPAP treatment probably due to the delay in treatment initiation, missing the period when ischemic brain tissue presumably would benefit the most from improved oxygenation.

Further prospective and randomized controlled studies should be conducted to define the role of NIV in the treatment of patients with stroke and OSA. If early treatment is proven to be beneficial, OSA should be considered a modifiable risk factor in stroke and treated aggressively after an acute stroke event. With current evidence, it appears that OSA treatment benefits stroke patients when initiated early, and noncompliance is minimized. Of note, compliance may be an issue in stroke patients with aphasia, severe motor dysfunction, or depression. ESS

scores should be documented, and a decrease in scores can be used as an indicator of treatment efficacy.

37.4 NIV and Neuromuscular Disease

Neuromuscular disease (NMD) is a group of disorders that affect any part of the nerve or muscle and includes conditions such as amyotrophic lateral sclerosis or ALS (affecting the motor neuron), muscular dystrophy (affecting muscle directly), and myasthenia gravis (affecting the neuromuscular junction). The predominant feature of neuromuscular disease is progressive deterioration of muscle strength. Involvement of respiratory muscles occurs at some point in patients with neuromuscular disease and leads to sleep disordered breathing and, eventually, respiratory failure [13].

Weaning and liberating patients with NMD from the ventilator is challenging. Repeated failed extubations and prolonged mechanical ventilation that ultimately requires tracheostomy is common. NIV has been investigated as a tool to promote successful weaning in patients with NMD and ventilatory failure. NIV likely prevents reintubation by overcoming the low vital capacity that is typically seen in NMD patients immediately after extubation.

A retrospective study [14] reports several cases of successful extubation of patients with NMD who experienced extubation failure via conventional weaning strategies but succeeded after NIV. In this study, patients were extubated directly to NIV support. NIV was provided via nasal or oronasal masks. NIV was adjusted to maintain an $SPO_2 \geq 95\%$ and $ETCO_2 < 45$ mmHg. Success was considered if reintubation has been avoided within the subsequent 5 days. First attempts failed in a portion of cases, but a second attempt led to successful extubation in all cases.

37.4.1 NIV in Myasthenia Gravis

Myasthenia gravis is an autoimmune disorder affecting the neuromuscular junction. This condition is caused by autoantibodies against the acetylcholine receptors at the postsynaptic side of the neuromuscular junction. The autoantibodies block the receptors, which are destroyed via complement-mediated mechanisms. With destruction of the receptors, muscles are unable to contract and become weak. Repeated stimulation of the involved muscles leads to fatigable muscle weakness because of the paucity of acetylcholine binding sites. Myasthenic crisis occurs when symptoms progressively worsen to cause respiratory failure. Myasthenic crisis can be triggered by multiple factors including infection, surgery, fever, and certain medications. Corticosteroids can precipitate crisis or cause further decompensation in patients with myasthenia gravis.

Several tests can be used to monitor respiratory status in myasthenic crises [15]. Pulse oximetry and arterial blood gas are not useful since PCO_2 rise and oxygen saturation drops occur late during myasthenic crisis. A normal PCO_2 or oxygen saturation also does not exclude the condition. Serial pulmonary function tests (i.e., every 2 h) may be more useful, with vital capacities <10–20 per kilogram or negative inspiratory force <−20 to −30 cm H_2O suggesting the need for closer monitoring in the intensive care unit and consideration of ventilator support. Another test that is useful in monitoring respiratory function in myasthenic crisis is the single breath test, which measures how many words are spoken by the patient in one breath. The patient takes one breath in and counts up as high as possible before requiring another inspiratory breath. Counting up to 15–20 or less correlates with poor respiratory status.

The mainstay of myasthenic crisis treatment is plasmapheresis or intravenous immunoglobulin, but either treatment takes days to weeks for full effect. In the meantime, patients with deteriorating respiratory status, but who are otherwise mentally alert and able to manage secretions, may be candidates for NIV as bridging therapy while awaiting improvement from IVIG or plasma exchange.

NIV has been shown to be successful in preventing intubation in patients with myasthenic crisis and reducing ventilator days and ICU and hospital length of stay [15]. Using a BiPAP

machine, continuous positive pressure can be delivered through a face mask. The breathing cycle is triggered by the patient's inspiratory effort. The machine provides inspiratory positive pressure to overcome upper airway resistance and reduce work of breathing and also provides end expiratory positive pressure to prevent airway collapse and decrease the amount of lung atelectasis.

The criteria for intubation is not well defined, but thresholds when one should consider ventilation include FVC < 15–20 mL/kg body weight, maximal inspiratory pressure <−40 cm H_2O, maximal expiratory pressure <40 cm H_2O, and evidence of respiratory muscle fatigue, hypercapnia, or hypoxia [16].

Several articles [16, 17] have shown that BiPAP is an effective treatment for respiratory failure in patients with myasthenia gravis. The mean duration of BiPAP in these studies in successful cases was 4–5 days. BiPAP can prevent intubation in 70% of NIV trials. The only predictor for BiPAP failure (defined as eventually requiring mechanical intubation) was a PCO_2 level exceeding 45 on initiation of BiPAP. Hypercapnia probably reflects a more severe degree of neuromuscular respiratory failure that cannot be supported by only positive pressure ventilation and thus requires a ventilator mode with volume control. Most failures occur within 24 h of BiPAP use. The studies show that BiPAP trial before the development of hypercapnia can prevent intubation and prolonged mechanical ventilation.

37.4.2 NIV in Muscular Dystrophy

Duchenne muscular dystrophy is an x-linked neuromuscular disorder that leads to progressive muscle weakness. Weakness of respiratory muscles results in ineffective cough, recurrent pneumonia, hypoventilation during sleep, and daytime respiratory insufficiency. Worsening pulmonary function is frequently missed early on as loss of ambulatory muscle strength sets in early and patients performs less exertional tasks. Respiratory involvement is the main cause of mortality.

Guidelines on respiratory care of patients with DMD have been published [18, 19] and recommend biannual assessments of respiratory function once patients lose ambulatory function. More specific guidelines on the threshold pulmonary function test values to trigger evaluations for sleep and awake hypoventilation as well as initiation of NIV are available.

Since the 1990s, nocturnal NIV has been offered to patients with DMD when home oximetry studies reveal sleep hypoxemia and FVC falls to ≤1.25 L. Initiation of nocturnal NIV increased mean age of survival to 25.3, compared to 14.4 in the 1960s. Another study reported a 50% survival to 39.6 years when NIV and mechanically assisted cough are used [20].

Recent guidelines [19] recommend that NIV should be initiated when pulmonary function tests show signs of hypoventilation, i.e., FVC is <30% predicted, baseline SPO_2 is <95% or pCO_2 on awake ABG, or end-tidal $PETCO_2$ is >45 mmHg. Use of NIV appears to be increasing but still occurred less often than recommended.

37.4.3 NIV in Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) or motor neuron disease (MND) is a neurodegenerative disorder characterized by loss of neurons in the motor cortex, the brainstem, or the spinal cord. In this disease, there is progressive impairment of upper and lower motor neurons which leads to weakness of all muscles. The etiology remains unknown, and the disease still remains incurable although treatments are available to manage symptoms and achieve the best possible quality of life.

As the disease progresses, respiratory muscle involvement leads to sleep-disordered breathing which initially occurs in the REM stages, then progresses to involve non-REM stages of sleep, and manifests as OSA that leads to nocturnal hypercapnia. This disturbance in sleep architecture results in repeated nights of poor sleep, and patients eventually complain of morning headaches, lethargy, persistent fatigue, lack of con-

centration, and breathlessness. Respiratory dysfunction is unfortunately irreversible in ALS, and respiratory failure typically occurs within 5 years of disease onset. The onset of respiratory muscle weakness cannot be reliably detected by symptoms alone as these may not be apparent until the weakness is severe. The degree of respiratory impairment is often underestimated by the clinician. Onset of symptoms such as orthopnea or daytime hypercapnia indicates that survival is likely to be only a few weeks or months [21].

Guidelines recommend that respiratory function should be tested regularly to detect early signs of impaired function (i.e., every 3 months) [22]. Periodic monitoring facilitates earlier discussions about NIV and reduces the risk of having to initiate NIV in an emergency. Respiratory function in ALS can be reliably measured by several methods. The measures of respiratory function that are recommended by the guidelines include nocturnal oximetry, supine functional vital capacity (FVC) and MIP and standing FVC, and sniff nasal inspiratory pressure (SNIP).

Nocturnal oximetry detects desaturations during sleep and is a more sensitive measure of nocturnal hypoventilation than FVC or MIP. It correlates with survival. FVC is the most commonly used respiratory measurement, correlates with ALS functional rating score, and is a significant predictor of survival. Measuring FVC requires a tight seal of the lips around a mouthpiece and may be difficult in ALS patients with bulbar involvement. Supine FVC is a better predictor of diaphragmatic strength compared to standing FVC. SNIP is another measure of respiratory function in ALS, one which can be performed independent of facial muscle strength. In this test, peak nasal pressure in one occluded nostril is measured during a maximal sniff performed from relaxed end expiration through the other nostril. Pressures obtained from the SNIP test correlates with diaphragmatic and sternocleidomastoid strength measured using more invasive tests. SNIP also correlates with apnea-hypopnea index on polysomnography. Values <40 cm H_2O correlate with nocturnal hypoxemia, and values <30 cm H_2O are associated with a median survival of 3 months. Finally elevated serum bicarbonate and low serum chloride levels correlate with respiratory symptoms and are predictive of death within 5 months [23].

Use of NIV in patients with good bulbar function can prolong survival by 7–18 months. In patients with poor bulbar function, NIV use does not improve survival rates but has been shown to improve quality of life [24]. Use of NIV during sleep helps support respiratory muscle function and restores serum oxygen and carbon dioxide levels to normal. By improving nocturnal hypercapnia, NIV restores central chemoreceptor sensitivity and improves daytime hypoventilation, thereby increasing participation in daytime activities and improving the quality of life across various domains.

37.5 Conclusion

NIV is a valuable tool in the management of pulmonary comorbidities in patients requiring neurointensive care. Established and innovative uses of NIV in a number of neurologic and neurosurgical conditions have been described. Further research on NIV in neurologic and neurosurgical conditions can be conducted to extend the use of NIV.

References

1. Yıldırım F, Esquinas A. Is CPAP treatment not effective after supratentorial craniotomy? J Clin Anesth. 2018;44:34.
2. Lee S, Berman M. Use of the draeger apollo to deliver bilevel positive pressure ventilation during awake frontal craniotomy for a patient with severe chronic obstructive pulmonary disease. A A Case Rep. 2015;5(11):202–5.
3. Fahim A, Johnson A. Chiari malformation and central sleep apnoea: successful therapy with adaptive pressure support servo-ventilation following surgical treatment. BMJ Case Rep. 2012;2012:bcr-2012-007143.
4. Venkatraghavan L, Perks A. Postoperative management of OSA after transsphenoidal pituitary surgery. J Neurosurg Anesthesiol. 2009;21(2):179–80. https://doi.org/10.1097/ana.0b013e3181993719.
5. Kopelovich J, de la Garza G, Greenlee J, Graham S, Udeh C, O'Brien E. Pneumocephalus with BiPAP use after transsphenoidal surgery. J Clin Anesth. 2012;24(5):415–8. https://doi.org/10.1016/j.jclinane.2011.12.003.

6. Zlotnik D, Taylor G, Simmoneau A, Viot-Blanc V, Devys J. Pneumencéphalie après ventilation non invasive en postopératoire de neurochirurgie par voie trans-sphénoïdale: à propos de deux cas. Annales Françaises d'Anesthésie et de Réanimation. 2014;33(4):275–8.
7. Russo A. Expert's comment concerning grand rounds case entitled "Subarachnoidal pleural fistula after resection of intradural thoracic disc herniation and multimodal treatment with noninvasive positive pressure ventilation (NPPV)" (H. R. Schlag, S. Muquit, T. B. Hristov, G. Morassi, B. M. Boszczyk, M. Shafafy). Eur Spine J. 2015;25(1):160–1.
8. Kurata Y, Yoshimoto M, Takebayashi T, Kawaguchi S, Yamashita T. Subarachnoid-pleural fistula treated with noninvasive positive pressure ventilation. Spine. 2010;35(18):E908–11.
9. Yoshor D, Gentry J, LeMaire S, Dickerson J, Saul J, Valadka A, Robertson C. Subarachnoid—pleural fistula treated with noninvasive positive-pressure ventilation. J Neurosurg Spine. 2001;94(2):319–22.
10. Schlag H, Muquit S, Hristov T, Morassi G, Boszczyk B, Shafafy M. Subarachnoidal pleural fistula after resection of intradural thoracic disc herniation and multimodal treatment with noninvasive positive pressure ventilation (NPPV). Eur Spine J. 2015;25(1):155–9.
11. Benbir G, Karadeniz D. A pilot study of the effects of non-invasive mechanical ventilation on the prognosis of ischemic cerebrovascular events in patients with OSA syndrome. Neurol Sci. 2011;33(4):811–8.
12. Hsu C. Sleep-disordered breathing after stroke: a randomised controlled trial of continuous positive airway pressure. J Neurol Neurosurg Psychiatry. 2006;77(10):1143–9.
13. Albdewi M, Liistro G, El Tahry R. Sleep-disordered breathing in patients with neuromuscular disease. Sleep Breath. 2017;22(2):277–86.
14. Kim S, Kang S, Choi Y, Park Y, Won Y. Successful extubation after weaning failure by NIV in patients with neuromuscular disease: case series. Ann Rehabil Med. 2017;41(3):450.
15. Roper J, Fleming M, Long B, Koyfman A. Myasthenia gravis and crisis: evaluation and management in the emergency department. J Emerg Med. 2017;53(6):843–53.
16. Seneviratne J, Mandrekar J, Wijdicks E, Rabinstein A. NIV in myasthenic crisis. Arch Neurol. 2008;65(1):54.
17. Rabinstein A, Wijdicks E. BiPAP in acute respiratory failure due to myasthenic crisis may prevent intubation. Neurology. 2002;59(10):1647–9.
18. Finder JD, et al. Respiratory care of the patient with duchenne muscular dystrophy. Am J Respir Crit Care Med. 2004;170(4):456–65.
19. Bushby K, Finkel R, Birnkrant D, Case L, Clemens P, Cripe L, Kaul A, Kinnett K, McDonald C, Pandya S, Poysky J, Shapiro F, Tomezsko J, Constantin C. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010;9(1):77–93.
20. Andrews J, Soim A, Pandya S, Westfield C, Ciafaloni E, Fox D, Birnkrant D, Cunniff C, Sheehan D. Respiratory care received by individuals with duchenne muscular dystrophy from 2000 to 2011. Respir Care. 2016;61(10):1349–59.
21. O'Neill C, Williams T, Peel E, McDermott C, Shaw P, Gibson G, Bourke S. Non-invasive ventilation in motor neuron disease: an update of current UK practice. J Neurol Neurosurg Psychiatry. 2011;83(4):371–6.
22. NICE. Motor neurone disease. London: National Institute for Health and Clinical Excellence; 2010.
23. Miller RG, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009;73(24):2134.
24. Cousins R, Ando H, Thornton E, Chakrabarti B, Angus R, Young C. Determinants of accepting noninvasive ventilation treatment in motor neurone disease: a quantitative analysis at point of need. Health Psychol Behav Med. 2013;1(1):47–58.

Noninvasive Ventilation in Cardiovascular Surgical Patients

38

George Robert

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38.1 Introduction

Open heart surgical patients present as a unique subset group, where an uneventful and successful recovery from the surgery is closely entwined with the recovery and state of health of other major organ systems, most notably the lungs, kidneys, gastrointestinal, and the central nervous system. Both presurgical and postsurgical factors contribute to postoperative scenarios that make NIV a valuable tool in the management of these patients.

Alterations in pulmonary function, along with hypoxemia, reduced lung volumes, and atelectasis [1], combined with a restrictive chest wall, secondary to incisional pain, and possible diaphragmatic dysfunction [2], happen early in the postoperative course and are usually transient.

Postoperative acute cardiac decompensation can happen in a predisposed group of patients,

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and again, NIV can play an important role by directly and indirectly facilitating improvement in cardiac function.

NIV strategies that prevent and treat ventilatory dysfunction in the postoperative period cannot only expedite the overall recovery process but can also play a major role in preventing the varied complications that can affect the postsurgical course in an adverse manner.

This chapter will attempt a concise review in looking at the role NIV plays, in the abovementioned scenario, along with the rationale for its use, and supporting studies if any.

38.1.1 Indications for NIV in Postoperative Phase of Cardiovascular Surgery

- Post-extubation support
- Hypoxemia/hypercapnia
- Atelectasis
- Pulmonary edema

38.2 Pulmonary

Pulmonary complications are frequent in the immediate postoperative phase of cardiac surgery. The etiology of these is multifactorial and involves surgical and postoperative factors, well reported in the literature [3, 4]. Early intervention is often necessary to avoid further degradation [5]. Atelectatic areas develop frequently even after the most routine and uncomplicated cardiac surgery. This finding is further compounded in patients who are obese or morbidly obese and in those whose respiratory efforts are limited secondary to incisional pain. Atelectasis can decrease the functional residual capacity and increases intrapulmonary shunting. These unventilated areas can account for up to 20% of the total lung volume, thus causing hypoxemia in the postoperative period [6]. Studies in postoperative cardiac surgery patients have shown that NIV can be used to help avoid alveolar collapse and to enable better alveolar recruitment, thereby reducing the formation of atelectasis and increasing functional residual capacity [6, 7].

38.3 NIV After Liberation from Mechanical Ventilation

38.3.1 Extubation After Cardiac Surgery

Previously, it was a generally accepted practice to leave patients intubated for 12–24 h, even after the most routine cardiac surgery. With changes in anesthetic techniques and with adequate intensive care or postanesthesia care monitoring, that concept has now largely become a thing of the past. According to a recent Cochrane review, fast-track cardiac care includes "administration of low-dose opioid-based general anesthesia or use of a time-directed extubation protocol, or both," with the goal of reducing ICU and hospital length of stay [8]. Scoring systems that identify patients to be fast-tracked have been developed, and with the Society of Thoracic Surgeons (STS) promoting the use of extubation within 6 h after cardiac surgery as a quality of care benchmark, patients who meet certain strict criteria are even extubated in the operating room [9]. There is some evidence even suggesting that those patients who are extubated early may have fewer postoperative complications, including postoperative delirium and a lower risk of acute kidney injury (AKI) [10, 11].

With all that said, the timing of extubation in the very sick cardiac surgical patients is usually based on a number of variables and left to a protocol being followed by the respective intensive care team. It is uncommon to have a patient extubated who is anticipated to have issues with work of breathing while at the same time being on significant inotrope and pressor support to manage a failing or recovering heart [12]. The combination of increased work of breathing along with a less than optimal pump function is not a clinical scenario anyone

would want to arrive at, at any point, during the early postoperative course of a cardiac surgery patient.

38.3.2 Post-extubation Issues After Cardiac Surgery

In an inception cohort study done at Cleveland Clinic by Rady MY et al., published in *Critical Care Medicine 1997*, investigators collected data on more than 1400 patients who had undergone cardiac surgery and concluded that the incidence of early postoperative pulmonary dysfunction is uncommon; but once developed, it is associated with increased morbidity and mortality after cardiovascular surgery. Advanced age, large body mass index, preoperative increased pulmonary arterial pressure, low stroke volume index, hypoalbuminemia, history of cerebral vascular disease, emergency surgery, and prolonged cardiopulmonary bypass time were found to be risk factors for early onset of severe pulmonary dysfunction after surgery [13].

38.3.3 Rationale for the Use of NIV

Because of the unique chest wall properties after cardiac surgery, like median sternotomy (in the case of most cardiac surgical patients), right mini-thoracotomy (for minimally invasive tricuspid and mitral surgery), or left mini-thoracotomy (for robotic-assisted minimally invasive coronary artery bypass), post-extubation ventilatory dysfunction can occur in the early postoperative period, with or without varying degrees of hypoxemia. Splinting, secondary to incisional pain, leading to suboptimal lung volumes causing a restrictive pattern of ventilation can lead to atelectasis and pneumonia, if left untreated. Use of NIV after extubation can be preventive as well as curative.

Aside from the specific characteristics that are encountered in cardiac surgical patients, prophylactic and curative use of NIV is similar to other conditions of pulmonary dysfunction that has a potential to worsen to an impending respiratory failure.

38.3.4 Timing and Application of NIV

Traditionally, in postoperative patients, chest physiotherapy and incentive spirometry are used to maintain and improve lung volumes. In patients with a restrictive chest wall physiology to begin with, like obesity, incisional pain and splinting might make this uncomfortable and could become a problem. After extubation, use of NIV with CPAP or bi-level support in a prophylactic manner might make it easier for these groups of patients to ventilate and oxygenate adequately and reduce work of breathing. Moreover, use of positive pressure may prove to be helpful in preventing or in opening up atelectatic areas and improving V/Q mismatch, which is the most common abnormality seen in these patients.

Patients with a history of COPD and asthma are another group where prophylactic application of NIV might prove to be beneficial. Fluid overload from surgery and immediate postsurgical volume resuscitation can cause edema of bronchial walls causing wheezing and airway restriction. Use of NIV in these groups of patients can be advantageous while their fluid status is being monitored and treated with diuretics.

There has been no consensus so far, as to the duration and schedule of NIV application, when it is used prophylactically to prevent complications. It usually varies with the workflow of the facility or unit where the patient is being treated. Working with respiratory therapists and nurses and scheduling intervals of NIV support throughout the day seem to be the most reasonable approach.

Nighttime application, while the patient is sleeping, can be continuous and beneficial, as long as it does not interfere with a restful night's sleep. Sedatives, if needed, can be chosen with the smallest dose, allowing mitigation of patient discomfort and obtaining the desired level of

sedation. It might also be prudent to not keep patients flat or fully supine in bed while on NIV support to minimize risk of aspiration.

Patient cooperation and willingness and separation from and timing with oral intake to reduce risk of aspiration are common precautions to follow. In patients who are mildly anxious, it is not uncommon to prescribe a low dose of anxiolytic, like dexmedetomidine, so as to facilitate use of NIV and expedite the healing process.

38.3.5 Weaning from NIV

Pulmonary dysfunction, when it occurs postoperatively in cardiac surgical patients, is usually transient, for reasons mentioned above. Therefore, weaning from NIV support to traditional oxygen supplementation with nasal canula should be carried out when a sustained improvement in ventilation and oxygenation is seen. Improvements and maintenance of baseline lung volumes and oxygenation are usually seen at this point as evidenced by volumes achieved during incentive spirometry and with the level of oxygenation.

38.3.5.1 Cardiac

Acute cardiac decompensation after heart surgery leads to a low cardiac output state, especially in patients with less than stellar ventricular function, identified preoperatively and again during surgery by transthoracic and transesophageal echocardiography. This is usually a dynamic process seen early in the postoperative course, usually requiring inotrope and/or pressor support with loading conditions that need to be titrated against desired hemodynamics, until the heart readjusts to a newer set of parameters (reperfusion, loading, wall tension). This, along with a lack of or inadequacy of vascular tone, usually the result of a self-limiting systemic inflammatory response syndrome (SIRS), calls for the right amount of chemical and mechanical support. NIV can play an adjunct role, in this aspect of mechanical support, and this usually happens during a critical time in the postoperative process.

38.3.5.2 Acute Pulmonary Edema After Extubation

Discontinuation of mechanical ventilatory support after cardiac surgery can often nullify the beneficial effects of positive pressure ventilation, and in some patients, this can lead to a weaning-induced cardiac failure.

The complex cardiovascular and hemodynamic changes underlying the occurrence of weaning-induced cardiac failure [14, 15] can be summarized as decrease in intrathoracic pressure, increase in work of breathing, and increase in sympathetic tone [16].

Discontinuation from mechanical ventilation changes the intrathoracic pressure from positive to negative. This in turn increases the pressure gradient for venous return, thereby causing an increase in RV preload. Consequently, there is a rise in RV cardiac output, in turn causing an increase in LV preload.

The decrease in intrathoracic pressure also causes an increase in the transmural pressure gradient across the LV, which then leads to an increase in LV afterload, i.e., the pressure generated by the LV to eject the blood out of the thorax.

As noted earlier in this chapter, the increase in the work of breathing, which is worsened in the case of respiratory failure, could pose a problem, as the huge amounts of oxygen consumed by the respiratory muscles can impair the oxygenation of critical organs.

Sympathetic tone increases as a response to the emotional stress and potentially by hypercapnia and hypoxia, which in turn could raise the systemic arterial pressure and thus the LV afterload. It can also increase the respiratory rate and worsen work of breathing.

It has been well recognized that patients with preexisting LV systolic dysfunction can be particularly at risk for developing cardiac failure after extubation. In addition, studies have also shown that the presence of LV diastolic dysfunction at baseline is associated with an increased risk of weaning-induced cardiac failure [17]. This particular study hypothesized that the inability of the rate of LV relaxation could be further enhanced during spontaneous breathing trials, thus playing an important role in weaning failure.

38.3.5.3 NIV for Acute Pulmonary Edema in Postoperative Cardiac Surgery

Studies so far, evaluating the beneficial effects of NIV in acute cardiogenic pulmonary edema (ACPE), were not limited to patients in the postoperative phase of cardiac surgery. A recent Cochrane database review evaluating the safety and efficacy of NIV compared to standard medical care in ACPE included patients presenting to the emergency department as well as inpatients in the intensive care setting [18]. NIV included both CPAP and BiPAP modes, and there was no differentiation between the two when evaluating the results. The authors concluded that their review provides support for continued clinical application of NIV for ACPE, to improve outcomes such as hospital mortality and intubation rates. NIV was found to be a safe intervention with similar adverse event rates to standard medical care alone.

38.3.5.4 Acute Right Ventricular Dysfunction After Cardiac Surgery

There is a need to briefly elaborate on acute right ventricular (RV) dysfunction, as a specific entity, in postoperative cardiac surgery patients and its interplay with the pulmonary system.

Compared to the left ventricle (LV), RV is thin walled and more compliant and is better suited to accommodate significant increases in preload but tolerates acute increases in afterload poorly. The starting point of acute RV dysfunction, when it happens in the postoperative cardiac surgery patient, is usually the result of volume or pressure overload in the right ventricle. This, in turn, leads to decreased RV contractility, which by a serial effect, causes a decrease in left ventricular (LV) preload, thereby setting the stage for low cardiac output, hypoperfusion, and eventual multiorgan failure.

In patients who became hemodynamically unstable after cardiac surgery, acute RV dysfunction was present in almost half of those affected. Factors that may be implicated are (a) long cardiopulmonary bypass time, (b) right coronary embolism or bypass graft occlusion—may be transient, but significant, if not de-aired adequately at the conclusion of the operation, (c) inadequate myocardial protection during surgery, (d) reperfusion lung injury with secondary pulmonary hypertension (PHT), (e) protamine-induced PHT, (f) atrial arrhythmias with loss of atrioventricular synchrony, and (g) preexisting pulmonary vascular disease [19, 20].

38.3.5.5 Rationale for NIV in Postoperative Ventricular Dysfunction

Unfortunately, there have been no reliable studies done so far, with regard to the effect of NIV on cardiac function, in the postoperative phase of cardiac surgery. But observational and anecdotal findings suggest that, in the right patient, NIV may help to alleviate some of the early problems seen with cardiac function, particularly in cases of right ventricular (RV) dysfunction. Postoperative RV dysfunction is usually transient, and the standard of care is to support the RV with optimal loading conditions with the use of pressors and inotropes as well as diuresis depending on volume status. However, in the extubated patient, especially in the obese and morbidly obese, and in those who are at risk for developing atelectasis, hypoxia, or hypercarbia, NIV could serve as a valuable tool in helping to prevent further deterioration of the situation.

PEEP can modify PVR and thereby RV afterload, by several mechanisms. It may reduce PVR by reducing the increased pulmonary vasomotor tone due to hypoxic pulmonary vasoconstriction. By recruiting collapsed alveoli, it can increase regional alveolar pO_2, thereby reducing hypoxic pulmonary vasoconstriction, which then causes a fall in pulmonary vasomotor tone and consequently increasing RV ejection or output [21, 22]. However, in the volume-depleted patient, addition of PEEP could be counterproductive as it can cause a fall in preload.

Cardiac surgical patients with preexisting pulmonary hypertension pose a specific risk postoperatively, especially in the early postoperative phase. After extubation, hypoxia, hypercarbia, acidosis, and fluid overload can all contribute to increased pulmonary vascular resistance.

Consequently, this can lead to increased RV afterload, in turn reducing the left ventricular (LV) preload, and thereby causing a fall in cardiac output (CO). Use of NIV, specifically bi-level support, as long as the PEEP is titrated against desirable hemodynamic parameters, can be hypothesized to mitigate this situation.

38.4 Timing and Application of NIV in Preventing or Attenuating Acute RV Dysfunction

The prevention of acute RV dysfunction after cardiac surgery begins with the identification of high-risk patients. Once identified, treatment should be aimed at treating any underlying reversible causes that are either primarily responsible or contributing to the progressive impairment of RV function.

As stated earlier, and illustrated in Fig. 38.1, in the postsurgical cardiac surgery patient, hypoxia, hypercarbia, atelectasis, and acidosis all contribute to increasing pulmonary vascular resistance, thereby affecting RV afterload. NIV used prophylactically or early during the onset of RV impairment should help to prevent or reverse these inciting factors. It is very important to note that while NIV can serve as an important adjunct while treating these patients, reversal of underlying factors, whether it's the volume status, need for inotrope, or pressor support, should be pursued aggressively for an optimal outcome.

Typically, in this patient population, a bi-level support, rather than continuous positive airway pressure (CPAP), is preferred. An inspiratory pressure support level, tolerable for the patient, is chosen, and PEEP is maintained at a low level, for example, at 5–10 cmH_2O. A general starting point would be a bi-level support of 10/5, with the FiO_2 titrated against a target oxygenation level. The duration of NIV in these patients can be individualized to patient tolerance and can be either a few hours at a time or continuous if applied during nighttime or sleeping hours. The difference in inspiratory and expiratory pressure settings can be titrated to the primary problem at

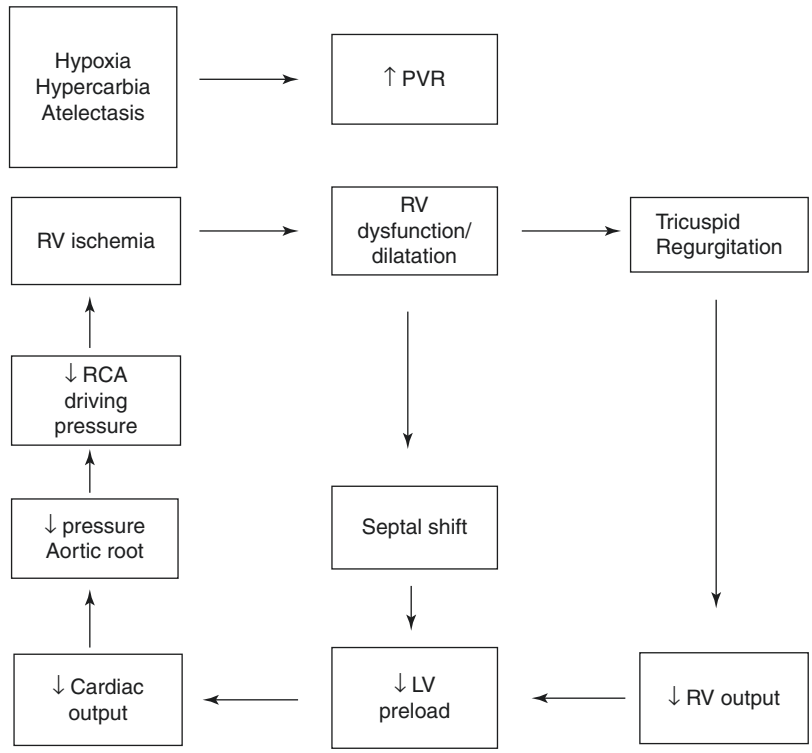

Fig. 38.1 Postoperative causes of right ventricular decompensation and role of pulmonary vascular resistance. *PVR* pulmonary vascular resistance, *RCA* right coronary artery

hand, that's targeted. For instance, if it's hypercarbia that's being treated, the inspiratory pressure can be dialed up slowly while PEEP is kept low. If, on the other hand, it's hypoxia, a combination of adequate FiO_2 and a PEEP level that doesn't affect the afterload adversely should be chosen.

38.5 Hemodynamic Implications with Positive Pressure Ventilation

Any discussion on positive pressure ventilation, in a postoperative cardiac surgery patient, is not complete without taking into effect its hemodynamic ramifications. As mentioned before, hemodynamic profile after cardiac surgery usually follows a dynamic pattern with changes that follow a recovering heart, whether it's healing from ischemia, after coronary bypass surgery, or regulating chamber pressures and volume after valve surgery. Adding to this is the recovery of vascular tone that can be severely affected by the cardiopulmonary bypass machine, which initiates a SIRS response that can vary greatly between individual patients.

Since the classic studies of Cournand et al., it's a well-known fact that PEEP usually decreases the cardiac output (CO), except in the failing ventricle [23]. They concluded that positive pressure ventilation, by causing elevated intrathoracic pressure, restricts venous flow into the thorax, thereby limiting RV filling and, as a serial consequence, reduced CO. As heart rate usually remains stable with PEEP [24], the entire fall in CO is a consequence of a reduction in LV stroke volume. Therefore, the discussion on PEEP-induced changes in CO can be limited to analyzing changes in stroke volume and its determinants: preload, afterload, contractility, and ventricular compliance.

An investigational study by Francois F et al., comparing the hemodynamic effects of BiPAP with CPAP in patients with or without heart failure, found pulmonary capillary wedge pressure (PCWP) to be the main determinant of cardiac output [25]. Patients with PCWP >12 showed an increase in CO, while those with lower PCWP had a decrease in the same. Yet another study by Bradley et al. arrived at the same conclusion [26]. Using low CPAP pressures (5 cmH_2O), in patients with high PCWP, they found an increase in CO and stroke volume. Extrapolating from these observations, one can safely deduce that, in the volume loaded cardiac surgical patients, NIV is a safe modality when indicated, with its benefits clearly outweighing the risks.

38.6 Summary

NIV can be safely utilized in the immediate postoperative period after cardiac surgery. With its many benefits, in alleviating the potential for pulmonary dysfunction that's frequently seen in these patients, it is both cost-effective and can be used both in prophylactic and curative ways. Lacking studies that are done on cardiac surgical patients so far, specifically looking at the implications for cardiac function, use of NIV in cardiac decompensation is an open topic. Suffice it to say, when hemodynamic challenges develop after cardiac surgery, especially when it's directly related to pump failure, NIV should only be thought of as an intervention that plays a supporting role while aggressively pursuing established treatment guidelines to reverse the situation. The complex hemodynamic interactions with various levels of positive pressure that's applied, which could be beneficial to the impaired left heart but less favorable to the diseased right side, require an expertly skilled team with continuous hemodynamic monitoring and echocardiographic assessment.

References

1. Duggan M, Kavanagh BP. Pulmonary atelectasis. A pathogenic perioperative entity. Anesthesiology. 2005;102:838–54.
2. Simonneau G, Vivien A, Sartene R, et al. Diaphragm dysfunction induced by upper abdominal surgery. Role of postoperative pain. Am Rev Respir Dis. 1983;128:899–9033.

3. Weissman C. Pulmonary complications after cardiac surgery. Semin Cardiothorac Vasc Anesth. 2004;8(3):185–211.
4. Huffmyer JL, Groves DS. Pulmonary complications of cardiopulmonary bypass. Best Pract Res Clin Anaesthesiol. 2015;29(2):163–75.
5. Matte P, Jaquet L, Van Dyck M, Goenen M. Effects of conventional physiotherapy, continuous positive airway pressure and non-invasive ventilatory support with bilevel positive airway pressure after coronary artery bypass grafting. Acta Anaesthesiol Scand. 2000;44(1):75–81.
6. Zarbock A, Mueller E, Netzer S, Gabriel A, Feindt P, Kindgen-Milles D. Prophylactic nasal continuous positive airway pressure following cardiac surgery protects from postoperative pulmonary complications: a prospective, randomized, controlled trial in 500 patients. Chest. 2009;135(5):1252–9.
7. Franco AM, Torres FC, Simon IS, Morales D, Rodrigues AJ. Assessment of noninvasive ventilation with two levels of positive airway pressure in patients after cardiac surgery. Rev Bras Cir Cardiovasc. 2011;26(4):582–90.
8. Wong WT, Lai VK, Chee YE, et al. Fast-track cardiac care for adult cardiac surgical patients. Cochrane Database Syst Rev. 2016;9:CD003587.
9. Subramaniam K, DeAndrade D, Mandell D, Althouse AD, Manmohan R, Esper SA, et al. Predictors of operating room extubation in adult cardiac surgery. J Thorac Cardiovasc Surg. 2017;154:1656–65.
10. Arenson BG, MacDonald LA, Grocott HP, Hiebert BM, Arora RC. Effect of intensive care unit environment on in-hospital delirium after cardiac surgery. J Thorac Cardiovasc Surg. 2013;146:172–8.
11. Heringlake M, Nowak Y, Schön J, Trautmann J, Berggreen AE, Charitos EI, Paarmann H. Postoperative intubation time is associated with acute kidney injury in cardiac surgical patients. Crit Care. 2014;18(5):547.
12. Suematsu Y, Sato H, Ohtsuka T, Kotsuka Y, Araki S, Takamoto S. Predictive risk factors for delayed extubation in patients undergoing coronary artery bypass grafting. Heart Vessels. 2000;15(5):214–20.
13. Rady MY, Ryan T, Starr NJ. Early onset of acute pulmonary dysfunction after cardiovascular surgery: risk factors and clinical outcome. Crit Care Med. 1997;25(11):1831–9.
14. Teboul JL, Monnet X, Richard C. Weaning failure of cardiac origin: recent advances. Crit Care. 2010;14:211.
15. Teboul JL. Weaning-induced cardiac dysfunction: where are we today? Intensive Care Med. 2014;40:1069–79.
16. Dres M, Teboul JL, Monnet X. Weaning the cardiac patient from mechanical ventilation. Curr Opin Crit Care. 2014;20(5):493–8.
17. Moschietto S, Doyen D, Grech L, et al. Transthoracic echocardiography with Doppler tissue imaging predicts weaning failure from mechanical ventilation: evolution of the left ventricle relaxation rate during a spontaneous breathing trial is the key factor in weaning outcome. Crit Care. 2012;16:R81.
18. Berbenetz N, Wang Y, Brown J, Godfrey C, Ahmad M, Vital FM, Lambiase P, Banerjee A, Bakhai A, Chong M. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database Syst Rev. 2019;5:4.
19. Vlahakes GJ. Right ventricular failure after cardiac surgery. Cardiol Clin. 2012;30(2):283–9.
20. Haddad F, Couture P, Tousignant C, Denault AY. The right ventricle in cardiac surgery, a perioperative perspective: II. pathophysiology, clinical importance, and management. Anesth Anal. 2009;108(2):423–33.
21. Marshall BE, Marshall C, Frasch F, Hanson CW. Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. 1. Physiologic concepts. Intensive Care Med. 1994;20:291–7.
22. Marshall BE, Hanson CW, Frasch F, Marshall C. Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. 2. Pathophysiology. Intensive Care Med. 1994;20:379–89.
23. Cournand A, Motley HL, Werko L, Richards D. Physiological studies on the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol. 1948;152:162–74.
24. Viquerat CE, Righetti A, Suter PM. Biventricular volumes and function in patients with adult respiratory distress syndrome ventilated with PEEP. Chest. 1983;83:509–14.
25. Philip-Joet FF, Paganelli FF, Dutau HL, Saadjian AY. Hemodynamic effects of Bilevel nasal positive airway pressure ventilation in patients with heart failure. Respiration. 1999;66:136–43.
26. Bradley TD, Holloway RM, McLaughlin PR, Ross BL, Walters J, Liu PP. Cardiac output response to continuous positive airway pressure in congestive heart failure. Am Rev Respir Dis. 1992;145:377–82.

Noninvasive Ventilation in Postoperative Patients

39

Habib Md Reazaul Karim, Margarita Oks, and Anup Singh

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Abbreviations

ARF	Acute respiratory failure
BPAP	Bi-level positive airway pressure
CABG	Coronary artery bypass graft
CPAP	Continuous positive airway pressure
FRC	Functional residual capacity
HFNO	High-flow nasal oxygen
ICU	Intensive care unit
IMV	Intermittent mechanical ventilation
NIV	Noninvasive ventilation
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
PPC	Postoperative pulmonary complications
RCT	Randomized control trial

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39.1 Introduction

General anesthesia causes physiological changes after surgery. There is a decrease in muscle tone in the upper airway with decreased airway reflexes which, when coupled with a reduction in tidal volume and respiratory rate, leads to a reduction in the minute ventilation. This leads to hypercarbia and hypoxemia. Hypoxemia is exaggerated by a decrease in the functional residual capacity (FRC). This is also confounded by an increase in the closure of the small airways of the lung which leads to dead space and shunt. Noninvasive ventilation (NIV) is gaining popularity for both the treatment and prevention of acute respiratory failure (ARF) in postoperative patients [1]. Postoperative pulmonary complications (PPC) can also affect patients' outcome in terms of morbidity, mortality, and economic burden [2, 3]. Therefore, prevention of PPCs is essential. This chapter aims to consolidate current knowledge regarding NIV use in the postoperative period. We will focus

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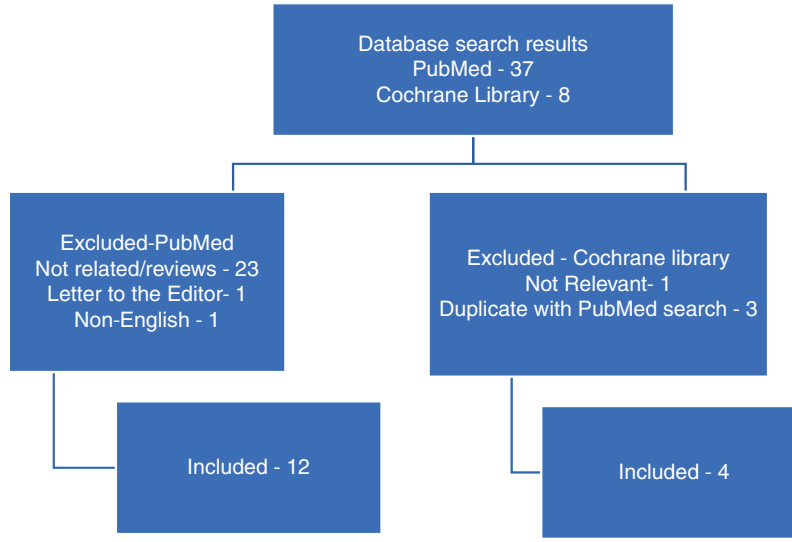

Fig. 39.1 Literature search strategy

on NIV use after abdominal, thoracoabdominal, and cardiac surgeries.

Electronic databases including PubMed and the Cochrane library were searched to find recent literature related to noninvasive ventilation in the postoperative period. The index words "noninvasive ventilation," "postoperative," "noninvasive ventilation postabdominal surgery," "noninvasive ventilation post cardiac surgery," and "noninvasive ventilation post-thoracoabdominal surgery" were used. Published articles between January 2005 and March 2019 were of interest for review preparation. A systematic search for recent literature was done for the period of January 2017 to March 2019. Clinical studies, systematic reviews, and meta-analyses were included. Only studies in English were considered. The search strategy flow chart is presented in Fig. 39.1.

39.2 Content

Surgery can exacerbate the sequelae of anesthesia because of the involvement of the diaphragm and abdominal wall. Postoperative pulmonary complications are highest after abdominal surgery, the most common of which is respiratory failure. Postoperative respiratory failure is defined as the need for mechanical ventilation for more than 48 h after surgery or requiring mechanical ventilation after extubation. Abdominal surgery is associated with the highest rate of postoperative pulmonary complications with up to 50% of patients affected. Postoperative pulmonary complications are associated with longer hospital stays and higher inpatient mortality [3]. Noninvasive ventilation is an essential tool in the prevention and even management of postoperative respiratory failure, as well as other complications.

Several studies have evaluated NIV use as a prophylactic and therapeutic measure for postoperative respiratory failure in the abdominal surgical population. While NIV use has been shown to improve postoperative oxygenation, reduce intensive care unit length of stay, decrease the rates of pneumonia, reduce atelectasis, and reduce intubation rates, there have been no studies that show a definitive mortality benefit [4–6]. It is important to note that in patients undergoing bariatric surgery, in whom obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS) are highly prevalent, NIV use may actually have a mortality benefit [7]. Likewise, intensive care unit mortality as a result of postoperative respiratory failure after liver, kidney, and lung solid organ transplantation may be reduced with NIV use [8, 9]. The most relevant and recent trials targeting NIV use after abdominal surgery are summarized in Table 39.1.

Table 39.1 Summary table of studies investigating noninvasive ventilation use after abdominal surgery

Study authors, year	Study population	Intervention	Outcomes/considerations
Squadrone et al. (2005) [4]	∗ Randomized, controlled, unblinded ∗ Patients with hypoxemia after abdominal surgery	∗ Oxygen (n = 104) versus Oxygen plus CPAP (n = 105)	∗ Reduction in intubation rate, pneumonia incidence, infection, sepsis with O_2/CPAP use ∗ Reduced ICU length of stay; no effect on hospital length of stay with O_2/CPAP use
El Solh et al. (2006) [7]	∗ Prospective, single-center, case-control ∗ ICU patients, with BMI >35 kg/m^2	∗ Conventional oxygen support versus NIV use immediately after successful weaning trial/extubation (n = 62)	∗ 16% ARR in reintubation with NIV use ∗ Reduction in respiratory failure in hypercarbic obese patients with NIV use ∗ Shorter ICU and hospital lengths of stay in the NIV group ∗ Reduced mortality in the hypercarbic subgroup with NIV use ∗ BPAP ST and S modes used, starting IPAP/EPAP of 12/4 cmH_2O (range IPAP 12–26, range EPAP 5–12) ∗ Mean use of BPAP was 16.2 ± 2.6 h/day
Glossop et al. (2012) [8]	∗ Meta-analysis; 16 randomized-controlled studies ∗ Varied (thoracic, abdominal thoracoabdominal, and solid transplant surgical populations)	∗ Three NIV cohorts: (1) NIV use in weaning; (2) NIV use in post-ICU extubation; (3) NIV use immediately post-surgery	∗ Reduced ICU length of stay, pneumonia, and reintubation rates with NIV use ∗ Increased hospital survival, not ICU survival, was noted with NIV use ∗ CPAP and other NIV modalities were grouped together
Ireland et al. (2014) [6]	∗ Meta-analysis, (Cochrane): ten studies; randomized control trials ∗ Elective or emergent major abdominal surgery	∗ Postoperative CPAP use as a preventative measure of major pulmonary complications and death after abdominal surgery	∗ Mortality benefit with CPAP use not determined because of study heterogeneity ∗ BPAP use was an exclusion criterion ∗ Reduction in atelectasis, pneumonia, and reintubation rates seen with CPAP use ∗ No reduction in severe hypoxemia with CPAP use
Das Faria et al. (2016) [5]	∗ Meta-analysis (Cochrane): two studies, randomized controlled trials ∗ Laparotomy cases ∗ Upper abdominal surgery	∗ Postoperative NIV (CPAP and BPAP) efficacy in acute respiratory failure as compared to conventional oxygen supplementation	∗ Reduction in intubation with NIV use ∗ Possible reduction in hospital length of stay with NIV use ∗ Inconclusive on whether NIV causes an anastomotic leak, reduces pneumonia-related complications and infections ∗ CPAP and BPAP
Jaber et al. (2016) [9]	∗ Multicenter, randomized, parallel-group clinical trial ∗ Elective and emergency abdominal surgery cases ∗ Most laparotomies	∗ Oxygen therapy (n = 150) versus NIV (n = 150) in preventing reintubation within 7 days, decreasing 90-day mortality, infections, ventilation-free days, and gas exchange	∗ Reduced intubation, infection incidence with NIV use ∗ Trend toward lower mortality in the NIV group ∗ BPAP: IPAP 5–15 cmH_2O, EPAP 5–10 cmH_2O

Numerous studies have addressed NIV use in the cardiac and thoracoabdominal populations (see Table 39.2). The study conducted by Mamo found that the composite outcome of postoperative pulmonary complications and ICU admission was very low with postoperative NIV use as compared to standard management, i.e., 2% vs. 57%; *P* 0.002 [10]. Stephan, in a post hoc analysis of an RCT, comparing HFNO versus NIV, found no significant difference in ICU mortality between the groups, 5.9% vs. 2.2%, respectively; *P* 0.22 [11]. The same study also found that the treatment failure rate in the NIV group was 13.3% vs. 15.4% in the HFNO group; *P* 0.62 [11]. Yu Y, comparing HFNC and conventional face mask oxygenation, found a significantly decreased rate of reintubation and treatment failure in HFNO group as compared to traditional oxygen therapy ($P < 0.05$) [12].

Interestingly, in this study use of IMV, and CPAP, BiPAP was used as a rescue treatment even for HFNC. The study by Zochios examined

Table 39.2 Summary table of studies investigating noninvasive ventilation use after thoracoabdominal surgery

Study authors, year	Study population	Intervention	Outcomes/considerations
Mamo et al. (2019) [10]	40 patients who underwent elective thoracoabdominal aortic surgery open repair	Prophylactic NIV	Prophylactic NIV prevents postoperative pulmonary complications
Marcondi et al. (2018) [17]	100 postoperative coronary artery bypass graft patients with left ventricular dysfunction	Postoperative NIV for 1 h after extubation	Useful in improving central venous oxygen saturation and decreasing blood lactate level
Elgebaly et al. (2018) [14]	44 postoperative cardiac surgical patients with acute respiratory failure	Therapeutic intermittent positive pressure ventilation versus NIV	NIV was safe and effective, but IPPV was superior to the NIV
Stephan et al. (2017) [11]	271 postoperative cardiothoracic patients total with obesity	NIV versus high-flow nasal oxygen therapy	Although the failure rate was higher in HFNO, it was not statistically different
Yu et al. (2017) [12]	110 postoperative thoracoscopic lobectomy patients	HFNO versus conventional oxygen therapy	HFNO improves oxygenation and reintubation rate
Olper et al. (2017) [16]	64 post-cardiac surgical patients with hypoxemia in the ward	CPAP versus standard oxygen therapy	CPAP was associated with improved respiratory outcome
Cavalcanti et al. (2018) [15]	50 obese adult postoperative Roux-en-Y gastric bypass patients	Preventive NIV versus control	NIV group had faster recovery, fewer postoperative complications
Zochios et al. (2018) [13]	100 Adult patients with preexisting respiratory disease undergoing elective cardiac surgery	Prophylactic postoperative HFNO versus conventional oxygen therapy	HFNO reduced hospital stay and ICU readmissions
Ferrand et al. (2019) [18]	91 neonates who underwent esophageal atresia-tracheoesophageal fistula repair	Postoperative NIV	NIV was associated with a significantly higher risk of anastomotic leak and mediastinitis
Pieczkoski et al. (2017) [20]	Systematic review and meta-analysis	Postoperative NIV in cardiac surgical patients	Prophylactic NIV did not significantly reduce the occurrence of pulmonary complications, reintubation rate, and ICU-LOS
Zhu et al. (2016) [21]	Systematic review and meta-analysis	Efficacy and safety of NIV in the cardiothoracic surgical population as compared to conventional management	Reduction in reintubation rates and improvement in oxygenation with NIV use

the effect of prophylactic HFNC oxygenation as compared to standard oxygenation by face mask in postoperative cardiac surgical patients [13]. The authors found that there was a 29% reduction in the length of stay; *P* 0.004 [13]. Use of prophylactic HFNC oxygenation was also associated with decreased ICU readmission; *P* 0.026. However, the study by Elgebaly did not find a significant difference in hospital or ICU stay among the IMV versus NIV group [14]. The study by Cavalcanti et al. also found no difference in hospital and ICU stay and ICU stay after Roux-en-Y surgery between NIV and control group [15].

Elgebaly found that oxygenation (PaO_2 and SpO_2) and ventilation were better in the IMV group as compared to the NIV in cardiac patients [14]. Olper examined the efficacy of CPAP in improving hypoxemia in postoperative cardiac surgery patients as compared to standard treatment with oxygen supplementation with a face mask and found that the PaO_2/FiO_2 was better in the CPAP group; *P* 0.003 [16]. Yu investigated the effect of HFNC and conventional face mask oxygenation on reducing hypoxemia and PPC in postoperative thoracoscopic lobectomy surgery patients [12]. The authors found that PaO_2, PaO_2/FiO_2, and SaO_2/FiO_2 were significantly improved in HFNO group as compared to conventional oxygen therapy ($P < 0.05$). Marcondi applied NIV after extubation in postoperative CABG patients who had left ventricular dysfunction and compared with those who were spontaneously breathing and found that the central venous oxygen saturation was significantly higher in the NIV group (*P* 0.04), and this effect persisted even after discontinuation of NIV [17]. The authors also found that global perfusion as measured by serum lactate was also significantly better (*P* 0.008) with NIV in this group of patients.

The study by Cavalcanti et al. found that the spirometric respiratory parameters were better in obese patients using prophylactic NIV after Roux-en-Y surgery, especially on the first postoperative day [15]. Elgebaly AS including postoperative cardiac surgical patients did not find a significant difference in the complication rates among the IMV versus NIV group [14]. The study conducted by Stephan, however, found increased pressure-related skin breakdown in the NIV group as compared to the HFNO group; *P* 0.01 [11]. A retrospective chart review by Ferrand found that use of NIPPV was associated with increased risk of mediastinitis (*P* 0.005), and use of HFNC was associated with increased risk of anastomotic leak and mediastinitis in the patient who underwent esophageal atresia-tracheoesophageal fistula repair [18]. However, Cavalcanti found no significant increase in anastomotic ulcers in the NIV group as compared to the standard treatment group in patients who underwent Roux-en-Y surgery [15]. Postoperative complications such as pneumonia and atelectasis were significantly less in the NIV group in the same study. A recent case report also suggests the development of acute parotitis as a complication of postoperative NIV [19].

References

1. Jaber S, De Jong A, Castagnoli A, Futier E, Chanques G. Non-invasive ventilation after surgery. Ann Fr Anesth Reanim. 2014;33(7-8):487–91. https://doi.org/10.1016/j.annfar.2014.07.742.
2. Warner DO. Preventing postoperative pulmonary complications: the role of the anesthesiologist. Anesthesiology. 2000;92(5):1467–72.
3. Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010;113:1338–50.
4. Squadrone V, Coha M, Cerutti E, Schellino MM, Biolino P, Occella P, Belloni G. Continuous positive airway pressure for treatment of postoperative hypoxemia. JAMA. 2005;293:589–95.
5. Faria DA, da Silva EM, Atallah ÁN, Vital FM. Noninvasive positive pressure ventilation for acute respiratory failure following upper abdominal surgery. Cochrane Database Syst Rev. 2015;(10):CD009134. https://doi.org/10.1002/14651858.CD009134.pub2.
6. Ireland CJ, Chapman TM, Mathew SF, Herbison GP, Zacharias M. Continuous positive airway pressure (CPAP) during the postoperative period for prevention of postoperative morbidity and mortality following major abdominal surgery. Cochrane Database Syst Rev. 2014;8:CD008930. https://doi.org/10.1002/14651858.CD008930.pub2.
7. El Solh AA, Aquilina A, Pineda L, Dhanvantri V, Grant B, Bouquin P. Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients. Eur Respir J. 2006;28:588–95.

8. Glossop AJ, Shepherd N, Bryden DC, Mills GH. Non-invasive ventilation for weaning, avoiding reintubation after extubation and in the postoperative period: a meta analysis. Br J Anaesth. 2012;109(3):305–14.
9. Jaber S, Lescot T, Futler E, Paugam-Burtz C, Seguin P, Ferrandiere M, Lasocki S, Mimoz O, et al. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: a randomized clinical trial. JAMA. 2016;315(13):1345–53.
10. Mamo D, Zangrillo A, Cabrini L, et al. Noninvasive ventilation after thoracoabdominal aortic surgery: a pilot randomized controlled trial. J Cardiothorac Vasc Anesth. 2019;33(6):1639–45. https://doi.org/10.1053/j.jvca.2018.10.041.
11. Stéphan F, Bérard L, Rézaiguia-Delclaux S, Amaru P, BiPOP Study Group. High-flow nasal cannula therapy versus intermittent noninvasive ventilation in obese subjects after cardiothoracic surgery. Respir Care. 2017;62(9):1193–202. Epub 2017 Aug 14. https://doi.org/10.4187/respcare.05473.
12. Yu Y, Qian X, Liu C, Zhu C. Effect of high-flow nasal cannula versus conventional oxygen therapy for patients with thoracoscopic lobectomy after extubation. Can Respir J. 2017;2017:7894631. https://doi.org/10.1155/2017/7894631.
13. Zochios V, Collier T, Blaudszun G, et al. The effect of high-flow nasal oxygen on hospital length of stay in cardiac surgical patients at high risk for respiratory complications: a randomised controlled trial. Anaesthesia. 2018;73(12):1478–88. https://doi.org/10.1111/anae.14345.
14. Elgebaly AS. Does bilevel positive airway pressure improve outcome of acute respiratory failure after open-heart surgery? Ann Card Anaesth. 2017;20(4):416–21. https://doi.org/10.4103/aca.ACA_95_17.
15. Cavalcanti MGO, Andrade LB, Santos PCPD, Lucena LRR. Non-invasive preventive ventilation with two pressure levels in the postoperative period of roux-en-y gastric bypass: randomized trial. Arq Bras Cir Dig. 2018;31(1):e1361. https://doi.org/10.1590/0102-672020180001e1361.
16. Olper L, Bignami E, Di Prima AL, et al. Continuous positive airway pressure versus oxygen therapy in the cardiac surgical ward: a randomized trial. J Cardiothorac Vasc Anesth. 2017;31(1):115–21. Epub 2016 Aug 10. https://doi.org/10.1053/j.jvca.2016.08.007.
17. Marcondi NO, Rocco IS, Bolzan DW, et al. Noninvasive ventilation after coronary artery bypass grafting in subjects with left-ventricular dysfunction. Respir Care. 2018;63(7):879–85. Epub 2018 Jun 12. https://doi.org/10.4187/respcare.05851.
18. Ferrand A, Roy SK, Faure C, Moussa A, Aspirot A. Postoperative noninvasive ventilation and complications in esophageal atresia-tracheoesophageal fistula. J Pediatr Surg. 2019;54(5):945–8. pii: S0022-3468(19)30060-0. [Epub ahead of print]. https://doi.org/10.1016/j.jpedsurg.2019.01.023.
19. Martinez E, Dicpinigaitis PV. Development of acute parotitis after non-invasive ventilation. J Thorac Dis. 2017;9(7):E605–8. https://doi.org/10.21037/jtd.2017.06.86.
20. Pieczkoski SM, Margarites AGF, Sbruzzi G. Noninvasive ventilation during immediate postoperative period in cardiac surgery patients: systematic review and meta-analysis. Braz J Cardiovasc Surg. 2017;32(4):301–11. https://doi.org/10.21470/1678-9741-2017-0032.
21. Zhu G, Huang Y, Wei D, Shi Y. Efficacy and safety of noninvasive ventilation in patients after cardiothoracic surgery: a PRISMA-compliant systematic review and meta-analysis. Medicine. 2016;95(38):e4734. https://doi.org/10.1097/MD.0000000000004734.

40 Application of Noninvasive Ventilation in the Obstetrical Patient

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40.1 Introduction

It is found that 9.1% of obstetric ICU admissions are due to pulmonary complications with the most common reasons being secondary to respiratory failure from asthma, pneumonia, cystic fibrosis, pulmonary edema, pulmonary embolism, acute respiratory distress syndrome (ARDS), and amniotic fluid embolism (Table 40.1) [1]. Acute respiratory failure (ARF) in pregnancy occurs in less than 0.1% [2] of pregnant patients, but is considered one of the most common indications for obstetric admissions into the intensive care units and cause for maternal and fetal mortality to be as high as 14% and 11% respectively [3, 4]. These are risks that are predisposed in these patients due to the anatomic and physiologic changes in the respiratory system that can affect overall management. Respiratory failure in pregnancy may be due to pregnancy-specific disease or exacerbation of previously existing respiratory disease.

In the pregnant patient, it is well described that intubation failure is eight times more common [5] with an incidence of fatal failed intubation to be 13 times higher when compared to the non-parturient [6, 7]. As a result, noninvasive modalities such as noninvasive positive pressure ventilation (NIPPV) and high-flow nasal canula (HFNC) can be considered to avoid the potential complications of endotracheal intubation and

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Table 40.1 Most common causes of respiratory failure in pregnancy

Asthma
Pulmonary infections
Pulmonary edema
Thromboembolic disease
Amniotic fluid embolism
ARDS
Restrictive lung disease
Aspiration

associated sedation protocols given that for its use will require the patient to be able to protect her airway, clear secretions, and co-operate.

The purpose of this review is to explore the literature and describe the utilization of NIV in the obstetrical patient.

40.2 Physiological and Anatomical Changes in Pregnancy

The phenomenon of pregnancy imposes many changes in the cardiorespiratory system that is needed to meet the increased demands induced by the gravid uterus. To meet the hormonal and metabolic requirements for both the mother and the fetus during gestational advancement, anatomical adaptations (in the upper airway, chest wall, diaphragm) and alterations in respiratory function (lung volumes, ventilation and gas exchange relationships) need to take place. In the critical care setting, understanding these physiologic adjustments will allow to discern between "normal physiologic dyspnea" in a pregnant patient from other more pathological entities.

40.2.1 Upper Respiratory Tract Changes

In the upper respiratory system, during pregnancy some of the histological changes in the mucosa that occur include hyperemia, glandular hyperactivity, increased phagocytic activity, and increased mucopolysaccharide content which was demonstrated by Toppozada et al. in 1982 [8]. These are changes that can be associated with edema and friability which often may cause nasal congestion and epistaxis also known as gestational rhinitis that occurs in the last few weeks of pregnancy and resolve after delivery [9]. This process is found to occur in 20–30% of pregnant patients [10, 11] and is theorized to be from the result of increasing levels of estrogen [12] and placental growth hormone. It is an entity that is clinically defined as "nasal congestion" lasting over 6 weeks during pregnancy without any evidence of respiratory tract infection or allergic cause. Increases in mucosal edema of the upper airway can lead to other consequences. Sleep-disordered breathing and snoring [13] can potentially contribute to maternal-fetal complications such as hypertension and preeclampsia through the reduced levels of inhaled nitric oxide (NO). Physiologically, as reviewed by Lungberg et al. [14], NO is primarily produced in the maxillary sinuses, and the nasal congestion and/or obstruction can lead to mouth breathing, resulting in decreased concentrations of the potent mediator of pulmonary vascular tone.

Increase in neck circumference [15] and decreases in the oropharyngeal junction size, leading to increases in mallampati scores [16], are adjustments that should also be understood. Factors that can potentially contribute to these modifications are described by White et al, where reduced volumes, particularly functional residual capacity (FRC), and fat infiltration of the upper airway can affect airway collapsibility [17]. During the course of pregnancy, it is found that patients can gain an average of 25–35 pounds, however similar to White and colleagues, Iczi et al. [15] also theorize that a decrease in airway patency is not related to the patient's body mass index but to the changes in FRC or changes in the upper airway interstitial fluid dynamics or edema. Overall, as a result of these upper airway changes from upper airway congestion and obstruction, this can contribute to difficulties in airway management which may lead to complicated nasogastric tube insertions and a higher risk of failed endotracheal intubations in pregnant patients.

40.2.2 Respiratory Function Changes

In pregnancy, the major effect occurs mostly in lung volumes while spirometry remains relatively unchanged. The forced expiratory volume (FEV1) was extensively studied in the pregnant population in the 1970s and 1980s, as it is a helpful measurement for evaluating patients with obstructive lung diseases, and was found to be unchanged [18]. In addition, the peak expiratory flow rate, a function of the large airway caliber, and forced expiratory flow at 50% and 25% (FEF 25–50) of vital capacity, which is representative of the small airway caliber, were also found to be unchanged demonstrated by the findings of Baldwin et al. [19] and Gazioglu et al. [20]. This coincides with the findings of Cugell et al. [21] and Ihrmann et al. [22], where the overall airway mechanics and respiratory muscle strength were found to be unchanged during pregnancy. As a result, spirometry is relatively stable during pregnancy and its interpretation for patients with obstructive diseases with asthma or COPD is unchanged during pregnancy. Therefore, an abnormal spirometry is likely to be from an underlying respiratory disease and not a sequela of pregnancy.

Total lung capacity is found to be unchanged or minimally decreased. As seen in Table 40.2, the function residual capacity (FRC), the addition of the expiratory reserve volume (ERV) and reserve volume (RV), is found to decrease by 20%, due to the mechanical adaptation of diaphragm elevation which consequently decreases the expiratory reserve volume and residual volume [23]. On the other hand, the inspiratory capacity which comprises of the inspiratory reserve volume (IRV) and tidal volume (TV) increases by 5–10% [24].

Table 40.2 Normal respiratory physiologic changes

Increase	Decrease	No change
IC	FRV (20–30%)	VC
TV (30–50%)	RV (7–22%)	RR
RR	FRC (10–25%)	Peak flow
MV (20–50%)	TLC	FEV1

40.3 Utilization of NIV in Pregnancy During Acute Respiratory Failure

Noninvasive positive pressure ventilation (NIPPV) is referred to ventilation that is delivered without the need for invasive endotracheal intubation, where positive pressure is able to reduce the patient's work of breathing and also improving gas exchange. HFNC is an alternative which also delivers high concentrations of humidified oxygen at a flow rate up to 60L/min with an added benefit of also generating a low positive end expiratory pressure (PEEP = 2–5 cmH_2O) subsequently improving gas exchange and decreasing work of breathing without increasing the risk of barotrauma. Treatment goals during respiratory failure in the pregnant patient are similar to those outside of pregnancy. These goals aim to maintain adequate ventilation and to provide hemodynamic and nutritional support to assist in determining the best timing for delivery, with fetal monitoring, when the mother is in respiratory distress or impending respiratory failure. In the review of the literature, the use of NIPPV and HFNC in pregnant patients with respiratory failure has only been demonstrated in case reports and case series summarized in Table 40.3. These reports convey favorable use of NIPPV and HFNC in a number of clinical scenarios ranging from obstructive lung disease like asthma, neuromusculoskeletal disorders, and in the perioperative/intraoperative setting. NIPPV has also been described to be beneficial for sleep disorders not only in the general population but also during pregnancy [25–27].

Ventilatory failure associated with neuromuscular diseases and severe kyphoscoliosis [28–30] were of the first cases described to utilize NIPPV in the pregnant patient. Kahler et al. [30] described the use of nasal BiPAP starting in the 20th week of gestation which was adapted throughout the pregnancy. This resulted in an improvement in exercise tolerance, fatigue, and nocturnal oxygen desaturations which lead to a successful cesarean section under combined spinal-epidural anesthesia with ongoing

Table 40.3 Summary of noninvasive ventilation use in pregnancy

Author	Year	Design	Modality	Patients (*n*)	Etiology of respiratory failure	Demonstrates benefit of use
Kahler [30]	2002	Case report	NIPPV	1	Ventilatory failure, severe kyphoscoliosis	Yes
Bach [31]	2003	Case series	NIPPV	4	Ventilatory failure, neuromuscular (severe poliomyelitis)	Yes
Diaz-Lobato [32]	2005	Case series	NIPPV	2	Ventilatory failure, neuromuscular (mitochondrial myopathy)	Yes
Reddy [28]	2005	Case report	NIPPV	1	Ventilatory failure, severe kyphoscoliosis	Yes
Terajima [38]	2006	Case report	NIPPV	1	Noncardiogenic pulmonary edema	Yes
Al-Ansari [45]	2007	Case series	NIPPV	4	ARDS, acute chest syndrome	Yes
Perbet [36]	2008	Case report	NIPPV	1	Noncardiogenic associated with tocolytic agents	Yes
Banga [47]	2009	Case report	NIPPV	1	ARDS, community-acquired pneumonia	Yes
Bassani [46]	2009	Case report	NIPPV	1	ARDS/ATRA syndrome	Yes
Yuan [33]	2009	Case report	NIPPV	1	Ventilatory failure, neuromuscular (mitochondrial myopathy)	Yes
Guterres [52]	2010	Case report	NIPPV	1	Ventilatory failure, neuromuscular (high neuraxial blockade)	Yes
Djibre [50]	2010	Case report	NIPPV	1	ARDS, H1N1	Yes
Erdogan [53]	2010	Case report	NIPPV	1	Noncardiogenic pulmonary edema, severe preeclampsia	Yes
Frassanito [48]	2011	Case report	NIPPV	1	ARDS, sepsis	Yes
Rojas-Suarez [39]	2011	Case report	NIPPV	1	Noncardiogenic pulmonary edema, severe preeclampsia	Yes
Duan [34]	2012	Case report	NIPPV	1	Aspiration pneumonia	Yes
Dalar [42]	2013	Case report	NIPPV	1	Community-acquired pneumonia	Yes
Draisci [54]	2013	Case series	NIPPV	2	Ventilatory failure, obstructive lung disease	Yes
Fujita [35]	2014	Case report	NIPPV	1	Noncardiogenic pulmonary edema	Yes
Polin [51]	2015	Case report	NIPPV	1	Intraoperative support for neuraxial blockade	Yes
Jallian [37]	2015	Case report	NIPPV	1	Noncardiogenic pulmonary edema, severe preeclampsia	Yes
Shoji [43]	2017	Case report	HFNC	1	Hypoxic RF due to dermatomyositis related interstitial pneumonia	Yes
Plotnikow [44]	2018	Case report	HFNC	1	Hypoxic RF	Yes

NIPPV. Bach et al. [31] in 2003 reported four cases of continuous NIPPV in three females with poliomyelitis developing chronic respiratory failure and another developing ventilator insufficiency due to severe kyphoscoliosis. In all of these cases, NIPPV was utilized to successfully permit the natural completion of pregnancy. In terms of other neuromuscular diseases, Diaz-Lobato et al. [32] and Yuan et al. [33] echo the successful use of NIPPV involving patients in their third trimester suffering from chronic respiratory insufficiency due to mitochondrial myopathies.

The utilization of NIPPV for hypoxemic respiratory failure has not been proven and at best controversial. Nonetheless, its successful utilization has been described in the parturient developing hypoxemic respiratory failure, where causes can range from pneumonia [34] to pulmonary edema [35] associated with tocolytic therapy [36] and severe preeclampsia [37–39]. Asthma is a common chronic condition associated with complications during pregnancy. Its prevalence among pregnant females is increasing which subsequently increases perinatal risks which include pre-eclampsia, preterm birth, low birth weight, spontaneous abortion, and perinatal mortality [40]. Severe attacks from asthma are usually seen at 21–24 weeks, but can occur at any stage of pregnancy. NIPPV and its use in an asthma exacerbation leading to hypoxic respiratory failure is a provocative modality, however has been proven to be beneficial in chronic obstructive pulmonary disease where hypercapnic respiratory failure is the main pathophysiology [41]. Dalar et al. [42] reported a case of a 28-year-old female in her 16th week of pregnancy with community-acquired pneumonia who presented during an asthma attack, which led to hypoxic respiratory failure who was successfully treated using NIPPV by significantly decreasing her oxygen requirements within 48 h along with her respiratory and cardiac rates. High flow nasal cannula (HFNC) is another modality that can be considered in the setting of acute hypoxic respiratory failure, however there is an absence of compelling evidence regarding its use in the obstetrical population. Only two case reports describe its successful utilization for respiratory management in rapidly progressive interstitial pneumonia complicated by dermatomyositis [43] and acute hypoxic respiratory failure due to sepsis [44].

NIPPV application in ARDS has also been described to be efficacious as in the case depicted by Al-Ansari et al. [45], which involved four pregnant patients with sickle cell disease who presented with acute chest syndrome and ARDS, and successful treatment with NIPPV was achieved while avoiding endotracheal intubation. Cases of ARDS related to all-trans-retinoic acid syndrome [46], community-acquired pneumonia, sepsis and influenza (H1N1) have also been found in the literature. Banga et al. [47] described a case of a primigravida female with ARDS due to community-acquired severe pneumonia in whom with NIPPV, lead to the improvement in arterial oxygenation, reduction in respiratory rate, and of importance gradual disappearance of fetal distress. In another case by Frassanito et al. [48], a 32-year-old woman who developed ARDS requiring urgent cesarean section under epidural anesthesia, in the setting of membrane rupture of one of the twins, required intermittent NIPPV during the postoperative period, which helped to restore physiological gas-exchange and prevent common complications associated in invasive mechanical ventilation. In terms of H1N1-related ARDS, mortality rate can reach as high as 60% for those who require mechanical ventilation, which as discussed in the pregnant population may possibly be higher. In 2012, a prospective multi-centered study found that the early application of NIPPV, with the aim to avoid invasive ventilation during the H1N1 pandemics, was associated with an overall success rate of 48% of the patients with elevated SAPS II score, acute respiratory failure and pulmonary infiltrates and a 75% success rate in patients not needing immediate intubation for a life-threatening condition [49]. This success is further depicted by Djibre et al. [50] in a case of a 28-year-old pregnant female with ARDS from the H1N1 virus, where through intermittent NIPPV the patient was suc-

cessfully treated without the means of mechanical ventilation. This brings out the point of a possible role for NIPPV in reducing this morbidity by decreasing the number of required intubations, in not only the pregnant patient, but patients with isolated respiratory failure and ARDS from H1N1.

In addition to salvage respiratory therapies, other descriptions of NIPPV in pregnancy have also been noted in the perioperative setting, particularly in combination with spinal anesthesia for parturients with respiratory failure requiring emergency cesarean delivery [51–53]. Sedation and NIPPV has also been a topic of interest for many years. In the 1960s, Duan et al. [34] described a case of successfully applying NIPPV with dexmetomidine (a selective alpha-2 receptor agonist) in a 16-year-old primigravida woman who developed acute hypoxemic respiratory failure and allowed for the achievement of sufficient oxygenation along with anxiety reduction, providing good outcomes for both the child and the patient.

40.4 Conclusion

NIV constitutes multiple modalities that lack adequate extensive evidence in the parturient patient. Despite this, there is a potential role for use as evidenced by multiple case reports and series. NIV should not be applied routinely in pregnancy but may be considered on case by case basis. As in the setting for NIPPV, there are theoretical concerns for aspiration risk and obtaining a proper fit for oxygenation. Although further studies are needed, NIV modalities have similar indications and contraindications in the pregnant patient as the general population. It must be noted that NIV will not be appropriate if the need of prolonged ventilation is expected and/or in the setting of other organ failure and should only be utilized when the patient is alert, protecting her airway and where the need for assisted ventilation will be brief. As a result, criteria required for its use should include that the patient possesses an adequate respiratory drive, toleration of the face interface, hemodynamically stability, an ability to protect her airway, low aspiration risks, and lastly an experienced team with the use of NIPPV in a proper monitored setting (Table 40.4).

Table 40.4 Summary of learning points

• Respiratory distress is a common cause of morbidity during gestation
• Many pulmonary diseases are common indications for obstetric admissions into the intensive care units and cause for maternal and fetal mortality
• Understanding the physiologic and anatomical changes during pregnancy will allow to differentiate between “normal physiologic dyspnea” from other more pathological entities
• Although controversial, NIPPV has been shown to be safe and effective during pregnancy in case reports and series
• NIPPV may prevent invasive mechanical ventilation avoiding use of sedating medications
• Limited evidence for the utilization of HFNC in the obstetrical patient
• Although further studies are needed, NIV modalities have similar indications and contraindications in the pregnant patient as the general population

References

1. Ananth CV, Smulian JC. Epidemiology of critical illness in pregnancy. In: Critical care obstetrics. 5th ed. Hoboken, NJ: Blackwell; 2010.
2. Chen CY, Fau-Chen C-P, Chen CP, et al. Factors implicated in the outcome of pregnancies complicated by acute respiratory failure. J Reprod Med. 2003;48:641–8.
3. Jenkins TM, Troiano NH, Graves CR, et al. Mechanical ventilation in an obstetric population: characteristics and delivery rates. Am J Obstet Gynecol. 2003;188(2):549–52.
4. Christiansen L, Collin K. Pregnancy associated deaths: a 15-year retrospective study and overall review of maternal pathophysiology. Am J Foren Med Path. 2006;27:11–9.
5. King TA, et al. Failed tracheal intubation. Br J Anaesth. 1990;65:400–14.
6. Lyons G, et al. Failed intubation: six years’ experience in a teaching maternity unit. Anaesthesia. 1985;40:759–62.
7. Glassenberg R, et al. General anesthesia and maternal mortality. Semin Perinatol. 1991;15:386–96.
8. Toppozada H, et al. The human respiratory nasal mucosa in pregnancy. An electron microscopic and histochemical study. J Laryngol Otol. 1982;96(7):613.

9. Ellegard EK, et al. The incidence of pregnancy rhinitis. Gynecol Obstet Invest. 2000;49(2):98.
10. Gani F, et al. Rhinitis in pregnancy. Eur Ann Allergy Clin Immunol. 2003;35:306.
11. Ellegard EK, et al. The etiology and management of pregnancy rhinitis. Am J Respir Med. 2003;2:469.
12. Ellegard EK, et al. Rhinitis in the menstrual cycle, pregnancy, and some endocrine disorders. Clin Allergy Immunol. 2007;19:305.
13. Pien GW, et al. Sleep disorders during pregnancy. Sleep. 2004;27:1405–17.
14. Lundberg JO, et al. Nasal nitric oxide in man. Thorax. 1995;54:947–52.
15. Izci B, et al. Sleep-disordered breathing and upper airway size in pregnancy and post-partum. Eur Respir J. 2006;27:321–7.
16. Pilkington S, et al. Increase in Mallampati score during pregnancy. Br J Anaesth. 1995;74:638–42.
17. White DP, et al. Pathogenesis of obstructive and central sleep apnea. Am J Respir Crit Care Med. 2005;172:1363–70.
18. Ja M, et al. Large airways function during normal pregnancy. Br J Obstet Gynaecol. 1977;84(6):448.
19. Baldwin GR, et al. New lung functions and pregnancy. Am J Obstet Gynecol. 1977;127:235–9.
20. Gazioglu K, et al. Pulmonary function during pregnancy in normal women and in patients with cardiopulmonary disease. Thorax. 1970;25:445–50.
21. Cugell DW, et al. Pulmonary function in pregnancy. I. Serial observations in normal women. Am Rev Tuberc. 1953;67:568–97.
22. Ihrman K, et al. A clinical and physiological study of pregnancy in a material from northern Sweden. II. Vital capacity and maximal breathing capacity during and after pregnancy. Acta Soc Med Ups. 1960;65:147–54.
23. Bonica J. Maternal respiratory changes during pregnancy and parturition. Clin Anesth. 1974;10(2):1.
24. Bonica J. Principles and practice of obstetric analgesia and anesthesia. Philadelphia: FA Davis; 1962.
25. Edwards N, Blyton DM, Kirjavainen T, Kesby GJ, Sullivan CE. Nasal continuous positive airway pressure reduces sleep-induced blood pressure increments in preeclampsia. Am J Respir Crit Care Med. 2000;162:252–7.
26. Blyton DM, Sullivan CE, Edwards N. Reduced nocturnal cardiac output associated with preeclampsia is minimized with the use of nocturnal nasal CPAP. Sleep. 2004;27:79–84.
27. Guilleminault C, Kreutzer M, Chang JL. Pregnancy, sleep disordered breathing and treatment with nasal continuous positive airway pressure. Sleep Med. 2004;5:43–51.
28. Reddy R, et al. Pregnancy in kyphoscoliosis: benefit of non-invasive ventilatory support. J Obstet Gynaecol. 2005;25:267–8.
29. Sawicka EH, Branthwaite MA. Respiration during sleep in kyphoscoliosis. Thorax. 1987;42:801–8.
30. Kahler CM, et al. Management of respiratory deterioration in a pregnant patient with severe kyphoscoliosis by non-invasive positive pressure ventilation. Wien Klin Wochenschr. 2002;114:874–7.
31. Bach JR. Successful pregnancies for ventilator users. Am J Phys Med Rehabil. 2003;82:226–9.
32. Dıaz-Lobato S, et al. Two full-term pregnancies in a patient with mitochondrial myopathy and chronic ventilatory insufficiency. Respiration. 2005;72:654–6.
33. Yuan N, et al. Successful pregnancy and cesarean delivery via noninvasive ventilation in mitochondrial myopathy. J Perinatol. 2009;29:166–7.
34. Duan M, Lee J, Bittner EA. Dexmedetomidine for sedation in the parturient with respiratory failure requiring noninvasive ventilation. Respir Care. 2012;57:1967–9.
35. Fujita N, et al. Successful perioperative use of NIPPV in a pregnant woman with acute pulmonary edema. Masui. 2014;63(5):557–60.
36. Perbet S, et al. Ventilation non-invasive pour œdème pulmonaire attribue aux tocolytiques lors du travail d'une grossesse gémellaire [Non-invasive ventilation for pulmonary edema associated with tocolytic agents during labour for a twin pregnancy]. Can J Anaesth. 2008;55:769–73.
37. Jalilian L, Delgado Upegui C, Ferreira R, Simmons L, Ciliberto C. Intraoperative treatment of fetal asystole after endovascular repair of aortic coarctation in a pregnant woman with mitral stenosis. A A Case Rep. 2015;6(6):150–3.
38. Terajima K, et al. Non-invasive positive pressure ventilation and subarachnoidal blockade for Caesarean section in a parturient with pulmonary oedema. Acta Anaesthesiol Scand. 2006;50(10):1307–8.
39. Rojas-Suarez J, et al. Ventilacioń mecańica no invasiva como estrategia adyuvante en el manejo del fallo respiratorio agudo secundario a edema pulmonar periparto por preeclampsia severa [Non-invasive mechanical ventilation as adjuvant strategy in the management of acute respiratory failure secondary to peripartum pulmonary edema in severe preeclampsia]. Med Intensiva. 2011;35:518–9.
40. Murphy VE, et al. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. Thorax. 2006;61(2):169–76.
41. Ferrer M, Esquinas A, Leon M, et al. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med. 2003;168:1438–44.
42. Dalar L, et al. Application of non-invasive mechanical ventilation in an asthmatic pregnant woman in respiratory failure: a case report. J Thorac Dis. 2013;5(1):97–100.
43. Shoji T, Umegaki T, Nishimoto K, et al. Use of High-flow nasal cannula oxygen therapy in a pregnant woman with dermatomyositis-related interstitial pneumonia. Case Rep Crit Care. 2017;2017:4527597.
44. Plotnikow GA, Vasquez D, Pratto R, et al. High-flow nasal cannula in the treatment of acute hypoxemic respiratory failure in a pregnant patient: case report. Rev Bras Ter Intensive. 2018;30(4):508–11.

45. Al-Ansari MA, Hameed AA, Al-jawder SE, et al. Use of noninvasive positive pressure ventilation during pregnancy: case series. Ann Thorac Med. 2007;2:23–5.
46. Bassani MA, et al. Noninvasive ventilation in a pregnant patient with respiratory failure from all-trans-retinoic-acid (ATRA) syndrome. Respir Care. 2009;54(7):969–72.
47. Banga A, Khilnani GC. Use of non-invasive ventilation in a pregnant woman with acute respiratory distress syndrome due to pneumonia. Indian J Chest Dis Allied Sci. 2009;51(2):115–7.
48. Frassanito L, et al. Successful application of helmet non-invasive ventilation in a parturient with acute respiratory distress syndrome. Minerva Anestesiol. 2011;77(11):1121–3.
49. Nicolini A, Tonveronachi E, Navalesi P, Antonelli M, Valentini I, Melotti RM, et al. Effectiveness and predictors of success of noninvasive ventilation during H1N1 pandemics: a multicenter study. Minerva Anestesiol. 2012;78(12):1333–40.
50. Djibré M, et al. Non-invasive management of acute respiratory distress syndrome related to Influenza A (H1N1) virus pneumonia in a pregnant woman. Intensive Care Med. 2010;36(2):373–4.
51. Polin CM, et al. Anesthetic management of supermorbidly obese parturients for cesarean delivery with a double neuraxial catheter technique: a case series. Int J Obstet Anesth. 2015;24(3):276–80.
52. Guterres AP, Newman MJ. Total spinal following labour epidural analgesia managed with non-invasive ventilation. Anaesth Intensive Care. 2010;38:373–5.
53. Erdogan G, Okyay DZ, Yurtlu S, et al. Non-invasive mechanical ventilation with spinal anesthesia for cesarean delivery. Int J Obstet Anesth. 2010;19:438–40.
54. Draisci G, Volpe C, Pitoni S, et al. Non-invasive ventilation for acute respiratory failure in preterm pregnancy. Int J Obstet Anesth. 2013;22:169–71.

Noninvasive Ventilation in Hospice and Palliative Care

41

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Abbreviations

ARF	Acute respiratory failure
BiPAP	Bilevel positive airway pressure
CHF	Congestive heart failure
CMO	Comfort measures only
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
DNI	Do not intubate
HCP	Healthcare proxy
HFNC	High flow nasal cannula
NIPPV	Noninvasive positive-pressure ventilation
NIV	Noninvasive ventilation (including HFNC, BiPAP, and CPAP)

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41.1 Introduction

Noninvasive ventilation (NIV) has been used for certain indications in the palliative care and hospice settings. Palliative care refers to care that aims to reduce patient suffering and maximize quality of life. It can occur at any point for a patient affected by a life-limiting illness. Hospice care is an important Medicare benefit in the United States. Patients in the hospice setting have been given a prognosis of under 6 months (if the

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disease follows its usual course), and the focus of treatment has shifted away from curative intent entirely, to prioritize comfort.

Breathlessness is a common symptom at the end-of-life, brought about by several etiologies including end-stage lung disease, recurrent pneumonia (often from aspiration), heart failure both systolic and diastolic, progressive neuromuscular disease, and neoplastic disease. Since the late 1980s, NIV has been used with frequency in the treatment of acute and chronic respiratory failure seen in a variety of clinical situations. The use of NIV via facemask, nasal mask, and high flow nasal cannula can be effective in reducing the need for endotracheal intubation and mechanical ventilation. Some practitioners see it as a form of treatment when the patient has previously chosen to avoid "invasive" ventilation.

Determining the correct clinical setting for the use of this technology—or any "newer" technology for that matter—may be particularly difficult. Many innovations thought to be major breakthroughs are applied to all comers and then re-evaluated for effectiveness, outcome, and burden to narrow the application to patients most able to benefit [1]. The differentiation of endotracheal intubation and mechanical ventilation versus NIV may be difficult to explain to patients and their families, and the limitations and constraints created by the use of NIV may not be fully clarified. Patients may say that they "don't want to be on a machine" at the end of life. Is the NIV technology machinery? Is the patient making a literal statement, or are refusals based on conceptual issues such as dependence, loss of control, becoming a burden, and prolonged death? Are our clinical algorithms and recommended conversations adequate to address the needs of patients to make appropriate decisions regarding the acceptance of NIV when suffering from advanced end-stage disease?

In the following pages, we will review recent publications regarding the benefits and burdens of NIV in patients with respiratory failure from a palliative perspective, acknowledging that decisions are made in the setting of relative uncertainty in prognostication. From a Palliative Medicine point of view, it may be most valuable to recognize that clinicians and patients are not choosing what the outcome of treatment will be in these advanced disease settings, but choosing what death might look like and how it may be experienced.

Also, we have provided some recommended algorithms to identify patients who might benefit from NIV. Recommended conversations are also reproduced here—although we urge all practitioners to develop a style that works best for them in clarifying patients' goals to help put any decision in the proper personal context [2, 3] (Fig. 41.1).

NIV has some limited but important applications in the palliative setting. The principal consideration when deciding to use NIV in this patient population is whether this form of treatment aligns with the patient's goals. The goals of the family are also considered if the patient is unable to communicate, often as substituted judgment, but also because palliative medicine considers the family unit as an extension of the patient and treats the family unit as a whole.

A 2007 review by the Society of Critical Care Medicine Palliative Noninvasive Positive Pressure Ventilation (NIPPV) Task Force established the rationale for using NIPPV in three different contexts: firstly, as life support in cases where no limitations on life support measures have been established; secondly, as life support in cases where patient decides to forgo intubation; and thirdly, as a comfort measure only [4].

In the first context, NIPPV is applied to support a patient while the underlying cause of acute respiratory failure (ARF) is treated or resolves. In the second and third context, is where the application of NIPPV changes from its typical use as a therapy bridge to its application specifically focused on patient goals. If the underlying cause of ARF cannot be reversed or patient declines NIPPV, comfort measures are intensified. Patients may be encouraged to tolerate some level of discomfort associated with NIPPV while it is helping them achieve their other goals or if NIPPV alleviates symptoms and allows for communication with loved ones. If NIV is being used strictly to alleviate dyspnea, patients should not be encouraged to tolerate any degree of dis-

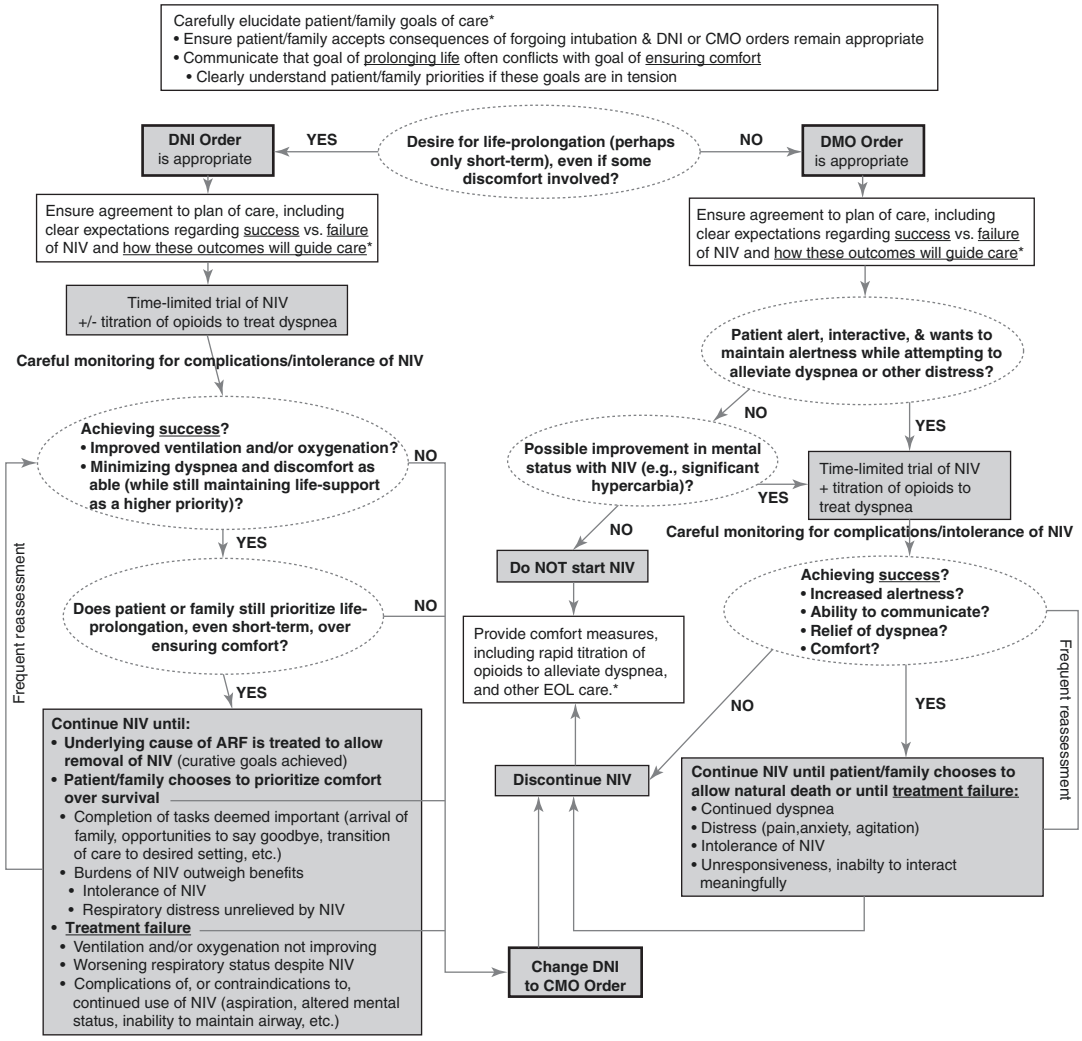

Fig. 41.1 Suggested treatment algorithm for using noninvasive ventilation (NIV) in patients with acute respiratory failure (ARF) who have chosen do-not-intubate (DNI) or comfort-measures-only (CMO) orders. Recommend seeking palliative care assistance, if possible. Note that the outcomes which define success or failure of NIV will vary, depending upon the overarching goals of care, which should be reflected by choosing the appropriate DNI or CMO treatment pathway. Key questions, which should guide care decisions and should be discussed with patients and families, are *circled*. Effective communication with patients and/or their surrogate decision-makers is crucial throughout the process. *EO* end of life. (Wilson et al. NIV in patients with DNI and CMO orders: a sys rev and meta-analysis. Crit Care Med. 2018. https://www.ncbi.nlm.nih.gov/pubmed/29498939)

comfort. The Task Force emphasizes that there is no justification to using NIPPV in patients who cannot express their response on the effect of this therapy on their subjective breathlessness. See Tables 41.1 and 41.2 below.

There are four indications for NIV in the palliative setting:

1. for symptomatic relief of dyspnea,
2. to buy time for important decision-making and clarification of patient/family goals,
3. to allow a patient to achieve important end-of-life goals,
4. to allow for more definitive comfort-focused treatment modalities to be effective.

Table 41.1 Potential phrases to use in communicating with family about the goals of care using noninvasive positive pressure ventilation (NPPV)

	Primary goals of care	Potentially helpful phrases to clarify goals with family and/or patient[a]
Category 1	Goal is to restore health; will use intubation if necessary and indicated	MD: "I recommend we use the mask (NPPV) to try to get him over this without having to put the breathing tube in his throat. If this doesn't improve things or is too uncomfortable for him, we'll use the breathing tube. Does this plan fit with your understanding of what he'd want?"
Category 2	Goal is to restore health without using endotracheal intubation and without causing unacceptable discomfort	MD: "I recommend we use the mask (NPPV) to try to get him over this. He has been very clear that he doesn't want the breathing tube. So, if the mask doesn't improve things or is too uncomfortable for him, we will plan to stop using it and focus all of our efforts on keeping him comfortable. In this situation, it would mean that he would likely die, although we would make it as comfortable as possible for him. Does this plan fit with your understanding of what he'd want?"
Category 3	Goal is to maximize comfort while minimizing adverse effects of opiates	MD: "I think it may be reasonable to try the mask (NPPV) to see if it makes him more comfortable. We know that it won't fix the underling problem, but it might make his breathing a little easier temporarily. If it doesn't make him more comfortable, we will stop it and try something else so his death will be as comfortable as possible. Does this plan fit with your understanding of what he'd want?"

Curtis JR, Cook DJ, Sinuff T, et al. Noninvasive positive pressure ventilation in critical and palliative care settings: understanding the goals of therapy. Crit Care Med. 2007;35:932–9

[a]Note: These are example phrases developed by the authors and do not represent actual quotes from qualitative research

Table 41.2 Overview of the three-category approach to using noninvasive positive pressure ventilation (NPPV) for acute respiratory failure

Approach	Category 1	Category 2	Category 3
Definition	Life support without preset limits	Life support with preset limit (do not intubate)	Comfort measures only
Primary goals of care	Assist ventilation and/or oxygenation Alleviate dyspnea Achieve comfort Reduce risk of intubation Reduce risk of mortality Avoidance of intubation	Includes same as category 1 except intubation declined Also could include briefly prolonging life for a specific purpose (e.g. arrival of family member)	Palliation of symptoms (relief of dyspnea)
Main goals to communicate with patient and family	Goal is to restore health and use intubation if necessary and indicated	Goal is to restore health without using endotracheal intubation and without causing unacceptable discomfort	Goal is to maximize comfort while minimizing adverse effects of opiates
Determination of success	Improved oxygenation and/or ventilation Tolerance of NPPV or minor discomfort that is outweighed by potential benefit	Improved oxygenation and/or ventilation Tolerance of NPPV or minor discomfort that is outweighed by potential benefit	Improved symptoms Tolerance of NPPV
Endpoint for NPPV	Unassisted ventilation adequately supporting life Intolerance of NPPV	Unassisted ventilation adequately supporting life Intolerance of NPPV	Patient is *not* more comfortable having NPPV on or wants NPPV stopped Patient becomes unable to communicate
Response to failure	Intubation and mechanical ventilation (if indicated)	Change to comfort measures only and palliate symptoms without NPPV	Palliate symptoms without NPPV

Table 41.2 (continued)

Likely location of NPPV	ICU but may include step-down unit or acute care bed in some hospitals with appropriately monitored setting and trained personnel	Variable but may include ICU or step-down unit or acute care bed	Acute care bed but could be applied in hospice by appropriately trained personnel

ICU intensive care unit

Curtis JR, Cook DJ, Sinuff T, et al. Noninvasive positive pressure ventilation in critical and palliative care settings: understanding the goals of therapy. Crit Care Med. 2007;35:932–9

41.2 Symptom Relief

Breathlessness is a commonly encountered symptom in palliative care associated with a variety of etiologies; unfortunately, as disease progresses this symptom often intensifies. The mainstay of dyspnea treatment in the setting of incurable illness is opioids. In certain scenarios however, the opioid dose required to achieve relief from dyspnea may cause other side effects such as sedation, which the patient may wish to avoid or defer. Studies have looked at NIV as potential additive therapy to reduce dyspnea as well as minimizing the opioid dose required to achieve acceptable relief.

In one randomized feasibility study, Nava et al. recruited patients with solid tumors causing acute respiratory failure and distress from centers in Italy, Spain, and Taiwan. Patients had a life expectancy of less than 6 months and had decided on ensuring comfort in the late stages of disease. The study aimed to assess the acceptability and effectiveness of NIV therapy in patients who had a desire to maintain some cognition and the ability to communicate. Compared to oxygen therapy, NIV resulted in quicker decrease in dyspnea measured using the Borg scale (although it is debatable whether the magnitude of the decrease is clinically significant). The most benefit was seen after the first hour and in hypercapnic patients. Additionally, the total dose of morphine during the first 48 h was also lower in the NIV group. Given the easy availability of opioids in most clinical settings and lack of mention of increased side effects in the higher dose group, the focus on this particular outcome measure is less clear. In this study, 11% of the NIV patients discontinued the NIPPV treatment due to facial interface intolerance as well as anxiety [5].

High flow nasal cannula (HFNC) is a form of NIV that delivers oxygen at a high flow rate through the nares without a mask interface. It can be used for any cause of hypoxemic ARF including cancer, pneumonia, and interstitial lung disease. It is less well studied in hypercapnic ARF. Because it does not form a seal around the mouth and nose, it can be more comfortable than other forms of NIV. In the case of HFNC especially however, the endpoint must be carefully considered. Clinicians and patients sometimes find themselves on the "bridge to nowhere"—patients do not have the potential to get better, but death might be delayed by days or weeks while the patient is on HFNC. Because HFNC cannot currently be delivered outside of an acute care setting, patients get "stuck" without a clear transition plan, raising concern about hospital resource utilization. Some home hospices may be able to make HFNC available at home, though at lower flow rates of 20–25 Liters per hour (L/h) [6].

Another randomized trial by Hui et al. investigated the feasibility of applying HFNC or BiPAP in advanced cancer patients to examine the changes in dyspnea, physiologic parameters, and adverse effects of these modalities. Patients again noted improvement in dyspnea score in both groups [7]. BiPAP and HFNC both resulted in decreased respiratory rates, however only HFNC had significantly improved oxygen saturation. No significant adverse effects were observed though patients assigned to the BiPAP arm had more trouble sleeping than HFNC patients, which confirms previously published research that HFNC is more comfortable than BiPAP [8].

Koyauchi et al. retrospectively reviewed the records of interstitial lung disease (ILD) patients in hypoxic ARF with DNI orders. HFNC was compared to NIPPV in terms of 30-day survival, in-hospital mortality, patient request for interruption or discontinuation, adverse events, oral intake, and communication ability at the end of life. HFNC was found to be a suitable alternative to NIPPV. It was more tolerable with fewer adverse events including epistaxis, pneumomediastinum, and skin breakdown. There were fewer interruptions at patient request. There was no significant difference in efficacy as measured by 30-day survival and in hospital mortality as well as no difference in dyspnea scores. Among the patients that died in the hospital, HFNC allowed for significantly better eating and speaking until right before death [9]. This single-center non-randomized retrospective chart review study has its clear limitations; however, it suggests that HFNC is a reasonable, if not preferred, palliative treatment in these patients. It is unclear if these results would hold for patients suffering from other causes of respiratory failure at the end of life.

A French survey of pediatricians' opinions and practices regarding NIV in palliative care revealed that 84% felt it was reasonable to use in a do-not-intubate (DNI) child, while only 35% felt it reasonable to in a "comfort measures only" (CMO) child with ARF. Similar statistics were seen when addressing progressive respiratory failure (68% and 30% respectively). No specific physiologic parameters were noted to be followed when assessing response to treatment. Child comfort and family satisfaction were main driving factors of continued NIV application [10]. Clinician preference in this pediatric palliative care context may suggest that relief of dyspnea is not a principal characteristic of NIV, limiting its applicability as a comfort tool (Fig. 41.2).

A New Zealand study that explored the experiences of patients using NIV revealed that patients greatly disliked the BiPAP/CPAP mask, citing feelings of suffocation and claustrophobia. They also reported feelings of discomfort associated with subjective dissynchrony with the NIV machine [11]. Other studies of patients who experienced dyspnea from potentially reversible

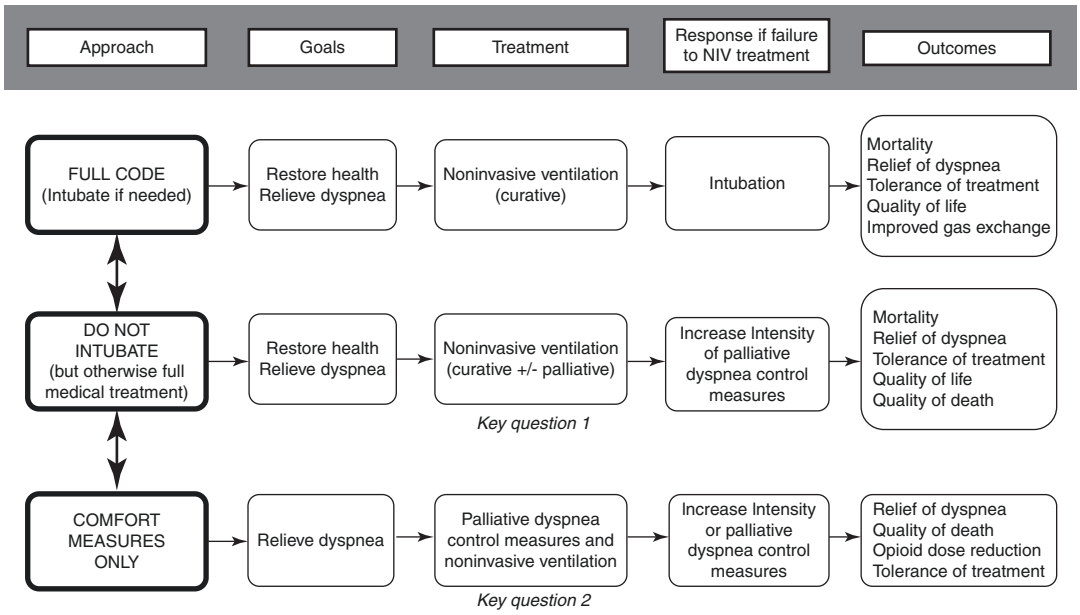

Fig. 41.2 Factors that matters while considering NIV for patients with do-not-intubate or comfort measures only. (Esbensen K. What matters most when considering noninvasive ventilation for patients with do-not-intubate or comfort measures only orders? Crit Care Med. 2018;46(8):1367–70)

causes (CHF or COPD exacerbation, etc.) corroborated that the discomfort associated with NIV would cause some patients to choose not to undergo it again, or to feel like they would be agreeing to NIV under duress [12].

In summary, the effectiveness of NIV for the symptomatic management of dyspnea remains under debate, with some studies concluding that the benefit outweighs the burden, and others stating the contrary. Patient response must be assessed on a case by case basis, and it may be impossible to predict which patients will find relief and which patients will fail to tolerate NIV. A Palliative Medicine approach might be to consider a time-limited trial as a reasonable way forward if the balance of burdens versus benefits of NIV appears unclear [13].

41.3 Allowing Time for Decision-Making

If NIV is adequately tolerated by the patient, it can be used to "buy time" in some very limited scenarios. This can allow for clarification of a diagnosis in a way that influences decision-making, or for participation in advance care planning.

A 2018 UK report illustrates this by presenting the case of a 39-year-old female, admitted through the emergency department in acute hypoxemic respiratory failure, requiring 9 L of oxygen to maintain her saturations. Application of HFNC and then BiPAP stabilized her long enough to complete an initial workup, which revealed widely metastatic disease with rapid progression. NIPPV allowed time for goals of care to be established, with the patient and her family opting to focus on comfort. The eventual aim was to stabilize the patient enough to return home, her preferred place of death. She ultimately died still on HFNC in the hospital and in the presence of family, but having avoided endotracheal intubation. Pathology eventually confirmed a non-gestational trophoblastic tumor, likely of pulmonary origin, resulting from choriocarcinomatous differentiation within a high-grade primary [14].

The emergency room (ER) is a particularly unique environment for the end-of-life treatment because there is usually very limited information about the patient available to the clinician. Advanced directives, goals of care, and even health care proxies (HCP) are often not readily accessible. NIV can be used on a time-limited basis to allow the treating team to gather the appropriate background information, medical records, advance directives, and initial workup. If investigation reveals that the patient has made it clear that they do not want invasive machines, consider using a handheld fan or conventional oxygen supplementation via nasal cannula rather than NIV. Clinicians should keep in mind that opioids are the mainstay of treatment of symptomatic breathlessness at the end of life, including in the ED setting [15].

A 2017 Norwegian study examining the illness experience and involvement in medical decision-making of end-stage COPD patients revealed that none of the participants had spoken to their providers about prognosis, goals for treatment and care when their condition permitted such a dialogue [16]. Though NIV can sometimes buy enough time for decision-making, comprehensive advance care planning requires much more diligence. Patients who are expected to develop respiratory symptoms should have advance care planning initiated early in their disease course. Indeed, the need for NIV can be seen as a trigger for need for advance directive discussions, especially in non-malignant diseases [17].

41.4 Short-Term Life Support to Achieve End-of-Life Goals

In the short term, NIV can allow patients an extended period of alertness during which to achieve important end-of-life goals. Examples include: attending a milestone family celebration, awaiting the birth of a child, finishing a legacy project, awaiting the arrival of distant family for important final conversations, etc. Patients may tolerate a certain amount of discomfort associated with NIV if they feel it is helping

them meet their other goals [16, 18]. The alignment of treatment plan with patient preference is paramount in this context.

Several studies noted that patients had gaps in recall, as well as delirium and hallucinations while on NIV. This has negative implications for its use as a measure to buy time for advance planning discussions [2, 11, 12].

A case report by Bassani et al. illustrates the use of NIV as short-term life support to allow a patient to achieve end-of-life goals. This case describes a 29-year-old pregnant patient with a previously resected soft tissue sarcoma, who presented to the emergency department in respiratory failure and preterm labor. After stabilization, and the premature cesarean section delivery of a live infant, she was admitted to ICU and endotracheally intubated for acute respiratory failure. Further workup revealed metastatic thoracic sarcoma. The patient eventually tolerated extubation to CPAP. Application of NIV allowed her time to bond with her newborn, and to breastfeed, which was an intensely important goal for her. The patient died on ICU day 6 [19].

41.5 Time for Other Comfort Treatment to be Effective

As a matter of practicality, NIV can be applied in the short term if a palliative/hospice patient is experiencing dyspnea from a potentially reversible cause, and is expected to derive symptomatic benefit soon from another intervention that requires time to become effective. For instance, if dyspnea is caused in whole or in part by pulmonary edema due to CHF, it may be reasonable to apply BiPAP while awaiting diuresis.

A 2018 systemic review and meta-analysis of NIV use in patients with DNI and CMO orders by Wilson et al. failed to meaningfully evaluate outcome measures of interest to patients or clinicians in the palliative/hospice setting [18]. It is important to note that the presence of a DNI order does not necessarily indicate NIV was used for purposes of palliation; one cannot conclude that these patients received NIV with palliative intent. Some observations were made regarding the effectiveness of NIV in patients with limits on life support in ARF. A significant portion of patients receiving NIV for ARF survived to hospital discharge and through 1 year. Hospital survival did not differ based on location of NIV use (i.e., general floor vs ICU). The analysis concluded "NIV achieves survival with an acceptable quality of life in a significant proportion of patients with DNI orders in contrast to claims by some experts that NIV in these patients merely prolongs the dying process." This analysis has been criticized for excluding patients who died, and did not examine whether NIV helped patients achieve a "good death." These omissions make this study of limited applicability to the palliative/hospice context [20].

41.6 Conclusion

There are limited but important indications for the use of NIV in the palliative care setting. Clinicians must carefully consider whether a patient will benefit from NIV. Benefit is always interpreted through the lens of patient/family goals. The use of NIV in this setting may be reasonable if a patient (1) derives symptomatic benefit of dyspnea that is not achievable through more conservative measures (hand-held fans, low-dose opioids), (2) wishes to prolong a period of alertness in order to achieve important end-of-life goals, (3) is willing to use it as a temporizing measure to allow for definitive delineation of patient/family treatment decisions, or (4) sees NIV as a reasonable bridge to definitive and achievable management of dyspnea. Nasal high flow may be more tolerable than CPAP/BiPAP, however this modality is currently not available outside the acute care setting at high flow rates.

As an approach, we recommend delineation of patient/family goals, clarification of level of burden patient is willing to endure and clarity in prognostication, if possible. Time-limited trials, well delineated by Quill and Hollaway, can be a way to navigate some of these very complicated clinical decisions with serious advanced illness [13].

References

1. McKinlay J. From "promising report" to "standard procedure": seven stages in the career of a medical innovation. Philadelphia: Saunders; 1981.
2. Matthews H. P154 The patients' experience of NIV. A phenomenological study. Thorax. 2010;65:A143–4.
3. D'Cruz RF, Kaltsakas G, Suh ES, Murphy PB, Hart N. Positive airway pressure devices for the management of breathlessness. Curr Opin Support Palliat Care. 2018;12:246–52.
4. Curtis JR, Cook DJ, Sinuff T, et al. Noninvasive positive pressure ventilation in critical and palliative care settings: understanding the goals of therapy. Crit Care Med. 2007;35:932–9.
5. Nava S, Ferrer M, Esquinas A, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. Lancet Oncol. 2013;14:219–27.
6. Shah N, Mehta Z, Mehta YHFNC. Therapy in palliative care #330. J Palliat Med. 2017;20(6):679–80.
7. Hui D, Morgado M, Chisholm G, et al. High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: a phase II randomized trial. J Pain Symptom Manage. 2013;46:463–73.
8. Milési C, Baleine J, le Bouhellec J, Pons-Odena M, Cambonie G. High flow on the rise-pediatric perspectives on the FLORALI trial. J Thorac Dis. 2015;7(8):E230–3.
9. Koyauchi T, et al. Efficacy and tolerability of HFNC oxygen therapy for hypoxemic respiratory failure in patients with interstitial lung disease with DNI orders: a retrospective single-Center study. Respiration. 2018;96(4):323–9.
10. Ringuier B, Troussier F, Boussicault G, Chapotte C, Rachieru P. Non invasive ventilation and pediatric palliative care. A French survey. Arch Pediatr. 2017;24(8):712–9.
11. Beckert L, et al. What can we learn from patients to improve their NIV experience? 'It was unpleasant; if I was offered it again, I would do what I was told. BMJ Support Palliat Care. 2016;0:1–6.
12. Smith TA, et al. Experience of acute NIV-insights from 'behind the mask': a qualitative study. BMJ Support Palliat Care. 2019;9(1):e11.
13. Quill TE, Holloway R. Time-limited trials near the end of life. JAMA. 2011;306(13):1483–4.
14. Green E, Stockton L, De Winton E. Non-invasive ventilation for a rapidly deteriorating palliative patient. BMJ Support Palliat Care. 2018;0:1–3.
15. Shreves A, Pour TR. Emergency department management of dyspnea in the dying patient. Emerg Med Pract. 2018;20(7):1–20.
16. Jerpseth H, Dahl V, Nortvedt P, Halvorsen K. Older patients with late-stage COPD: their illness experiences and involvement in decision-making regarding mechanical ventilation and noninvasive ventilation. J Clin Nurs. 2018;27:582–92.
17. Smith TA, Disler RT, Jenkins CR, et al. Perspectives on advance care planning among patients recently requiring non-invasive ventilation for acute respiratory failure: a qualitative study using thematic analysis. Palliat Med. 2017;31:566–74.
18. Wilson ME, et al. NIV in patients with DNI and CMO orders: a sys review & meta-analysis. Crit Care Med. 2018;46(8):1209–16.
19. Bassani MA, et al. The use of noninvasive mechanical ventilation in the palliative care of a patient with metastatic thoracic sarcoma: case report. Rev Bras Ter Intensiva. 2008;20(2):205–9.
20. Esbensen K. What matters most when considering noninvasive ventilation for patients with do-not-intubate or comfort measures only orders? Crit Care Med. 2018;46(8):1367–70.

Noninvasive Ventilation as a Weaning Strategy

42

Fatma Ciftci

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Although mechanical ventilation is a life-saving therapy in the treatment of acute respiratory failure, weaning should be performed as soon as possible to prevent complications of invasive ventilation. Weaning time is known to constitute half of the total mechanical ventilation time [1].

42.1 In Which Cases Should NIV be Used After Extubation?

Re-intubation is defined as extubation failure and has been shown to be associated with poor prognosis [2]. Since re-intubation is a clinical picture with increased mortality, methods to prevent respiratory failure after extubation have been developed. Thanks to its success, NIV is the treatment of choice in the treatment of acute respiratory failure [3].

42.2 To Prevent Acute Respiratory Failure After Extubation

To increase the success of weaning, the question of giving NIV to each patient after extubation comes to mind. However, NIV has been shown to be effective and successful only in the risky patient groups [4, 5]. It was observed that there was no decrease in re-intubation and mortality rates with NIV therapy in an unselected patient group. The risk factors predicted in the studies were defined as age over 65 years and having an underlying cardiac or respiratory disease. In two multicentric, randomized, and controlled trials, the positive effects of NIV treatment on re-intubation and mortality rates were shown immediately after planned extubation in selected patients [6, 7]. As a result, it is

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recommended to apply NIV only to selected, high-risk patients in order to prevent respiratory failure.

42.3 To Treat Acute Respiratory Failure After Extubation

Although there is not enough randomized controlled research in this subject, it is recommended not to use NIV in the treatment of patients with respiratory failure after extubation [3]. In this case, the individual and clinical characteristics of a patient and the experience of the center in NIV therapy are also important. As the number of COPD patients included in the research on this subject is low, this result may not be applicable for COPD patients.

42.4 To Facilitate Weaning

It is already known that NIV improves respiratory pattern and reduces inspiratory effort in patients intubated due to hypercapnic respiratory failure. It has been shown to be as effective as invasive mechanical ventilation to maintain adequate gas exchange in selected patients during weaning [8]. A meta-analysis evaluating data from 16 randomized controlled trials mostly composed of hypercapnic COPD patients showed that the rate of weaning failure was lower in the NIV group than in the conventional group [9]. Unlike hypoxemic patients, NIV is recommended to facilitate weaning from invasive ventilation in patients with hypercapnic respiratory failure.

On the other hand, NIV has been shown to be successful in a multicenter randomized controlled trial in comparison with standard oxygen therapy in patients with hypoxemic respiratory failure after abdominal surgery. It was also shown that the NIV group had a lesser rate of intubation, nosocomial infection, and duration of mechanical ventilation [10]. However, there are no adequate data to conclude on the success of NIV in hypoxemic patients.

According to the results of these researches, it is seen that there are factors that play a role in obtaining different results. Different results can be obtained in heterogeneous patient groups. In order to obtain more reliable results, studies should be carried out which are as homogenous and as large as possible. NIV should be used especially in the weaning period of COPD patients. Better results were obtained especially in the early period before respiratory failure develops. It is noteworthy that low pressures are used in studies that failed NIV administration. The tidal volume generated by the applied pressure must be checked and required pressure for sufficient tidal volume must be ensured. Appropriate pressures should be adjusted according to the clinical evaluation of the patient and the results of gas exchange. There are significant differences between the duration of NIV therapy in the studies. Although there is no consensus on this issue, the duration of NIV should be sufficient according to the clinical condition of the patient. NIV application experience is an another important factor. The experience of the team members who applied NIV in the clinic will increase the success rate and the safety of the patient with early recognition of failure and taking precautions when needed. When NIV therapy is contemplated, the patient should be monitored by selecting an appropriate interphase and ventilator mode. Most importantly, all the equipment required for intubation of the patient should be readily available.

References

1. Béduneau G, Pham T, Schortgen F, et al. Epidemiology of weaning outcome according to a new definition. The WIND Study. Am J Respir Crit Care Med. 2017;195:772–83.
2. Thille AW, Harrois A, Schortgen F, et al. Outcomes of extubation failure in medical intensive care unit patients. Crit Care Med. 2011;39:2612–8.
3. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi P Members of the Steering Committee, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof S Members of the Task Force. Official ERS/ATS clinical practice guidelines: noninvasive

ventilation for acute respiratory failure. Eur Respir J. 2017;50(2):1602426.
4. Su CL, Chiang LL, Yang SH, et al. Preventive use of noninvasive ventilation after extubation: a prospective, multicenter randomized controlled trial. Respir Care. 2012;57:204–10.
5. Jiang JS, Kao SJ, Wang SN. Effect of early application of biphasic positive airway pressure on the outcome of extubation in ventilator weaning. Respirology. 1999;4:161–5.
6. Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005;33:2465–70.
7. Ferrer M, Valencia M, Nicolas JM, et al. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006;173:164–70.
8. Vitacca M, Ambrosino N, Clini E, et al. Physiological response to pressure support ventilation delivered before and after extubation in patients not capable of totally spontaneous autonomous breathing. Am J Respir Crit Care Med. 2001;164:638–41.
9. Burns KE, Meade MO, Premji A, et al. Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review. CMAJ. 2014;186:E112–22.
10. Jaber S, Lescot T, Futier E, et al. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery. JAMA. 2016;315:1345–53.

43 Use of Noninvasive Ventilation for Diagnostic and Therapeutic Bronchoscopies in Patients with Respiratory Failure

Priyanka Makkar and Bryan Husta

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43.1 Introduction

Noninvasive ventilation (NIV) is defined as providing ventilatory support through the patient's upper airways (in contradiction to the techniques that bypass the upper airways) using a mask or a different interface [1]. Avoiding the complications associated with invasive ventilation and the fact that NIV is readily available without the need for skills to place endotracheal tube are the mainsprings behind the use of NIV. NIV can be delivered by the means of positive pressure (applied to the airways to inflate the lung) or by negative pressure (applied externally to the abdomen and thorax to allow air entry into the lungs) [2]. This chapter focuses on the use of noninvasive positive pressure ventilation (NIPPV). High flow nasal cannula (HFNC) is another means of NIV wherein heated and humidified oxygen is delivered through the nose [3].

Fiberoptic bronchoscopy is a widely used diagnostic and therapeutic procedure. In mechanically ventilated patients, studies suggest that there is an acceptable risk profile (occurrence or worsening of hypoxemia) of performing bronchoscopies [4]. In non-mechanically ventilated patients with severe hypoxemia, bronchoscopy is contraindicated because of the high risk of developing worsening hypoxemic respiratory failure or cardiac arrhythmias after an uncomplicated procedure [4, 5]. In these high-risk patients, the physician has two options: (1) Electively intubate the patients to

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perform bronchoscopy to ensure adequate gas exchange or (2) Avoid bronchoscopy and empirically treat the patient. Resorting to intubation and result in problems prior to, during intubation, and post extubation. Another scenarios in which NIV can be utilized is in patients who are "Do Not Intubate (DNI)", since NIV has been shown to lessen dyspnea, improve hypoxia and hypercapnia in patients with acute respiratory failure [6]. In this chapter, we look at evidence of safety and feasibility for using NIV by means of face mask positive pressure ventilation and HFNC for diagnostic and therapeutic bronchoscopies in high-risk patients in respiratory failure. We will look at the evidence for use of NIPPV to perform bronchoscopies in patients with hypoxemic and/or hypercapnic respiratory failure and the literature supporting the use of HFNC to perform bronchoscopies in patients with hypoxemic respiratory failure.

43.2 Use of NIV in the Form of BPAP or CPAP in Patients Undergoing Flexible Bronchoscopies

In this section, we will look at the evidence that supports the use of NIV delivered via a face mask in patients with hypoxemic and hypercapnic respiratory failure who require bronchoscopy for diagnostic and therapeutic reasons.

43.2.1 Background

NIPPV augments ventilation by allowing delivery of pressurized gas to the airways thus increase transpulmonary pressure, leading to inflation of the lungs. Exhalation occurs by means of elastic recoil [6]. Continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BPAP) are both means of NIPPV. CPAP refers to the delivery of continuous positive airway pressure and functions similarly to positive end-expiratory pressure. BPAP delivers at set inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). The difference between the IPAP and EPAP corresponds to the driving pressure which generates the tidal volume. The positive effects of NIPPV in patients with respiratory failure are due to a reduction in the respiratory muscle workload [7]. Studies that have looked at the use of NIPPV in acute applications indicate that these effects stem from improvements in gas exchange through augmentation of ventilation [8–11] and improvement in oxygenation via recruitment of alveoli leading to an increase in end-expiratory volume [12].

43.2.2 Application of NIPPV in Bronchoscopy in High-Risk Patients

43.2.2.1 Patients with Hypoxemia and/or Hypercapnia

Baumann et al. [13] studied the feasibility of performing flexible bronchoscopy in a patient with acute respiratory failure requiring NIPPV. This study was an observational, prospective cohort study and conducted in patients with acute hypoxemic respiratory failure with a P_AO_2/F_iO_2 of less than 300 and required NIV prior to bronchoscopy. The mean P_AO_2/F_iO_2 prior to initiation of bronchoscopy was 117 ± 72. They found that 10% (4/40) of the patients required intubation within 8 h of the bronchoscopy and it is unclear if this was due to the natural course of the disease or due to the bronchoscopy. They concluded that bronchoscopy could be performed with an acceptable risk in patients in acute hypoxemic respiratory failure requiring NIPPV. Can this be applied to patients who are not requiring NIPPV for their acute respiratory failure but are hypoxemic?

There are several case series and few randomized control trials looking at using NIPPV during bronchoscopy to prevent respiratory deterioration in patients breathing spontaneously [5, 14–20]. In 1996, Antonelli et al. [5] studied the use of NIPPV (CPAP) delivered via face mask to perform bronchoscopy in 8 immunocompromised patients in acute hypoxemic respiratory failure. They performed the procedure under local anesthesia and provided patients with 100% oxygen during the duration of the

procedure. They found that the patients tolerated the procedure well and none of the patients required intubation or reinstitution of NIPPV within 96 h of the procedure. Moreover, they were able to isolate the causative agent of the pneumonia in all 8 cases. Similarly, Chiner et al. [18] performed flexible bronchoscopies in 35 patients with acute hypoxic respiratory failure (P_AO_2/FiO_2 ratio 168 ± 63) using nasal NIPPV (BPAP) and a bite block with an elastic glove finger; 35 bronchoaspirates, 11 bronchoalveolar lavages, 21 protected brushings, and 8 biopsies were performed. They found that in 80% of the cases diagnosis made via the procedure resulted in a change in antibiotic regimen in patients with pneumonia and in other cases diagnosis of bronchogenic carcinoma and alveolar hemorrhage resulted in different therapeutic approaches. No complications were attributed to the procedure. In 14% of the cases the procedure was therapeutic and resulted in the resolution of respiratory failure. A double-blind, randomized control trial was performed by Maitre et al. [19] comparing NIPPV delivered via CPAP and nasal cannula in hypoxemia patients who required flexible bronchoscopies for diagnostic purposes. Fifteen patients in each study arm underwent bronchoscopies with BAL and 6 h post the procedure, 5 patients in the nasal cannula group versus none in the CPAP group required mechanical ventilatory support. They concluded that despite similar FiO_2 in both groups, CPAP was more efficacious in reducing the decrease in oxygen saturation during and 15 min post the procedure.

In the above-mentioned studies, patients who were hypercapnic or hypoxemic and hypercapnic were not included; so, is it feasible and safe to apply NIPPV in hypercapnic patients for bronchoscopy? In patients with emphysema, bronchoscopy increases air trapping by increase in functional residual capacity by 17% [21]. Patients with obesity hypoventilation syndrome who have awake hypercapnia, the risk of hypoxemia with bronchoscopy is also higher [22]. To assess the feasibility of bronchoscopy in patients with COPD, Conceiacao et al. [23] performed flexible bronchoscopy in 10 patients with COPD who were admitted to the intensive care unit for pneumonia. The patients had a $PaCO_2$ of 67 ± 11 mmHg and underwent bronchoscopy with BPAP via full face mask. No changes in $PaCO_2$ and PaO_2 were found at 1 h after the end of the procedure and none of the patients required invasive ventilation within 24 h of the procedure. This study concluded that it was safe to perform flexible bronchoscopies in patients with COPD and hypercapnia that were not in acute respiratory failure. This study was limited in that its sample size was small and that the patient was not in respiratory failure thus the question regarding the use of NIPPV for bronchoscopy in patients with acute hypercapnic respiratory failure remained unanswered [24].

43.2.2.2 Patients with Central Airway Pathology: Excessive Dynamic Airway Collapse (EDAC) and Tracheobronchomalacia (TBM)

EDAC is defined as >50% collapse of the airway diameter due to the laxity of the posterior membrane of the trachea with structurally intact cartilage rings. TBM is caused by the weakening of the anterior and lateral wall of the cartilage leading to airway collapse [24]. NIPPV (CPAP) is known to improve minute volume and reduce atelectasis. In patients with EDAC and TBM, it can act as a "pneumatic stent" by increasing the transmural pressure on the airways and thereby increasing its diameter [25]. The changes from EDAC and TBM may severely be affected when bronchoscopy is performed under deep sedation thus CPAP helps ameliorating these changes when used during bronchoscopy [22]. The utility of CPAP was demonstrated by Trachsel et al. [26] in young children who are at an increased risk for hypoxemia and hypercapnia during flexible bronchoscopy due to the small size and increased collapsibility of their airways. In their study, they noted that the use of CPAP during flexible bronchoscopy lead to reversal of decrease in tidal volumes, peak tidal expiratory flow, and peak tidal inspiratory flows that were first seen with transition of the bronchoscope through the vocal cords. This provides safety, feasibility, and allows for time to perform the examination.

43.2.2.3 Contraindications to Performing Bronchoscopy with NIV

The contraindications to performing bronchoscopy with NIV are same as those of using NIV. Patients who do not have the ability to protect their airways are at high risk for aspiration, have severe respiratory acidosis, or are unable to maintain oxygen saturation >85% despite high supplemental inspired fraction of oxygen are not ideal candidates for NIV. Mechanical issues such as presence facial deformities, and recent oral, gastric, or esophageal surgery are also contraindications to the use of NIV [17, 27]. In such instances, risks of performing bronchoscopy using NIPPV outweigh the benefits and such decision should be made by the clinician on a case by case bases.

43.3 Use of High Flow Nasal Cannula (HFNC) in Patients Undergoing Flexible Bronchoscopies

43.3.1 Background

HFNC is an open system that can deliver 100% heated and humidified oxygen up to 60 L per minute. It is an useful means of NIV because it reduces the work of breathing, increases volume of inspired gas, and recruits atelectatic alveoli thus reducing ventilation/perfusion mismatch [28]. The utility of HFNC in hypoxemic respiratory failure has been studied in FLORALI trial which showed that 90-day mortality was reduced and there was an increase in ventilator free days at day 28 in patients who received HFNC when compared to standard NIPPV, and oxygen therapy via face mask [29].

43.3.2 Clinical Utility of HFNC in Hypoxic Respiratory Failure and Bronchoscopy

Lucangelo et al. [30] prospectively studied the utility of HFNC in performing diagnostic bronchoscopies with BAL in patients who had resting oxygen saturations >90% and did not present in respiratory or cardiac failure. Forty-five patients were randomly assigned to three groups during bronchoscopy, one group received oxygen 40 L/min, FiO_2 = 0.5 through a Venturi mask, second received oxygen at 40 L/min, FiO_2 = 0.5 via HFNC, and third received oxygen through HFNC, but a higher flow rate was delivered (60 L/min, FiO_2 = 0.5). They found that at flow rates of 40 L/min both the HFNC and venture mask were equally effective; however, at higher flow rates of 60 L/min, the oxygenation was better than at flow rates of 40 L/min. With regards to carbon dioxide kinetics, they did not return to baseline 10 min post bronchoscopy in patients receiving flow at 40 L/min; however, they did return to baseline in patients receiving HFNC at 60 L/min. The mechanism of this is unclear but it is postulated that at high flow rates, a CPAP effect, a smaller possibility of the gas to dilute with room air and a constant fraction of inspired oxygen are responsible [31, 32]. This study showed that HFNC improves oxygenation; however, the patients who underwent bronchoscopy were not hypoxemic thus Simon et al. [33] performed a prospective randomized control trial to study the ability to maintain oxygen saturation during bronchoscopy in patients with acute hypoxic respiratory failure. They also compared HFNC to NIPPV. They found that NIPPV was superior to HFNC in maintaining oxygenation before, during, and after the completion of bronchoscopy. None of the patients required intubation within 8 h post procedure and patients in the HFNC group who had stable oxygen saturations for 15 min tolerated the procedure without difficulty. The clinical utility of the use of HFNC during bronchoscopic procedures in patients with hypoxemic respiratory failure was studied by Chung et al. [34] in a small retrospective review. Ten patients with mean pre-bronchoscopy oxygen saturation on 84% on room air underwent flexible bronchoscopy with diagnostic [7] and therapeutic purposes [3]. Diagnostic bronchoscopy was performed to elucidate the etiology of pulmonary infiltrates in 6 patients and in one case an endobronchial ultrasound-guided transbronchial needle aspiration of lymph node was performed to evaluate for metastatic disease. Patients who underwent therapeutic bronchoscopy did so for purposes of clot removal or

removal of an endobronchial mass. All patients tolerated the procedure well. Patients who underwent diagnostic bronchoscopy did not show decline in their oxygenation post procedure whereas those who underwent therapeutic bronchoscopy had an improvement in their oxygenation post procedure. This study was able to demonstrate clinical utility of using HFNC prior to bronchoscopy in patients who had hypoxemic respiratory failure; however, its small sample size and retrospective nature are limitations. Further research is required to study the utility of HFNC for performing bronchoscopies in patients with hypercapnia and/or hypoxemia. However, initial investigation and clinical reasoning seem to provide a logical clinical application (Table 43.1).

Table 43.1 Learning points

• Bronchoscopy in non-mechanically ventilated patients with severe hypoxemia is contraindicated because of high risk of developing worsening hypoxemic respiratory failure
• Advantages of noninvasive positive pressure ventilation include improved gas exchange through augmentation of ventilation, improvement in oxygenation through recruitment of alveoli and its successful application in "Do not intubate" patients to help reduce work of breathing
• The use of NIPPV to perform bronchoscopy in patients with hypoxic respiratory failure has been successfully used in both immunocompetent and immunocompromised hosts. Studies indicate that the procedure provided diagnosis that changed management of the patient and in many instances was also therapeutic
• NIPPV can be safely used to perform bronchoscopy in the patient with hypercapnia; however, its use in patients with acute hypercapnic respiratory failure needs further investigation
• In patients with excessive dynamic airway collapse and tracheobronchomalacia, NIPPV acts as a "pneumatic stent" and can help ameliorate airway collapse in these patients. This provides safety, feasibility, and allows for time to perform the examination
• Contraindications to the use of noninvasive ventilation include patients with altered mental status, those unable to protect their airways, presence of facial deformities, and recent oral, gastric, and esophageal surgeries
• High flow nasal cannula can be utilized to safely perform diagnostic and therapeutic bronchoscopy in patients with hypoxemic respiratory failure. Further, large prospective studies are required to assess its clinical applications

References

1. British Thoracic Society Standards of Care Committee. Non-invasive ventilation in acute respiratory failure. Thorax. 2002;57(3):192–211.
2. Scala R, Pisani L. Noninvasive ventilation in acute respiratory failure: which recipe for success? Eur Respir Rev. 2018;27(149):180029.
3. Frat J-P, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185–96.
4. Cracco C, Fartoukh M, Prodanovic H, et al. Safety of performing fiberoptic bronchoscopy in critically ill hypoxemic patients with acute respiratory failure. Intensive Care Med. 2013;39:45–52.
5. Antonelli M, Conti G, Riccioni L, Meduri GU. Noninvasive positive-pressure ventilation via face mask during bronchoscopy with BAL in high-risk hypoxemic patients. Chest. 1996;110:724–8.
6. Mehta S, Hill NS. Noninvasive ventilation. Am J Respir Crit Care Med. 2001;163(2):540–77.
7. Carrey Z, Gottfried SB, Levy RD. Ventilatory muscle support in respiratory failure with nasal positive pressure ventilation. Chest. 1990;97(1):150–8.
8. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet. 1993;341(8860):1555–7.
9. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med. 1995;151(6):1799–806.
10. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333(13):817–22.
11. Angus RM, Ahmed AA, Fenwick LJ, Peacock AJ. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. Thorax. 1996;51(10):1048–50.
12. Lin M, Yang YF, Chiang HT, Chang MS, Chiang BN, Cheitlin MD. Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema. Short-term results and long-term follow-up. Chest. 1995;107(5):1379–86.
13. Baumann HJ, Klose H, Simon M, et al. Fiber optic bronchoscopy in patients with acute hypoxemic respiratory failure requiring noninvasive ventilation-a feasibility study. Crit Care. 2011;15:R179.
14. Antonelli M, Conti G, Rocco M, et al. Noninvasive positive-pressure ventilation vs conventional oxygen supplementation in hypoxemic patients undergoing diagnostic bronchoscopy. Chest. 2002;121:1149–54.
15. Antonelli M, Pennisi MA, Conti G, et al. Fiberoptic bronchoscopy during noninvasive positive pressure ventilation delivered by helmet. Intensive Care Med. 2003;29(1):126–9.
16. Chiner E, Llombart M, Signes-Costa J, et al. Description of a new procedure for fiberoptic bron-

choscopy during noninvasive ventilation through a nasal mask in patients with acute respiratory failure. Arch Bronconeumol. 2005;41(12):698–701.
17. Heunks LM, de Bruin CJ, van der Hoeven JG, van der Heijden HF. Non-invasive mechanical ventilation for diagnostic bronchoscopy using a new face mask: an observational feasibility study. Intensive Care Med. 2010;36(1):143–7.
18. Chiner E, Sancho-Chust JN, Llombart M, Senent C, Camarasa A, Signes-Costa J. Fiberoptic bronchoscopy during nasal non-invasive ventilation in acute respiratory failure. Respiration. 2010;80(4):321–6.
19. Maitre B, Jaber S, Maggiore SM, et al. Continuous positive airway pressure during fiberoptic bronchoscopy in hypoxemic patients: a randomized double-blind study using a new device. Am J Respir Crit Care Med. 2000;162:1063–7.
20. Agarwal R, Khan A, Aggarwal AN, Gupta D. Bronchoscopic lung biopsy using noninvasive ventilatory support: case series and review of literature of NIV-assisted bronchoscopy. Respir Care. 2012;57(11):1927–36.
21. Matsushima Y, Jones RL, King EG, Moysa G, Alton JD. Alterations in pulmonary mechanics and gas exchange during routine fiberoptic bronchoscopy. Chest. 1984;86(2):184–8.
22. Murgu SD, Pecson J, Colt HG. Flexible bronchoscopy assisted by noninvasive positive pressure ventilation. Crit Care Nurse. 2011;31(3):70–6.
23. Da Conceiçao M, Genco G, Favier JC, Bidallier I, Pitti RJ. Fiberoptic bronchoscopy during noninvasive positive-pressure ventilation in patients with chronic obstructive lung disease with hypoxemia and hypercapnia. Ann Fr Anesth Reanim. 2000;19:231–6.
24. Murgu SD, Colt HG. Treatment of adult tracheobronchomalacia and excessive dynamic airway collapse: an update. Treat Respir Med. 2006;5(2):103–15.
25. Esquinas A, Zuil M, Scala R, Chiner E. Bronchoscopy during non-invasive mechanical ventilation: a review of techniques and procedures. Arch Bronconeumol. 2013;49(3):105–12.
26. Trachsel D, Erb TO, Frei FJ, Hammer J. Use of continuous positive airway pressure during flexible bronchoscopy in young children. Eur Respir J. 2005;26(5):773–7.
27. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004;350(24):2452–60.
28. Ni YN, Luo J, Yu H, et al. Can high-flow nasal cannula reduce the rate of endotracheal intubation in adult patients with acute respiratory failure compared with conventional oxygen therapy and noninvasive positive pressure ventilation?: a systematic review and meta-analysis. Chest. 2017;151(4):764–75.
29. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185–96.
30. Lucangelo U, Vassallo FG, Marras E, et al. High-flow nasal interface improves oxygenation in patients undergoing bronchoscopy. Crit Care Res Pract. 2012;2012:506382.
31. Kernick J, Magarey J. What is the evidence for the use of high flow nasal cannula oxygen in adult patients admitted to critical care units? A systematic review. Aust Crit Care. 2010;23(2):53–70.
32. Wettstein RB, Shelledy DC, Peters JI. Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. Respir Care. 2005;50(5):604–9.
33. Simon M, Braune S, Frings D, Wiontzek A-K, Klose H, Kluge SJCC. High-flow nasal cannula oxygen versus non-invasive ventilation in patients with acute hypoxaemic respiratory failure undergoing flexible bronchoscopy—a prospective randomised trial. Crit Care. 2014;18(6):712.
34. Chung SM, Choi JW, Lee YS, et al. Clinical effectiveness of high-flow nasal cannula in hypoxaemic patients during bronchoscopic procedures. Tuberc Respir Dis. 2019;82(1):81–5.

Role of Sedation and Analgesia During Noninvasive Ventilation

44

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Abbreviations

ACPE	Acute cardiogenic pulmonary edema
ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
NIV	Noninvasive ventilation

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44.1 Introduction

In the last decades, NIV has gained its application particularly in different subsets of patients with acute respiratory failure (ARF). There is evidence that suggests the additional use of NIV to standard care in order to improve the outcomes in chronic obstructive pulmonary disease (COPD) and acute cardiogenic pulmonary edema (ACPE) [1, 2]. The technique is also used to back up the ventilation in patients with ARF from other etiologies. However, successful endpoints are achieved by the appropriate patient selection and tolerance of the patient subset. The reasons for interruption of NIV application are a pain, discomfort or claustrophobia [3]. The relative contraindications to the use of NIV are delirium and agitation [4]. Therefore, even though sedation is not mandatory for NIV, it may help in some

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situations for better tolerance of NIV in the selected population to achieve the desired endpoints. The choice of which sedative/analgesic to use during noninvasive ventilation remains controversial. Practice guideline in this aspect is also missing. This chapter faces up the use of sedatives and analgesics during the application of NIV.

44.2 Literature Review

44.2.1 The Use of Sedation in NIV

To date, there are not principles or algorithm useful to guide the situations that can benefit from the use of sedation during NIV [5]. Observational studies and clinical trials have assessed the potential use of sedative or analgesic drugs to avoid patient's discomfort and to prevent or to treat NIV intolerance [6]; however, there is a lack of robust data to guide the development of best practice in this field.

There are several reasons that could be related to poor NIV acceptance and any decision to resort to sedation must be taken as the last stage in a careful evaluation of the causes of actual or pending failure, as shown in Fig. 44.1 [5]. For example, the patient acceptance varies according to the type of mask that is used, as it is greatest with the least constricting interfaces, such as the helmet, and declines with more intrusive forms of a mask. Also, the assisted ventilation pattern can influence patient compliance, as bilevel positive airways pressure often produces a need for sedation whereas spontaneous breathing models such as continuous positive airways pressure seldom require such interventions. Despite numerous non-pharmacological strategies may be employed to avert NIV failure, some patients remain intolerant and uncooperative with a poor patient-ventilator synchrony; under these circumstances, administration of analgesia and sedation in the attempt to reverse the situation may be worthwhile before the intubation.

Sedation and/or analgesia can relieve the patient-ventilator asynchrony. However, whether

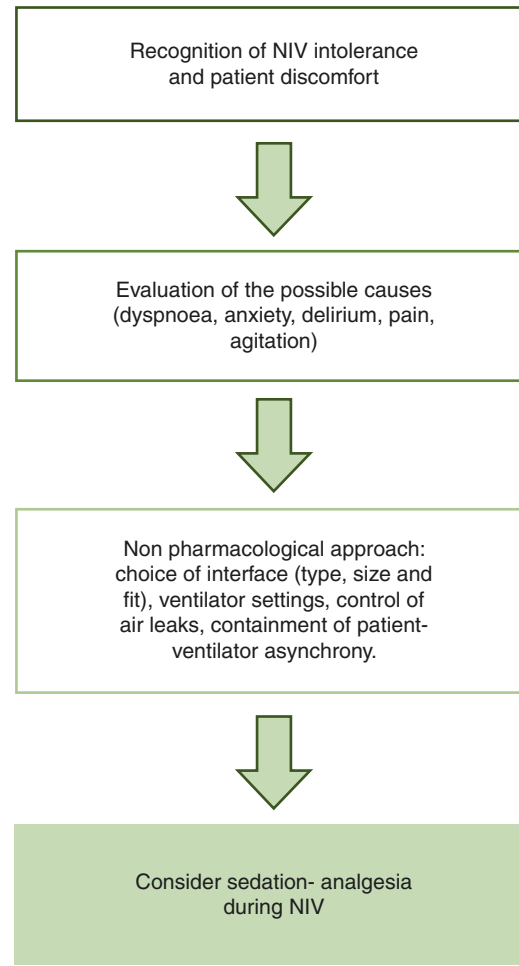

Fig. 44.1 Causes for poor NIV acceptance

sedation and/or analgesia can benefit the clinical outcome of the patients with interface intolerance is still unclear.

Yue-Nan et al. performed a retrospective study on patients with interface intolerance who received noninvasive -positive pressure ventilation (NIPPV) after extubation in seven intensive care units (ICU). Of a total of 80 patients, 41 received sedation and/or analgesia treatment (17 used analgesia, 11 used sedation, and 13 used both) at some time during NIPPV. They showed a decrease of NIPPV failure rate (15% vs. 38%, $p = 0.015$), mortality rate (7% vs. 33%, $p = 0.004$), and the length of ICU stay after extubation [7].

44.2.2 Side Effects of Sedation

Intensivists and nurses managed frequently sedative and analgesic drugs, that are commonly used to improve patient comfort and tolerance, to minimize reactions to painful stimuli and the physiologic stress response, and to modulate patient respiratory efforts. The management of these drugs can be very challenging because of the different sensitivities and rates of metabolism between patients. For example, chronic users of benzodiazepines or opiates may require high doses of these drugs, because they developed tolerance, whereas naive users may exhibit profound respiratory depression, even with relatively small doses [8]. Thus, sedation and analgesia should be administered by experienced staff using the minimum doses required to achieve tolerance, avoiding over-sedation. This should be in a setting where electrocardiogram and oximetry tracings can be monitored continuously. Several sedation scales are available and may be helpful in ensuring that the level of sedation is minimized; but, once again, application of these requires trained staff [8]. In consideration of the fact that the use of the NIV is not the prerogative of the intensive care units, particular attention must be paid to the use of sedatives and analgesics in less intensively monitored environments.

Furthermore, it is not clear if sedation is per se a factor contributing to the success or failure of NIV [5]. Even though sedation can improve patient acceptance and tolerance, there is no robust evidence that it will affect situations where the response rate to NIV is intrinsically poor. Indeed, adding sedation may be disadvantageous by obscuring a failure of NIV due to the underlying pathology and thus delaying necessary intubation [9].

44.2.3 Sedatives and Analgesics in NIV in Clinical Scenarios

Muriel et al. aimed to assess the impact of analgesic and/or sedative drugs on the risk of NIV failure (defined as the need for invasive mechanical ventilation) [10]. They studied patients who received at least 2 h of NIPPV as first-line therapy in a prospective observational study carried out in 322 intensive care units from 30 countries. Using a marginal structural model analysis, they showed no deleterious effect on NIV outcome when sedation or analgesia was used alone, but their combination was significantly associated with NIV failure, ICU mortality, and 28-day mortality. They found that sedation and analgesia were administered in only about 20% of patients using NIV, confirming the results of an earlier web-survey performed in North America and Europe. That survey revealed that opioids alone were more likely to be used in European countries while benzodiazepines were the preferred agent in the United States, demonstrating that not only sedation is infrequently used in NIV, but also that practices vary widely depending on configuration and geographical areas, based on clinical experience with different agents [11].

Several observational studies [12–16] and three randomized trials comparing midazolam and dexmedetomidine or placebo [17–19] have assessed the potential use of sedative and/or analgesic drugs to reduce discomfort and risk of NIV failure (Table 44.1).

Table 44.1 Summary of studies assessing the drugs used in NIV

References	Number of patients	Sedative and/or analgesic drugs used
Rocker et al. [12]	9/12	Midazolam/morphine
Constantin et al. [13]	13	Propofol/remifentanil
Akada et al. [14]	10	Dexmedetomidine
Rocco et al. [15]	36	Remifentanil
Clouzeau et al. [16]	10	Propofol
Senoglu et al. [17]	40	Dexmedetomidine vs. midazolam
Huang et al. [18]	62	Dexmedetomidine vs. midazolam
Devlin et al. [19]	33	Dexmedetomidine vs. placebo ± midazolam and/or fentanyl

44.2.4 Drugs Used for NIV

Evidence to define a specific sedative drug during NIV is lacking [5]. In the choice of the "ideal" drug, some criteria should be considered, such as the preservation of ventilatory drive, the delirium avoidance, the promotion of sleep, the effects on airways patency, the hemodynamic impact, and the anxiolysis. No specific drugs fully satisfy all these criteria, so the decision reflects the process that involved the clinical practice [5].

Data obtained during invasive ventilation suggest caution in using **propofol** and **opiates** as a sedation strategy during NIV, in view of the potentially negative effects on the respiratory pattern. Measuring the electrical activity of the diaphragm (EAdi), Vaschetto et al. [20] showed in intubated patients that propofol significantly interferes with the patient-ventilator synchrony in pressure support ventilation (PSV) at doses producing deep sedation. Both during PSV and neurally adjusted ventilator assistance (NAVA), propofol reduced neural drive and effort, while not significantly affecting respiratory timing.

On the contrary, a continuous infusion of opiates did not reduce respiratory drive but showed detrimental effects on respiratory timing both when airway occlusion pressure at 0.1 s (P 0.1) was assessed [21, 22] or when EAdi was directly measured [23].

From a pharmacological point of view, **benzodiazepines** can be avoided during NIV as the use of benzodiazepines has been associated with delirium. **Dexmedetomidine** seems to have a most suitable overall pharmacological profile: the absence of respiratory side effects could be of interest in patients receiving NIV but more data are required. Nowadays there are only a few studies regarding the use of dexmedetomidine, with reduced sample size and with conflicting results. Senoglu et al. compared 24-h infusions of dexmedetomidine and midazolam in 40 uncooperative patients receiving NIV for ARF due to acute exacerbations of chronic obstructive pulmonary disease [17]. Though no patient experienced NIV failure during the study period, compared to midazolam, dexmedetomidine required fewer dosing adjustments to maintain adequate sedation ($p < 0.01$). This study, however, considers only the first 24 h of NIV and does not provide valuable information on any outcome variable.

Huang et al. randomized 62 hypoxemic patients with acute pulmonary edema refusing to continue the NIV sessions because of discomfort [18] into two groups of treatment: midazolam or dexmedetomidine. This study did not report serious adverse events, and none of the patients interrupted the study protocol; bradycardia occurred more with dexmedetomidine (18.2% vs. 0, $p = 0.016$). The rate of failure (e.g., endotracheal intubation) was overall 32%. In the dexmedetomidine group of patients, NIV failure was lower (21%) than in the midazolam group (45%), $p = 0.043$. In addition, dexmedetomidine led to a more desired level of awake sedation, shortened the duration of mechanical ventilation and the length of ICU stay.

Devlin et al. enrolled 33 adult patients with ARF within 8 h after starting NIV and divided them into two groups to receive dexmedetomidine (preventive approach) or placebo up to 72 h [19]. Patients with agitation or pain could also receive a bolus of midazolam or fentanyl by intravenous administration, as needed. The administration of dexmedetomidine after NIV initiation neither prevented the occurrence of NIV tolerance nor helped to maintain adequate level sedation.

Ketamine does not determine respiratory depression at doses given for analgesia or procedural sedation [24]. Furthermore, it decreases airway resistance, improves dynamic compliance, and preserves functional residual capacity, minute ventilation, and tidal volume, while retaining protective pharyngeal and laryngeal reflexes [25]. Ketamine can produce hypersalivation and emergency reactions [25]. Because of its effects on the sympathetic nervous system, ketamine should not be used in decompensated heart failure (typically cardiogenic pulmonary edema in the context of NIV). Several studies investigated the use of ketamine for procedural sedation [26], but there are no data during the application of NIV [5].

44.3 Recent Evidence

Electronic databases (Google Scholar, PubMed, and Cochrane library) from 2017 to 2019 were searched to find out the recent literature related to sedation in noninvasive ventilation. The search strategy flow chart is presented in Fig. 44.2 and the included results are presented in Table 44.2.

The study conducted by Shutes et al. retrospectively reviewed the chart of the patients who received dexmedetomidine infusion for >24 h and their discontinuation pattern and its relation with hemodynamics of the patients and withdrawal [27]. The study found that the dexmedetomidine sedation was having a predictive hemodynamic effect. The cumulative dose was associated with withdrawal, but symptoms were manageable with short-term enteral clonidine. Venkatraman et al. also conducted a retrospective evaluation including pediatric patients who received NIV and dexmedetomidine infusion within 48 h of ICU admission [28]. The study found the dexmedetomidine infusion as the single continuous sedative was effective; however, dose titration was required to get rid of mild cardiorespiratory events. Piastra et al. also performed one retrospective analysis of data from 40 pediatric group patients who were receiving NIV for ARF [29]. They analyzed the effectiveness of dexmedetomidine as infusion sedative and found that early dexmedetomidine infusion in such patients was safe and effective in reducing patient-ventilator synchronization and permitting lung recruitment. Ni et al. also conducted one retrospective study including 80 adult patients [30]. They evaluated the effect of sedation and/or analgesia as rescue treatment during NIV in the patients with interface intolerance after extubation and found that sedation and/or analgesia treatment can decrease the rate of NIV failure. The study also found decreased hospital mortality rate and ICU LOS in patients who received analgesia and/or sedation. Our search, however, could not find a prospective, randomized trial and future such trial will help in generating better evidence.

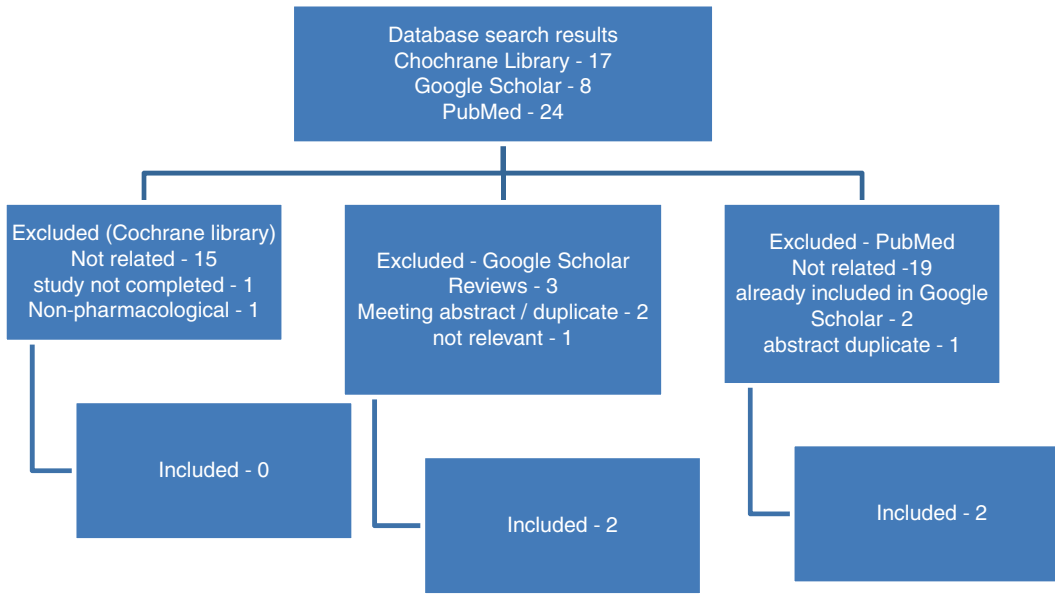

Fig. 44.2 Flow chart showing the search strategy

Table 44.2 List of articles included for review and analysis

Authors (year)	Number of patients	Drugs/intervention	Results/remarks
Shutes (2018) [27]	382 children	Dexmedetomidine	The objective was to know the effect of hemodynamics and withdrawal
Venkatraman (2017) [28]	202 children	Dexmedetomidine	Effective sedation
Piastra (2018) [29]	40 children	Dexmedetomidine	Safety and efficacy as a sedative
Ni (2017) [30]	80 adults		Analgesia and sedation

44.4 Conclusions

Current evidence suggests that sedation in patients receiving NIV has a potential benefit. However, it is not devoid of adverse effects. Pharmacological sedation should be chosen only if non-pharmacological one fails. No single sedative agent is available that fulfills the criteria for an ideal drug and further studies are required to determine it. However, dexmedetomidine is noted as an emerging drug as a sedative in such patients. Further study, especially randomized controlled trial or active control trial, will be required in the future. All patients receiving sedation should be monitored and evaluated at a frequent interval and dose needs to be titrated as required.

References

1. Hillberg RE, Johnson DC. Non-invasive ventilation. N Engl J Med. 1997;337:1746–52.
2. Mehta S, Hill NS. Non-invasive ventilation. Am J Respir Crit Care Med. 2001;163:540–77.
3. Carlucci A, Richard JC, Wysocki M, Lepage E, Brochard L, SRLF Collaborative Group on Mechanical Ventilation. Non-invasive versus conventional mechanical ventilation. An epidemiologic survey. Am J Respir Crit Care Med. 2001;163:874–80.
4. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet. 2009;374:250–9.
5. Longrois D, Conti G, Mantz J, Faltlhauser A, Aantaa R, Tonner P. Sedation in non-invasive ventilation: do we know what to do (and why)? Multidiscip Respir Med. 2014;9:56.
6. Hilbert G, Navalesi P, Girault C. Is sedation safe and beneficial in patients receiving NIV? Yes. Intensive Care Med. 2015;41:1688–91.
7. Ni Y-N, Wang T, Yu H, Liang B-M, Liang Z-A. The effect of sedation and/or analgesia as rescue treatment during noninvasive positive pressure ventilation in the patients with Interface intolerance after extubation. BMC Pulm Med. 2017;17:125.
8. Conti G, Hill NS, Nava S. Is sedation safe and beneficial in patients receiving NIV? No. Intensive Care Med. 2015;41:1692.
9. Glossop AJ, Shephard N, Bryden DC, Mills GH. Non-invasive ventilation for weaning, avoiding reintubation after extubation and in the postoperative period: a meta-analysis. Br J Anaesth. 2012;109:305–14.
10. Muriel A, Peñuelas O, Frutos-Vivar F, et al. Impact of sedation and analgesia during noninvasive positive pressure ventilation on outcome: a marginal structural model causal analysis. Intensive Care Med. 2015;41:1586.
11. Devlin JW, Nava S, Fong JJ, Bahhady I, Hill NS. Survey of sedation practices during noninvasive positive-pressure ventilation to treat acute respiratory failure. Crit Care Med. 2007;35(10):2298–302.
12. Rocker GM, Mackenzie MG, Williams B, Logan PM. Non invasive positive pressure ventilation: successful outcome in patients with acute lung injury/ARDS. Chest. 1999;115:173–7.
13. Constantin JM, Schneider E, Cayot-Constantin S, Guerin R, Bannier F, Futier E, Bazin JE. Remifentanil based sedation to treat noninvasive ventilation failure: a preliminary study. Intensive Care Med. 2007;33:82–7.
14. Akada S, Takeda S, Yoshida Y, Sakamoto A. The efficacy of dexmedetomidine in patients with non invasive ventilation: a preliminary study. Anesth Analg. 2008;107:167–70.
15. Rocco M, Conti G, Alessandri E, Morelli A, Spadetta G, Laderchi A, Di Santo C, Francavilla S, Pietropaoli P. Rescue treatment for noninvasive ventilation failure due to interface intolerance with remifentanil analgosedation: a pilot study. Intensive Care Med. 2010;36:2060–5.
16. Clouzeau B, Bui HN, Vargas F, Grenouillet-Delacre M, Guilhon E, Gruson D, Hilbert G. Target-controlled infusion of propofol for sedation in patients with non-invasive ventilation failure due to low tolerance: a preliminary study. Intensive Care Med. 2010;36:1675–80.
17. Senoglu N, Oksuz H, Dogan Z, Yildiz H, Demirkiran H, Ekerbicer H. Sedation during noninvasive mechanical ventilation with dexmedetomidine or midazolam: a randomized, double-blind, prospective study. Curr Ther Res. 2010;71:141–53.

18. Huang Z, Chen YS, Yang ZL, Liu JY. Dexmedetomidine versus midazolam for the sedation of patients with non-invasive ventilation failure. Intern Med. 2012;51:2299–305.
19. Devlin JW, Al-Qadheeb NS, Chi A, Roberts RJ, Qawi I, Garpestad E, Hill NS. Efficacy and safety of early dexmedetomidine during noninvasive ventilation for patients with acute respiratory failure: a randomized, double-blind, placebo-controlled pilot study. Chest. 2014;145:1204–12.
20. Vaschetto R, Cammarota G, Colombo D, et al. Effects of propofol on patient-ventilator synchrony and interaction during pressure support ventilation and neurally adjusted ventilatory assist. Crit Care Med. 2014;42(1):74–82.
21. Cavaliere F, Antonelli M, Arcangeli A, et al. A low-dose remifentanil infusion is well tolerated for sedation in mechanically ventilated, critically-ill patients. Can J Anaesth. 2002;49:1088–94.
22. Conti G, Arcangeli A, Antonelli M, et al. Sedation with sufentanil in patients receiving pressure support ventilation has no effects on respiration: a pilot study. Can J Anaesth. 2004;51(5):494–9.
23. Costa R, Cammarota G, Spinazzola G, et al. Effects of Remifentanil on respiratory drive and timing during PSV and NAVA. Intensive Care Med. 2010;36(2):S346.
24. Morel DR, Forster A, Gemperle M. Noninvasive evaluation of breathing pattern and thoraco-abdominal motion following the infusion of ketamine or droperidol in humans. Anesthesiology. 1986;65:392–8.
25. Miller AC, Jamin CT, Elamin EM. Continuous intravenous infusion of ketamine for maintenance sedation. Minerva Anestesiol. 2011;77:812–20.
26. Parashchanka A, Schelfout S, Coppens M. Role of novel drugs in sedation outside the operating room: dexmedetomidine, ketamine and remifentanil. Curr Opin Anaesthesiol. 2014;27:442–7.
27. Shutes BL, Gee SW, Sargel CL, Fink KA, Tobias JD. Dexmedetomidine as single continuous sedative during noninvasive ventilation: typical usage, hemodynamic effects, and withdrawal. Pediatr Crit Care Med. 2018;19(4):287–97. https://doi.org/10.1097/PCC.0000000000001451.
28. Venkatraman R, Hungerford JL, Hall MW, Moore-Clingenpeel M, Tobias JD. Dexmedetomidine for sedation during noninvasive ventilation in pediatric patients. Pediatr Crit Care Med. 2017;18(9):831–7. https://doi.org/10.1097/PCC.0000000000001226.
29. Piastra M, Pizza A, Gaddi S, Luca E, Genovese O, Picconi E, De Luca D, Conti G. Dexmedetomidine is effective and safe during NIV in infants and young children with acute respiratory failure. BMC Pediatr. 2018;18(1):282. https://doi.org/10.1186/s12887-018-1256-y.
30. Ni YN, Wang T, Yu H, Liang BM, Liang ZA. The effect of sedation and/or analgesia as rescue treatment during noninvasive positive pressure ventilation in the patients with interface intolerance after extubation. BMC Pulm Med. 2017;17(1):125. Published 2017 Sep 15. https://doi.org/10.1186/s12890-017-0469-4.

Noninvasive Ventilation in Immunocompromised Patients

45

Jun Duan, Linfu Bai, Xiaoli Han, and Lintong Zhou

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45.1 Introduction

In recent years, the survival significantly increased in critically ill immunocompromised patients due to improvements in medical management, as well as new indications for immunosuppressive treatment [1]. Most of the critically ill immunocompromised patients required admission to ICU for intensive care and oxygen support due to acute respiratory failure. However, the mortality was very high in these patients, especially in those who received invasive mechanical ventilation. And invasive mechanical ventilation strongly predicts mortality, possibly because of the risks of invasive ventilation itself [2]. Therefore, avoidance of intubation for invasive mechanical ventilation is a major treatment goal.

Noninvasive oxygen including noninvasive ventilation (NIV), high-flow nasal cannula (HFNC) and conventional oxygen therapy is the main technique to avoid intubation. The evidences on the use of these techniques have been improved in the last 2 years. The aim of this review was to summarize the evidences of different oxygen techniques on critically ill immunocompromised patients.

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45.2 Research Strategy

We searched the PubMed on the topic of NIV or HFNC in immunocompromised patients published from Jan first, 2017 to Mar 31th, 2019. The primary keywords were "noninvasive ventilation", "high flow nasal cannula", and "immunosuppression". The synonym included "noninvasive mechanical ventilation", "noninvasive positive pressure ventilation", "continuous positive airway pressure", and "high flow oxygen therapy". Immunosuppression resulted from various reasons such as solid tumor, malignancy, organ transplantation, immunodeficiency, and administration of steroids and immunosuppressants. These words were also included. Finally, we enrolled 12 original articles, 3 systemic reviews and meta-analysis, and a guideline in this review.

45.3 Epidemiology of NIV and HFNC in Immunocompromised Patients

An international, multicenter, prospective cohort study was performed in 459 ICUs from 50 countries across 5 continents during 4 consecutive weeks to investigate the incidence of acute respiratory distress syndrome (ARDS) in patients undergoing invasive or noninvasive ventilation [3]. Cortegiani et al. [4] performed a secondary analysis focused on immunocompromised patients with ARDS. The incidence of immunocompromised patients was 20.8% in the ARDS population. The major reason for ARDS was pneumonia (70.5%) in immunocompromised patients. The major reason for immunosuppression was hematologic and/or active neoplasm (61.1%). However, 38.9% of patients had unknown reasons for immunosuppression. Among the immunocompromised patients, 20.9% of patients received NIV. The NIV failure rate, ICU mortality, and hospital mortality were much higher in immunocompromised patients than in immunocompetent subjects (48% vs. 40%, 58% vs. 29%, and 63% vs. 40%, respectively). However, in patients who experienced NIV failure, the ICU and hospital mortality significantly increased compared with subjects who initially received intubation for invasive mechanical ventilation (58% vs. 46% and 63% vs. 53%, respectively).

In addition, in the 1004 cancer patients with ARDS, Neuschwander et al. [5] reported that 38.6% of patients received NIV intervention. NIV failure rate was very high (up to 71%). In this study, the severe ARDS (OR = 1.89, 95% CI: 1.05–1.19), pulmonary infection (OR = 1.81, 95% CI: 1.08–3.03), and modified sequential organ failure assessment (SOFA) score (without respiratory score) (OR = 1.13, 95% CI: 1.06–1.21) were associated with NIV failure. Moreover, NIV failure was associated with death in hospital (OR = 2.52, 95% CI: 1.56–4.07).

In another multinational observational prospective cohort study in 16 countries (68 centers), Azoulay et al. [6] assessed the initial oxygenation strategy on mortality in 1611 immunocompromised patients. The disease proportion was hematological malignancies 51.9%, solid tumors 35.2%, systemic diseases 17.3%, and solid organ transplantation 8.8%. The main acute respiratory failure etiologies were bacterial (29.5%), viral (15.4%), and fungal infections (14.7%), or undetermined (13.2%). On admission, 56.8% of patients were not intubated for invasive mechanical ventilation. Among them, 53.9% of patients received standard oxygen, 20.3% for HFNC, 17.2% for NIV, and 8.6% for NIV + HFNC. There was no difference in hospital and 90-day mortality among different oxygenation strategies excluded first-line invasive mechanical ventilation. First-line invasive mechanical ventilation was associated with mortality (OR = 2.55, 95% CI: 1.94–3.29). However, it was much higher in patients with NIV failure (OR = 3.65, 95% CI: 2.05–6.53) or HFNC failure (OR = 5.54, 95% CI: 3.27–9.39). Similar mortality with first-line invasive mechanical ventilation was found in NIV + HFNC failure (OR = 2.31, 95% CI: 1.09–4.91).

Early identification of NIV failure and early intubation is potential for decreasing mortality. Our team developed a scale considering heart

Table 45.1 Characteristics of the included studies in epidemiological review

Study/year	Study design	Number of patients	Main outcomes
Cortegiani et al. (2018) [4]	Cross-section survey	2813	Immunosuppression is frequent in patients with ARDS, and infections are the main risk factors for ARDS. Compared with immunocompetent subjects, they have higher mortality regardless of ARDS severity. Nonetheless, nearly half of these patients survive to hospital discharge
Neuschwander et al. (2017) [5]	Post-hoc analysis of a multicenter database	1004	NIV failure in ARDS patients with malignancy is frequent and related to ARDS severity, SOFA score, and pulmonary infection. NIV failure is associated with in-hospital mortality
Azoulay et al. (2017) [6]	Prospective cohort study in 16 countries	1611	First-line invasive mechanical ventilation was associated with mortality. HFNC has an effect on intubation but not on mortality rates. Failure of NIV or HFNC was associated with increased mortality

rate, acidosis, consciousness, oxygenation, and respiratory rate (HACOR score) to predict NIV failure in patients with hypoxemic respiratory failure [7]. In the pulmonary cancer subgroup analysis, 83 subjects were enrolled. Using 5 points of HACOR score as cutoff value, the sensitivity and specificity to predict NIV failure were 73% and 94%, respectively. Moreover, the overall predictive accuracy reached 81%. The HACOR score is a promising tool to manage immunocompromised patients undergoing NIV to avoid delayed intubation (Table 45.1).

45.4 NIV in Patients with Immunosuppression

Kotecha et al. [8] reported the domiciliary NIV in patients post lung transplantation. They retrospectively screened 488 patients with lung transplantation and found that 20 patients (4.1%) required NIV support during 6.5 years. The main indications for NIV were the development of chronic lung allograft dysfunction and diaphragm palsy. The median time from lung trasplantation to NIV was 9 months. However, the mortality was 45%, continuous use of NIV was 40%, and liberation off NIV was only 15%.

Rathi et al. [9] retrospectively enrolled 1614 cancer patients to compare the efficacy of first-line NIV ($N = 793$) to first-line invasive mechanical ventilation ($N = 821$). In patients with first-line NIV, 38% of them experienced NIV failure and received intubation for invasive mechanical ventilation. The ICU mortality was lowest in NIV success patients (28.2%), median in first-line invasive mechanical ventilation group (61.5%), and highest in NIV failure group (71.3%). Variables independently associated with NIV failure included younger age (OR = 0.99, 95% CI: 0.98–0.99), non-Caucasian race (OR = 1.61, 95% CI: 1.14–2.26), presence of a hematologic malignancy (OR = 1.87, 95% CI: 1.33–2.64), and a higher SOFA score (OR = 1.12, 95% CI: 1.08–1.17). Variables independently associated with hospital mortality included NIV success vs. NIV failure (OR = 0.29, 95% CI: 0.20–0.40), first-line invasive mechanical ventilation vs. NIV failure (OR = 0.43, 95% CI: 0.31–0.61), and a higher SOFA score (OR = 1.18, 95% CI: 1.14–1.21).

Liu et al. [10] retrospectively enrolled 79 patients with hematologic malignancy for NIV. Of them, 65% of patients experienced NIV failure. Patients with acute leukemia, higher $PaCO_2$ at baseline, and required higher FiO_2 were more likely to have experienced NIV failure. Mortality at 3 months was much higher in patients with NIV failure compared to NIV successful patients (76% vs. 21%).

Dumas et al. [11] performed a post hoc joint analysis of three previously published studies conducted in 847 critically ill immunocompromised patients. Different from previous studies, this study focused on predicting the need for

intubation on the coming day (the first 3 days), and not discriminate among ICU patients of those who will be intubated or not. The probability of intubation at day+1 was higher in the NIV group vs. oxygenation therapy (OR = 1.64, 95% CI: 1.09–2.48) or vs. the standard oxygen group (OR = 2.05, 95% CI: 1.29–3.29); it was also increased in the HFNC group compared to standard oxygen (OR = 2.85, 95% CI: 1.37–5.67). However, all these differences disappeared by handling confounding-by-indication in the weighted samples, as well as in the pooled model.

Chen et al. [12] enrolled 58 respiratory failure patients with lung cancer for NIV. Of them, 33 patients were first-line intervention by NIV and 25 patients were used for post-extubation respiratory failure. The 28-day, 90-day, and 1-year mortality rates were 39.7%, 63.8%, and 86.2%, respectively. NIV as the first-line therapy for respiratory failure (reference post-extubation respiratory failure) was independently associated with 28-day mortality (OR = 35.37, 95% CI: 3.30–378.68) (Table 45.2).

45.5 HFNC in Patients with Immunosuppression

Kang et al. [13] retrospectively analyzed the efficacy of HFNC in 91 immunocompromised patients. This study originally used the SpO_2/FiO_2 (SF ratio) to assess the response to HFNC. In patients with SF ratio improved at 48 h of HFNC, the 28-day mortality was significantly decreased compared with subjects who had no improvement. However, it was not confirmed in multivariate analysis. Anyway, this study has potential application prospect as the SF ratio is simple and reproducible to assess the response to HFNC in immunocompromised patients.

Kim et al. [14] retrospectively enrolled 52 non-HIV-related pneumocystis pneumonia patients to analyze the efficacy of HFNC. The HFNC failure rate was high (up to 56%). The baseline SOFA score was independently associated with HFNC failure (OR = 1.74 per each score unit increase, 95% CI: 1.05–2.89). Furthermore, HFNC failure was independently

Table 45.2 Characteristics of the included studies in NIV review

Study/year	Study design	Comparison	Number of patients	Main outcomes
Kotecha et al. (2018) [8]	Retrospective	No	20	Mortality was high in patients with domiciliary NIV in post lung transplantation
Rathi et al. (2017) [9]	Retrospective	NIV vs. invasive mechanical ventilation	1614	First-line invasive mechanical ventilation and first-line NIV failure were two independent risk factors for ICU mortality. Patients with first-line invasive mechanical ventilation had better outcomes than those who received NIV but experienced NIV failure
Liu et al. (2017) [10]	Retrospective	No	79	Acute leukemia, high $PaCO_2$ at baseline and requirement of high FiO_2 were predictors of NIV failure. NIV failure was associated with increased 3-month mortality
Dumas et al. (2018) [11]	Post hoc analysis of three previously published studies	NIV vs. oxygen therapy; NIV vs. standard oxygen; HFNC vs. standard oxygen	847	Ventilation/oxygenation management had no impact on the probability of intubation on the coming day
Chen et al. (2018) [12]	Retrospective	No	58	Mortality was high in lung cancer patients who used NIV due to respiratory failure. Patients with first-line NIV had higher 28-day mortality than subjects who used NIV due to post-extubation respiratory failure

Table 45.3 Characteristics of the included studies in HFNC review

Study/year	Comparison	Study design	Number of patients	Main outcomes
Kang et al. (2018) [13]	No	Retrospective	91	SpO_2/FiO_2 ratio measured at 48 h of HFNC was associated with decreased 28-day mortality in univariate analysis but not in multivariate analysis
Kim et al. (2017) [14]	No	Retrospective	52	Baseline SOFA score was associated with HFNC failure, and HFNC failure was associated with 60-day mortality
Azoulay et al. (2018) [15]	HFNC vs. standard oxygen	Multicenter RCT with 1:1 randomization	778	HFNC did not significantly reduce 28-day mortality and intubation rate
Lemiale et al. (2017) [16]	HFNC vs. standard oxygen	Post hoc analysis of an RCT	353	HFNC did not significantly reduce 28-day mortality and intubation rate

associated with 60-day mortality (OR = 6.92, 95% CI: 1.24–38.62).

A multicenter randomized control study was performed by Azoulay et al. [15] to explore the efficacy of HFNC in immunocompromised patients. This study was performed in 32 France ICUs from May 19, 2016 to December 31, 2017. A total of 778 patients were randomly allocated (1:1) to HFNC and standard oxygen groups. The major population was hematologic malignancy and solid tumor (76% vs. 82%). The median PaO_2/FiO_2 was 136 vs. 128 mmHg and median SOFA score was 6 in both the groups. There were no significant differences in all-cause 28-day mortality (36% vs. 36%), intubation rate (39% vs. 44%), ICU acquired infection (10% vs. 11%), ICU length of stay (8 vs. 6 days), and hospital length of stay (24 vs. 27 days).

Lemiale et al. [16] performed a post hoc analysis to compare the efficacy of HFNC to standard oxygen. This study was applied in 29 ICUs in France and Belgium and 353 patients were enrolled in the final analysis. Most of the patients were malignancies (84%). The major etiology of respiratory failure was pneumonia (44.4%) and opportunistic infection (21.5%). After propensity score matching, 180 patients were enrolled in HFNC and standard oxygen group. HFNC was neither associated with a lower intubation rate (HR = 0.42, 95% CI: 0.11–1.61) nor day 28 mortality (HR = 0.80, 95% CI: 0.45–1.42). However, nearly half of the patients received NIV at day 1 of admission to ICU. This confounder may skew the results (Table 45.3).

45.6 Systematic Review, Meta-Analysis, and Guidelines in Patients with Immunosuppression

We searched the PubMed from Jan first, 2017 to March 31st, 2019 and found 3 systematic review and meta-analysis on the issue of NIV or HFNC in immunocompromised patients [17–19]. One guideline involving this topic was enrolled too [20]. One study aimed to compare the efficacy of NIV versus oxygen therapy and two studies aimed to compare the efficacy of HFNC versus conventional oxygen therapy. The main outcomes were short-term mortality or intubation rate. Short-term mortality was defined as ICU or hospital or 28-day or 30-day mortality. Long-term mortality was defined as mortality occurring after 3 months of follow-up.

Huang et al. [17] enrolled 5 randomized controlled trials including 592 patients to compare the efficacy of NIV to oxygen therapy. The five RCTs were performed between 2001 and 2015. The inclusion criteria were acute hypoxemic respiratory failure with respiratory rate more than 25 or 30 breaths/min. The authors concluded that early NIV significantly reduced the length of ICU stay (MD = −1.71 days, 95% CI: −2.98 to 1.44), short-term mortality (RR = 0.62, 95% CI:

Table 45.4 Characteristics of the included studies in systematic review, meta-analysis, and guidelines

Study/year	Comparison	Enrolled studies	Number of patients	Main outcomes
Huang et al. (2017) [17]	NIV vs. oxygen therapy	5 RCTs	592	NIV reduced short-term mortality, intubation rate, and ICU length of stay, but not long-term mortality
Rochwerg et al. (2017) [20]	NIV vs. conventional oxygen therapy	4 RCTs	506	NIV reduced mortality, intubation rate, and nosocomial pneumonia
Cortegiani et al. (2019) [18]	HFNC vs. conventional oxygen therapy	One RCT, 2 RCT's post-hoc analysis and one retrospective studies	1052	HFNC reduced intubation rate but did not reduce short-term and 28-day mortality
Huang et al. (2018) [19]	HFNC vs. conventional oxygen therapy	One RCT, 2 RCT's post-hoc analysis and four retrospective studies	667	HFNC reduced intubation rate and short-term mortality

0.40 to 0.97) and intubation rate (RR = 0.52, 95% CI: 0.32 to 0.85) compared to oxygen therapy alone. But, NIV did not reduce the long-term mortality (RR = 0.92, 95% CI 0.74 to 1.15).

Rochwerg et al. [20] have published a guideline involving NIV in patients with acute respiratory failure. One question is should NIV be used for acute respiratory failure in immunocompromised patients? On this question, four RCTs were enrolled. Pooled analysis demonstrated that use of NIV led to a decrease in mortality (RR = 0.68, 95% CI: 0.53–0.88), the need for intubation (RR = 0.71, 95% CI: 0.58–0.87), and the rates of nosocomial pneumonia (RR = 0.39, 95% CI: 0.20–0.76). Based on these evidences, they suggested early NIV for immunocompromised patients with ARF (conditional recommendation, moderate certainty of evidence).

Cortegiani et al. [18] enrolled one RCT, two RCT's post-hoc analysis, and one retrospective study to explore the efficacy of HFNC compared to conventional oxygen therapy. These studies were performed between 2015 and 2018 involving 1052 patients. There were no differences in short-term and 28-day mortality. But HFNC significantly reduced the intubation rate (OR = 0.74, 95% CI: 0.55 to 0.98) compared to conventional oxygen therapy. However, in another meta-analysis and systematic reviewer reported by Huang et al. [19], the use of HFNC was significantly associated with a reduction in short-term mortality (RR = 0.66, 95% CI: 0.52 to 0.84) and intubation rate (RR = 0.76, 95% CI: 0.64 to 0.90). This meta-analysis enrolled 7 original studies involving 667 patients, which was performed between 2015 and 2017. The 7 original studies came from 4 retrospective studies, two RTC's post-hoc analysis and one RCT (Table 45.4).

45.7 Conclusion

In the last 2 years, several original studies, systematic reviews, and guideline focused on the oxygen strategies in immunocompromised patients have been published. Based on these evidences, we concluded that NIV reduced short-term mortality and intubation rate compared to standard oxygen therapy. HFNC may reduce intubation rate concluded from low-quality studies. In addition, NIV failure and HFNC failure were associated with increased mortality. Early identification of high-risk patients and early intubation is necessary. However, most of the studies were retrospectively designed for post hoc analysis. As the study quality is very low, the evidences should be cautiously explained. Furthermore, it is urgent to need multicenter randomized controlled trials to confirm the efficacy of different oxygen strategies in immunocompromised patients.

References

1. Azoulay E, Schellongowski P, Darmon M, et al. The intensive care medicine research agenda on critically ill oncology and hematology patients. Intensive Care Med. 2017;43:1366–82.
2. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med. 2001;344:481–7.
3. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315:788–800.
4. Cortegiani A, Madotto F, Gregoretti C, et al. Immunocompromised patients with acute respiratory distress syndrome: secondary analysis of the LUNG SAFE database. Crit Care. 2018;22:157.
5. Neuschwander A, Lemiale V, Darmon M, et al. Noninvasive ventilation during acute respiratory distress syndrome in patients with cancer: trends in use and outcome. J Crit Care. 2017;38:295–9.
6. Azoulay E, Pickkers P, Soares M, et al. Acute hypoxemic respiratory failure in immunocompromised patients: the Efraim multinational prospective cohort study. Intensive Care Med. 2017;43:1808–19.
7. Duan J, Han X, Bai L, et al. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. Intensive Care Med. 2017;43:192–9.
8. Kotecha S, Buchan C, Parker K, et al. Domiciliary non-invasive ventilation post lung transplantation. Respirology. 2018;23:96–9.
9. Rathi NK, Haque SA, Nates R, et al. Noninvasive positive pressure ventilation vs invasive mechanical ventilation as first-line therapy for acute hypoxemic respiratory failure in cancer patients. J Crit Care. 2017;39:56–61.
10. Liu J, Bell C, Campbell V, et al. Noninvasive ventilation in patients with hematologic malignancy. J Intensive Care Med. 2017;1:885066617690725.
11. Dumas G, Chevret S, Lemiale V, et al. Oxygenation/non-invasive ventilation strategy and risk for intubation in immunocompromised patients with hypoxemic acute respiratory failure. Oncotarget. 2018;9:33682–93.
12. Chen WC, Su VY, Yu WK, et al. Prognostic factors of noninvasive mechanical ventilation in lung cancer patients with acute respiratory failure. PLoS One. 2018;13:e0191204.
13. Kang YS, Choi SM, Lee J, et al. Improved oxygenation 48 h after high-flow nasal cannula oxygen therapy is associated with good outcome in immunocompromised patients with acute respiratory failure. J Thorac Dis. 2018;10:6606–15.
14. Kim WY, Sung H, Hong SB, et al. Predictors of high flow nasal cannula failure in immunocompromised patients with acute respiratory failure due to non-HIV pneumocystis pneumonia. J Thorac Dis. 2017;9:3013–22.
15. Azoulay E, Lemiale V, Mokart D, et al. Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in Immunocompromised patients with acute respiratory failure: the HIGH randomized clinical trial. JAMA. 2018;320:2099–107.
16. Lemiale V, Resche-Rigon M, Mokart D, et al. High-flow nasal cannula oxygenation in immunocompromised patients with acute hypoxemic respiratory failure: a Groupe de Recherche Respiratoire en reanimation Onco-Hematologique study. Crit Care Med. 2017;45:e274–80.
17. Huang HB, Xu B, Liu GY, et al. Use of noninvasive ventilation in immunocompromised patients with acute respiratory failure: a systematic review and meta-analysis. Crit Care. 2017;21:4.
18. Cortegiani A, Crimi C, Sanfilippo F, et al. High flow nasal therapy in immunocompromised patients with acute respiratory failure: a systematic review and meta-analysis. J Crit Care. 2019;50:250–6.
19. Huang HB, Peng JM, Weng L, et al. High-flow oxygen therapy in immunocompromised patients with acute respiratory failure: a review and meta-analysis. J Crit Care. 2018;43:300–5.
20. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1602426.

NIV in Patients with Solid and Hematological Malignancies

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Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BMT	Bone marrow transplantation
ETI	Endotracheal intubation
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
NIV	Noninvasive ventilation
PEEP	Positive end expiratory pressure
SOFA	Sequential organ failure assessment

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46.1 Search Methodology

The systematic review was performed in the following databases: PUBMED/MEDLINE (1980 to 2018), EMBASE (1980 to 2018), and the Cochrane (1981 to 2018). The search strategy involved the crosschecking of keywords selected based on the Medical Subjects Headings (Mesh)—United States National Library of Medicine (intervention + population), with filters to limit the search to clinical trials (Phases I–IV), controlled clinical trials, multicenter studies, randomized controlled trials, pragmatic clinical trials, and systematic reviews. There was no language restriction. The following keywords were used: **Intervention:** Positive-Pressure Respiration [MeSH], Intermittent Positive-Pressure Breathing [MeSH], Continuous Positive Airway Pressure [MeSH], Intermittent Positive-Pressure Ventilation [MeSH], Noninvasive Ventilation [MeSH]; **Population:** Neoplasms [MeSH], Neoplasm Metastasis [MeSH], Neoplasms, Second Primary [MeSH]; **Outcomes:**

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Mortality [MeSH], Hospital Mortality [MeSH], Intubation [MeSH], Intubation, Intratracheal [MeSH]. We considered studies with experimental group receiving NIV compared with control group or with other intervention group.

46.2 Introduction

The use of ventilatory support in oncology patients who develop ARF has been very frequent in the intensive care unit (ICU). In general, up to 65% of cancer patients will require the use of NIV or IMV in the course of their disease. In these patients, mechanical ventilation is administered in approximately 64–89% of patients with febrile neutropenia and in approximately 90% of patients with shock septic [1]. In addition, patients with solid tumors are less frequently submitted to ventilatory support when compared to patients with hematological diagnoses [2, 3].

NIV is among the most current strategies for the treatment of cancer patients who are admitted with or who develop ARF during their stay in the ICU. The objective of NIV is it attenuates the need for IMV in the selected group of patients; the so-called protective effect of NIV. Conversely, failure of NIV therapy and delay in starting IMV can have devastating effects on the prognosis of critically ill cancer patients, resulting in multiple organ dysfunction [3]. A recent study demonstrated an NIV failure rate of 40%, with an estimated mortality of around 74% for this subgroup. However, in patients with NIV success the mortality rate was significantly lower at 15%. Furthermore, several risk factors such as male sex, admission due to a serious clinical condition, high admission severity illness score, and respiratory infection as the cause of ARF were considered as risk factors for NIV failure [4].

The common indications for starting ventilatory support in critically ill cancer patients were sepsis, acute respiratory distress syndrome (ARDS), ARF secondary to treatment of cancer and/or direct involvement of the respiratory system by cancer (Table 46.1). The latter is the cause of ventilatory support in approximately 8–11% of cases, and is a risk factor for higher hospital mortality [2]. Typically, patients who are in need of IMV have required prolonged hospital stay, greater degree of ARF severity requiring high doses of oxygen therapy, presence of extensive infiltrates on chest X-ray, extrapulmonary dysfunction, higher frequency of infections, and higher frequency of hemodynamic disorders on the first day of ICU admission. In patients who require NIV, the use of high oxygen fractions on admission to ICU is a risk factor for NIV failure. However, despite the greater severity of illness in patients with hematological malignancies, the rate of IMV use is not different from that of patients with other types of cancer [5].

Table 46.1 Causes of acute respiratory failure in cancer patients

Infectious
• Pulmonary—bacterial, viral, fungal
• Extra-pulmonary—severe sepsis/septic shock
Non-infectious
• Related to cancer
– Invasion/infiltration by cancer
– Massive malignant pleural effusion
– Neuromyopathy—paraneoplastic
– Diffuse alveolar hemorrhage
– Idiopathic pneumonia syndrome
• Related to cancer treatment
– Pulmonary drug toxicity
– Transfusion-related acute lung injury
• Not directly related to cancer
– Altered mental status
– Pulmonary embolism
– Co-morbid illnesses—COPD, pulmonary fibrosis, pulmonary edema

The type of ventilatory support to be used, as well as the modification of one type of support to another, is an important risk factor that directly influences the mortality rate of these patients. The use of IMV is associated with a higher mortality (around 73–88%), especially when its onset occurs after the third day of ICU stay. This is followed by failure to use NIV as first-line therapy, and delayed IMV post unsuccessful NIV (around 69–72%). Lowest mortality was with the successful use of NIV alone (around 37–40%) [2, 5–8]. It is very important to know that the mortality rate remains the same between patients who failed first-line NIV and requiring second-line

IMV, and patients requiring first-line IMV without prior NIV use [5]. Moreover, the use of NIV as first-line therapy in cancer patients may have a protective effect, with a decrease in the need for IMV.

Since the ICU mortality with the use of first-line NIV is lower than either first-line IMV or failed NIV requiring second-line IMV, it is appropriate to consider a trial of NIV in critically ill cancer patients with ARF. However, this needs to be done under a strict protocol and closer monitoring, with early identification of NIV failure needing IMV. In patients receiving IMV support, the presence of organ dysfunction, especially extrapulmonary, poor performance status, high sequential organ failure assessment (SOFA) scores on day 1, and increased score at 1 week of ICU admission are independent predictors of poor outcome [2, 6, 7, 9]. Hence, as mentioned previously, cautious use of NIV with continuous monitoring, and rapid modification of ventilatory strategy in the event of NIV failure are highly recommended in clinical practice [4].

In patients with solid tumor, despite the limitation of evidence-based studies in the literature, the use of NIV among other strategies has significantly contributed to an improved survival. Studies have demonstrated the use of NIV in critically ill patients with solid tumors, is a feasible option with reasonable benefits in both short- and long-term survival [10–12]. Almost half of solid tumor patients requiring some type of ventilatory support have underlying pneumonia, followed by other conditions such as extrapulmonary infections, pneumonitis, alveolar hemorrhage, and progression of disease itself [10, 13]. NIV in patients who developed ARF after pulmonary resection surgeries resulted in significantly greater benefit with decreased mortality, and reduced need for ETI when compared to standard oxygen therapy. However, as in other patient population, the failure of NIV in solid tumors correlates to an increase in mortality and with survival rates of only around 10%. Failure rates in NIV vary greatly between studies with a range between 17 and 43% and this could be a topic for further large-scale multicenter trial. In addition, some risk factors such as increased respiratory rate, high SOFA scores, need for vasopressors, leukopenia, and longer time spent on NIV are considered to be independent risk factors for the occurrence of NIV failure in these patients [10]. The benefits of NIV in hematologic patients have been consistent in several studies [14]. However, in the study by Schnell et al., some disagreement to the benefits noted in other studies are due to several factors such as time to implementation of NIV, purpose of NIV (prophylactic or curative), environment where the ventilatory support is administered (ICU or ward), and finally the etiology of ARF. These data are corroborated by Depuydt et al., who highlighted methodological biases such as sample size, heterogeneity among patients, and even study designs that were impacting more consistent and relevant inferences about the mortality benefits of NIV when compared to conventional therapies in these patients. In addition, NIV has been shown to be unsuccessful in some situations, such as a significant deterioration in the level of consciousness, moderate to severe hypoxemia ($PaO_2/FiO_2 < 200$), septic shock with ARF, multiple organ failure, and persistent tachypnea at 1 h of NIV initiation. Generally, in these situations NIV should be avoided [15]. On the other hand, the success of NIV in these patient groups is associated with reduced IMV time, hospital stay, and mortality. In critically ill patients with hematological malignancies, the risk factors for high mortality include the use of IMV, multiorgan failure, and need for vasopressors, affecting approximately 71% of these patients. Despite an overall reduction in the mortality rate for hematological patients from 80 to 95% between the 1980s and 1990s, to around 65–85% in more recent studies, the rate still remains extremely high today [16]. In general, mechanical ventilatory support is used in a little more than half (66%) of these patients during their hospitalization, with approximately one-third receiving first-line NIV [17, 18]. Typically, NIV has been used in these patients for a variable period of 2–11 days and for 4–16 h daily, with positive end-expiratory pressure (PEEP) levels between 3 and 10 cmH_2O and inspiratory pressure between 10 and 15 cmH_2O. Previous

systematic review has shown that NIV is more advantageous on IMV in reducing in-hospital mortality (OR 0.43, 95% CI 0.23 to 0.80, *P* value = 0.007) and 30-day mortality (OR 0.34, 95% CI 0.20 to 0.61, *P* value <0.0001) mainly for less severe hematological malignancies patients [19]. While high mortality rates of around 70–80% are found in hematologic patients requiring IMV, the overall mortality for those who undergo NIV is around 15–65% [20]. As a counterpoint, in their study, Depuydt and colleagues showed a high failure rate with use of NIV and the authors attribute these results to a greater severity of illness scores in patients included in their study, worse oxygenation index measured by the PaO_2/FiO_2 ratio, and ARF due to conditions with slower resolution such as non-bacterial pneumonia and non-infectious lung diseases [16, 18]. These latter factors were confirmed by more recent studies that demonstrated a higher success rate of NIV in ARF where the causes are characterized by a faster resolution [3, 4]. In addition, other factors such as age, heart failure, and presence of bacteremia are independent risk factors for NIV failure [3]. Thus, there is a clear uncertainty in the real protective effect of NIV for these patient groups [16] as well as the impact of initial ventilation management on the probability of intubation and IMV [21]. In a recent study by Lemiale and colleagues who compared NIV to standard oxygen therapy, the authors demonstrated an absence of "protective" benefit of NIV not only in mortality, but also in the need for ETI, hospital and ICU length of stay, as well as duration of IMV [22]. In addition, despite progressive reduction in cases of invasive pulmonary aspergillosis in hematological malignancy, half of the patients admitted to the ICU with this diagnosis are submitted to some type of ventilatory support. A smaller proportion of those who underwent first-line NIV and failed, leading to second-line IMV had significant increase in mortality. However, this was still lower when compared to patients who underwent first-line IMV [6].

Among patients with hematologic malignancy who underwent bone marrow transplantation (BMT), the use of IMV in post-transplantation period was associated with complications that considerably reduce their survival, with rates ranging from 3 to 26% [23–26]. In addition, renal failure and delayed recovery of platelet levels are independent factors of worsening survival in up to 100 days of post BMT patients requiring IMV. Predictors of higher survival in this patient group include low disease risk, umbilical cord cell transplantation, good lung function, presence of graft versus host disease grade II or lower, and normal values for bilirubin, creatinine, platelets, and albumin [23, 27].

Finally, robust evidence found in literature regarding the use of NIV in hematologic patients is in contrary to the limited literature in the use of NIV in solid tumors. In addition, analyses of previous studies with samples from mixed populations, as well as small sample size, do not allow us to infer or conclude with adequate consistency the findings of NIV intervention specifically for patients with solid tumors.

46.3 Conclusions

In conclusion, we observed that there is a broad and growing evidence showing the benefits of NIV in patients with hematological diseases, based on robust evidences in the literature about clinical implications of this intervention in this patient group. Despite sparse evidence for NIV in solid tumor patients with ARF, studies have shown that this intervention has contributed significantly to improved survival. In addition, as in patients with hematological diseases, the failure of NIV in solid tumor correlates to an increase in mortality and low survival rates. The decision to initiate NIV in a cancer patient with ARF as opposed to IMV should be individualized depending on the etiology of the ARF, hemodynamic status, and goals of care (Fig. 46.1).

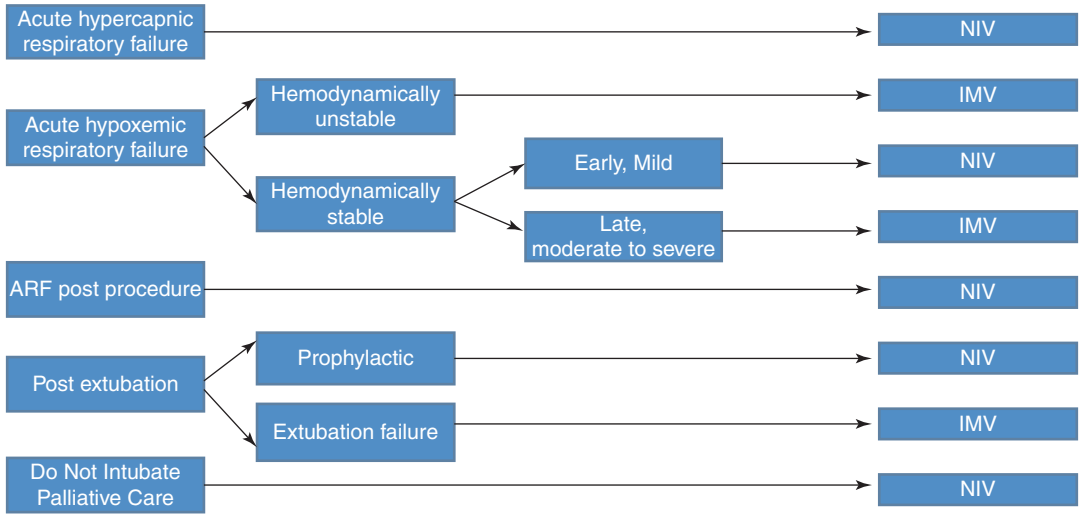

Fig. 46.1 Suggested initial ventilatory approach to management of acute respiratory failure in cancer patients. *IMV* invasive mechanical ventilation, *NIV* noninvasive mechanical ventilation

References

1. Soares M, Depuydt PO, Salluh JI. Mechanical ventilation in cancer patients: clinical characteristics and outcomes. Crit Care Clin. 2010;26(1):41–58.
2. Azevedo LCP, Caruso P, Silva UVA, et al. Outcomes for patients with cancer admitted to the ICU requiring ventilatory support: results from a prospective multicenter study. Chest. 2014;146(2):257–66.
3. Molina R, Bernal T, Borges M, et al. Ventilatory support in critically ill hematology patients with respiratory failure. Crit Care. 2012;16(4):R133.
4. Ferreira JC, Medeiros P Jr, Rego FM, Caruso P. Risk factors for noninvasive ventilation failure in cancer patients in the intensive care unit: a retrospective cohort study. J Crit Care. 2015;30(5):1003–7.
5. Lemiale V, Lambert J, Canet E, et al. Identifying cancer subjects with acute respiratory failure at high risk for intubation and mechanical ventilation. Respir Care. 2014;59(10):1517–23.
6. Burghi G, Lemiale V, Seguin A, et al. Outcomes of mechanically ventilated hematology patients with invasive pulmonary aspergillosis. Intensive Care Med. 2011;37(10):1605–12.
7. Geerse DA, Span LF, Pinto-Sietsma SJ, van Mook WN. Prognosis of patients with haematological malignancies admitted to the intensive care unit: Sequential Organ Failure Assessment (SOFA) trend is a powerful predictor of mortality. Eur J Intern Med. 2011;22(1):57–61.
8. Price KJ, Cardenas-Turanzas M, Lin H, Roden L, Nigam R, Nates JL. Prognostic indicators of mortality of mechanically ventilated patients with acute leukemia in a comprehensive cancer center. Minerva Anestesiol. 2013;79(2):147–55.
9. Belenguer-Muncharaz A, Albert-Rodrigo L, Ferrandiz-Selles A, Cebrian-Graullera G. Ten-year evolution of mechanical ventilation in acute respiratory failure in the hematogical patient admitted to the intensive care unit. Med Intensiva. 2013;37(7):452–60.
10. Vanderschuren A-P. Noninvasive ventilation in high-risk infections and mass casualty events. Berlin: Springer; 2014.
11. Kramer MR, Marshall SE, Starnes VA, Gamberg P, Amitai Z, Theodore J. Infectious complications in heart-lung transplantation. Analysis of 200 episodes. Arch Intern Med. 1993;153(17):2010–6.
12. Kothe H, Dalhoff K. Pneumonia in the immunocompromised patient. Eur Respir Mon. 2006;36:13.
13. Park SY, Lim SY, Um SW, et al. Outcome and predictors of mortality in patients requiring invasive mechanical ventilation due to acute respiratory failure while undergoing ambulatory chemotherapy for solid cancers. Support Care Cancer. 2013;21(6):1647–53.
14. Huang HB, Xu B, Liu GY, Lin JD, Du B. Use of noninvasive ventilation in immunocompromised patients with acute respiratory failure: a systematic review and meta-analysis. Crit Care. 2017;21(1):4.
15. Schnell D, Mayaux J, Lambert J, et al. Clinical assessment for identifying causes of acute respiratory failure in cancer patients. Eur Respir J. 2013;42(2):435–43.
16. Depuydt PO. Noninvasive mechanical ventilation in patients with hematological diseases. Spain: Springer; 2014.
17. Cornish M, Butler MB, Green RS. Predictors of poor outcomes in critically ill patients with hematological malignancy. Can Respir J. 2016;2016:9431385.
18. Fujiwara Y, Yamaguchi H, Kobayashi K, et al. The therapeutic outcomes of mechanical ventilation in hematological malignancy patients with respiratory failure. Intern Med. 2016;55(12):1537–45.

19. Wang T, Zhang L, Luo K, et al. Noninvasive versus invasive mechanical ventilation for immunocompromised patients with acute respiratory failure: a systematic review and meta-analysis. BMC Pulm Med. 2016;16(1):129.
20. Squadrone V, Ferreyra G, Ranieri VM. Non-invasive ventilation in patients with hematologic malignancy: a new prospective. Minerva Anestesiol. 2015;81(10):1118–26.
21. Dumas G, Chevret S, Lemiale V, et al. Oxygenation/non-invasive ventilation strategy and risk for intubation in immunocompromised patients with hypoxemic acute respiratory failure. Oncotarget. 2018;9(72):33682–93.
22. Lemiale V, Mokart D, Resche-Rigon M, et al. Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure: a randomized clinical trial. JAMA. 2015;314(16):1711–9.
23. Solh M, Oommen S, Vogel RI, Shanley R, Majhail NS, Burns LJ. A prognostic index for survival among mechanically ventilated hematopoietic cell transplant recipients. Biol Blood Marrow Transplant. 2012;18(9):1378–84.
24. Faber-Langendoen K, Caplan AL, McGlave PB. Survival of adult bone marrow transplant patients receiving mechanical ventilation: a case for restricted use. Bone Marrow Transplant. 1993;12(5):501–7.
25. Bach PB, Schrag D, Nierman DM, et al. Identification of poor prognostic features among patients requiring mechanical ventilation after hematopoietic stem cell transplantation. Blood. 2001;98(12):3234–40.
26. Afessa B, Tefferi A, Dunn WF, Litzow MR, Peters SG. Intensive care unit support and acute physiology and chronic health evaluation III performance in hematopoietic stem cell transplant recipients. Crit Care Med. 2003;31(6):1715–21.
27. Wermke M, Schiemanck S, Hoffken G, Ehninger G, Bornhauser M, Illmer T. Respiratory failure in patients undergoing allogeneic hematopoietic SCT—a randomized trial on early non-invasive ventilation based on standard care hematology wards. Bone Marrow Transplant. 2012;47(4):574–80.

Nutrition in Critically Ill Patients on Noninvasive Ventilation

47

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and Habib Md Reazaul Karim

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Abbreviations

ARF	Acute respiratory failure
EN	Enteral nutrition
FiO_2	Fraction of inspired oxygen
HHHFNC	Heated humidified high flow nasal cannula
ICU	Intensive care units
NIV	Noninvasive ventilation

47.1 Introduction

For the past two decades, the use of noninvasive ventilation (NIV) has taken the prime place for the management of acute as well as chronic respiratory failure. As the use of NIV has increased, it came with its own set of shortcomings. One of the major issues is nutrition during NIV. Lack of sufficient evidence for the safe practice of enteral feeding during NIV makes it a grey area. Oral nutritional support is still the major form of feeding as compared to enteral and parenteral route for the patients on NIV in a majority of the intensive care units (ICU) [1]. But intermittent NIV disconnection during oral feed leads to respiratory distress in acutely ill patients, which many a time leads to inadequate nutrition. Two significant causes for lack of adequate nutrition during

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NIV are, firstly, the fear of conversion to invasive ventilation which prefers a nil per os status and secondly, the gastric distension during NIV leading to aspiration [2]. A recent study has shown that it is excessive calories and not the route that is responsible for the complications associated with parenteral nutrition [3]. The present chapter is prepared to review the current evidence on nutritional support and its effect on and during NIV.

47.2 Methods

Electronic database PubMed was searched with index words "noninvasive ventilation" AND "nutrition" for including articles published between January 2017 and March 2019 in the field of Title/Abstract. An initial screening of the title, abstract, and keywords of every record identified was performed. The next step was to retrieve the full text of potentially relevant studies. Only studies in English and from all age group were considered.

47.3 Results

After applying the above search terms, we got 24 articles, out of which 19 were excluded due to various reasons (Fig. 47.1). The remaining 5 articles were analyzed for the preparation of this chapter (Table 47.1).

47.4 Analysis of Search Results

In a single-center retrospective cohort study, Kogo et al. evaluated the effects of enteral nutrition in subjects receiving NIV for acute respiratory failure [4]. The main outcomes were the frequency of airway complications during NIV treatment, NIV failure, NIV days, hospital days, in-hospital mortality, and the type of discharge. Enteral feeding caused more airway complication and longer durations of NIV and hospitalization than the other routes of nutrition. But enteral nutrition had no influence over

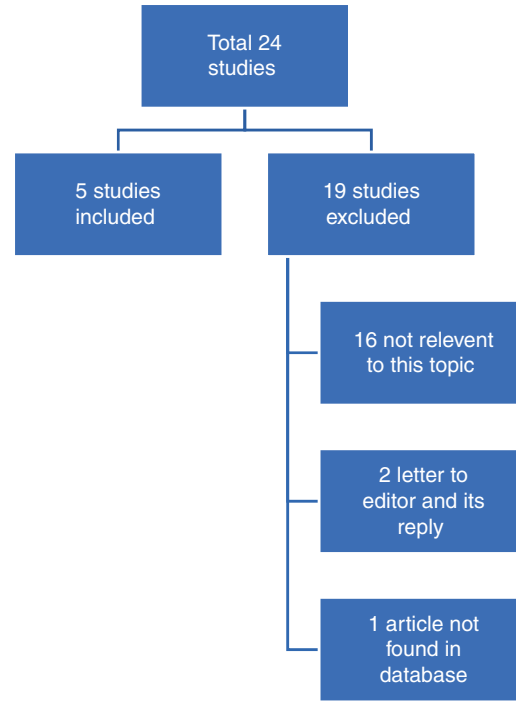

Fig. 47.1 Summary of searched articles from PubMed

mortality and NIV failure in their study. Due to its small sample size and retrospective in the design there was no control over the population characteristics resulting in a heterogeneous group which was not comparable. Thus the validation of outcomes is required with further studies.

Another multi-centric observational retrospective cohort study was conducted by Terzi et al., which included 20 French adult ICUs and included patients who required at least 2 days NIV for acute respiratory failure [1]. They assessed associations between nutritional groups and the need for mechanical ventilation, the occurrence of nosocomial infection and death. To their surprise, they found out that about three-fifths of the patients did not receive any kind of nutrition in the first 48 h. In contrast to the previous finding, early enteral feeding was independently associated with higher 28-day mortality and fewer ventilator-free days. Due to selection bias and lack of specific protocol for NIV and type of nutrition, the results obtained cannot be accepted well.

Table 47.1 Summary of searched articles from PubMed

Authors (year)	Patients	Intervention	Outcome/remarks
Terzi et al. (2017) [1]	Adult patients with acute respiratory insufficiency	Received NIV for 2 consecutive days during admission to ICU and nutrition in various routes	Nearly three-fifths of patients receiving NIV fasted for the first 2 days Lack of feeding or underfeeding was not associated with mortality
Kogo et al. (2017) [4]	Adult patients with acute respiratory failure	Received NIV for >48 h and enteral nutrition	Enteral nutrition was associated with an increased risk of airway complications but did not affect mortality
Leroue et al. (2017) [5]	Pediatrics patients of age >30 days with acute respiratory distress	Received NIV for greater than or equal to 24 h and enteral nutrition	Majority of the patients started on enteral feed within 24 h of NIV initiation Less than half of the patients received the desired calorie and protein need
Bozzetti et al. (2017) [6]	Infants from birth to 23 months of age in respiratory distress		
Singer et al. (2018) [7]	Adults and pediatric patient with acute respiratory distress.		Prompts to practice newer methods of NIV and choosing an appropriate route of nutrition

A similar study was conducted in the Children's Hospital Colorado (CHCO) by Leroue et al., and data were collected retrospectively from Virtual PICU Systems (VPS) LLC database and the Children's Hospital Colorado (CHCO) electronic health records (EHRs) [5]. This study specifically focused on the specific population requiring NIPPV. Almost two-thirds of patients on NIV received nutrition within 24 h of NIV initiation and almost all within 48 h. The need for bi-level NIV and continuous dexmedetomidine for sedation was associated with a decreased likelihood of enteral nutrition initiation within 24 h in this study. However, less than half achieved caloric and protein goals during their PICU admission. Though the use of a feeding tube was associated with improved delivery of nutrition as compared to oral feeding, limited data exist to determine whether gastric or transpyloric enteral nutrition is preferable for patients on noninvasive positive pressure ventilation.

Bozzetti et al. reviewed the challenges to meet the adequate caloric intake in very low birth weight babies on NIV for respiratory distress [6]. They formulated strategies of enteral feeding of preterm infants requiring NIV.

The paper by Singer et al. gives us an overview of nutrition during NIV. The dilemma of whether to eat or not during NIV should not be the question [7]. Rather, the use of the newer kind of NIV equipment gives us the hope of better coordination between eating and breathing. More trials are required to see the efficacy of equipment such as high-frequency nasal cannula with regards to the facilitation of nutrition is needed.

These above studies contribute to our limited knowledge of the effect of nutrition on critically ill patients requiring NIV. Further research on early enteral nutrition, the optimal mode of delivery, and the impact on clinical outcomes, including adverse, remains essential.

47.4.1 Early Enteral Nutrition Versus Nil per Os During NIV

According to the European Society of Parenteral Nutrition (ESPEN) guideline, starting early enteral feed is advantageous for early recovery of ventilated patients [8]. Leroue MK et al. have shown in their retrospective cohort study that patients who started Enteral nutrition (EN) within

24 h of admission to the PICU had an increased likelihood of meeting goal EN rate and an adequate cumulative calorie and protein intake [5]. Further, they described the decreased likelihood of initiation of NIV within 24 h of admission in patients on the bi-level mode of NV and on continuous dexmedetomidine independently on multivariable analyses [5]. However, early enteral feeding is associated with a higher incidence of respiratory complications as compared to no feeding at all [1]. In clinical practice, only a few patients in ICU get nutrition on the first day of admission. Bendavid et al. showed, in a large prevalence study of nutrition practice in intensive care, that enteral feeding was prescribed to only 10% of the patients on the first day, but this number increased to more than 40% of the patients after 5 days [9].

47.4.2 Enteral and Parenteral Nutrition During NIV

Oral feeding is the prime route for nutrition in most of the ICUs which needs interruption in NIV leading to a respiratory compromise in acutely ill patients. Avoiding the enteral route in acute care settings may avoid interruptions. However, enteral route feeding has its own benefit too; structural and functional gut integrity and the gut microbiome are maintained. However, Kogo et al., in their retrospective observational study, showed that receiving enteral nutrition during NIV was associated with a significantly higher rate of airway complications (53 vs. 32%, $P = 0.03$) and longer NIV duration (16 vs. 8 days, $P = 0.02$) compared to patients who did not receive enteral nutrition [4]. Kogo et al. indicated mucus plug formation, gastric distension, and vomiting during NIV as reasons for it. In critically ill patients, the gut motility is also compromised, causing an increase in gastric residual volume. This further increases the chance of aspiration. But this finding should not lead the patient to starve. Work of breathing is a major source of energy expenditure which itself may lead to respiratory deterioration if calorie needs are not met. Parenteral nutrition is associated with more chance of catheter site infection, systemic infection, hyperglycemia, and dyselectrolytemia as compared to enteral nutrition. But there are large randomized trials in recent years showing no increase in the infection rate for a parenteral route as compared to the enteral route [10].

47.4.3 Type of Interfaces Facilitating Nutrition in NIV

Use of a feeding tube for enteral feeding is a potential source of a leak during NIV via various interfaces. Although 30–40% of the leak is compensated by the recent ventilators, still using a full face mask and nasal-only mask with feeding tube in-situ are not free from NIV failure. While this problem may be managed with special NIV masks with a port for the nasogastric tube, these are not always available and are costly. Helmet interface is of some advantage over face mask as it does not hinder speech and cough, but leakage is still possible during nutrition via a feeding tube. As a patient is more cooperative to this kind of interface, providing nutrition can be more coordinated as compared to other interfaces. However, to date, no study has been established regarding the identification of a suitable interface for facilitating nutrition. Heated humidified high flow nasal cannula (HHHFNC) is simpler to use and apply than NIV and appears to be a good alternative treatment for hypoxemic acute respiratory failure (ARF). Frat JP et al., in their article, has shown that HHHFNC is better tolerated than NIV [11]. It delivers a high fraction of inspired oxygen (FiO_2), generates a low level of positive pressure and provides washout of dead space in the upper airways, thereby unloading inspiratory muscles during ARF [11]. A patient has an improved speech and secretion clearance ability with HHHFNC. So this might be a good alternative to traditional NIV masks for providing nutrition. However, large randomized studies are required for establishing the suitable modality for NIV.

47.4.4 The Complication of Enteral/Parenteral Feeding During NIV

Complication related to airways such as mucus plugging and aspiration pneumonia is most common in the enteral feeding group. Kogo et al., in their trial, show that rates of mucus plug (50% vs. 30%), aspiration pneumonia (17% vs. 4%), and airway complications (53% vs. 32%) were higher in the enteral feeding than in the non-enteral feeding group [4]. Reliable airway protection from aspiration is far from actual in patients on NIV and a feeding tube in-situ across the lower gastroesophageal sphincter and gastric hypomotility increases the chance of aspiration further. Independent association of nutrition (enteral and parenteral) with higher incidence of nosocomial infection ($P = 0.02$), VAP ($P = 0.002$), and 28-day mortality ($P = 0.02$) was shown by Terzi et al. [1]. This result is coherent with the fact that the enteral and parenteral nutrition groups were associated with a higher need for invasive MV. But surprisingly ICU acquired infection incidence is not significantly associated with enteral feeding ($P = 0.18$) [1].

The duration of NIV and hospitalization were significantly longer in the enteral feeding group ($P < 0.05$ each). Also, the 28-day mortality was significantly higher in the enteral group as compared to no nutrition at all [4].

47.5 Conclusion

Supplementation of nutrition is essential during noninvasive ventilation. Enteral feeds show a tendency towards increased complications and some patients may not tolerate well the interruption required for feeding. Tube feeding can be given to avoid interruption in such patients. However, dedicated NIV machine which can compensate for the high leak will be required. Interface with a port for feeding tube can be also helpful. Present evidence also suggests that parenteral nutrition can also be provided. With the present evidence, individualized decision to choose a route of nutrition should be practiced. Further, randomized trials will be required to recommend one route over another.

References

1. Terzi N, Darmon M, Reignier J, Ruckly S, Garrouste-Orgeas M, Lautrette A, Azoulay E, Mourvillier B, Argaud L, Papazian L, Gainnier M, Goldgran-Toledano D, Jamali S, Dumenil AS, Schwebel C, Timsit JF, OUTCOMEREA Study Group. Initial nutritional management during noninvasive ventilation and outcomes: a retrospective cohort study. Crit Care. 2017;21(1):293.
2. Gay PC. Complications of noninvasive ventilation in acute care. Respir Care. 2009;54(2):246–57, discussion 257–258.
3. Elke G, van Zanten ARH, Lemieux M, McCall M, Jeejeebhoy KN, Kott M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care. 2016;20:117.
4. Kogo M, Nagata K, Morimoto T, Ito J, Sato Y, Teraoka S, et al. Enteral nutrition is a risk factor for airway complications in subjects undergoing noninvasive ventilation for acute respiratory failure. Respir Care. 2017;62:459–67.
5. Leroue MK, Good RJ, Skillman HE, Czaja AS. Enteral nutrition practices in critically ill children requiring noninvasive positive pressure n ventilation. Pediatr Crit Care Med. 2017;18(12):1093–8.
6. Bozzetti V, Angelis CD, Tagliabue PE. Nutritional approach to preterm infants on noninvasive ventilation: an update. Nutrition. 2017;37:14–7.
7. Singer P, Rattanachaiwong S. To eat or to breathe? The answer is both! Nutritional management during noninvasive ventilation. Crit Care. 2018;22(1):27.
8. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN guideline: clinical nutrition in surgery. Clin Nutr. 2017;36(3):623–50.
9. Bendavid I, Singer P, Theilla M, Themessl-Huber M, Sulz I, Mouhieddine M, Schuh C, Mora B, Hiesmayr M. Nutrition Day ICU: a 7-year worldwide prevalence study of nutrition practice in intensive care. Clin Nutr. 2017;36(4):1122–9.
10. Elke G, van Zanten AR, Lemieux M, McCall M, Jeejeebhoy KN, Kott M, Jiang X, Day AG, Heyland DK. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care. 2016;20(1):117.
11. Frat JP, Coudroy R, Marjanovic N, Thille AW. High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure. Ann Transl Med. 2017;5(14):297.

Noninvasive Ventilation and Post-Extubation

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Subrata Kumar Singha and Fatma Ciftci

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Although mechanical ventilation is a life-saving therapy in the treatment of acute respiratory failure, weaning should be performed as soon as possible to prevent complications of invasive ventilation. Weaning time is known to constitute half of the total mechanical ventilation time [1].

48.1 To Prevent Acute Respiratory Failure After Extubation

Post-extubation respiratory failure is a complication that increases the morbidity and mortality and hence requires strategies to prevent the same [2]. Noninvasive ventilation (NIV) has become an important tool for ventilatory support in adults as well as pediatric patients. Its application reduces the use of accessory muscles, heart rate, and respiratory rate [2, 3]. The main advantage of NIV is that it prevents endotracheal intubation and, thereby, any associated risk [2]. A European survey reported that post-extubation respiratory failure was the second most common indication in Germany and the United Kingdom [4], and a recent French study also demonstrated a substantial increase of NIV use in this subset of population [4, 5]. Based on previous multicenter randomized studies, NIV may reduce re-intubation and mortality rates when applied immediately after planned extubation in selected patients at high-risk for respiratory failure [6].

However, the choice of mask is crucial for the success of NIV and it usually depends on considerations regarding patient comfort, air-leaks, and cost [4]. A facial (oro-nasal) mask is the most

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widely used method for patients with acute respiratory failure. However, helmets are increasingly being used in some countries [4]. Apart from the facial mask in NIV, high-flow nasal cannula (HFNC) oxygen therapy has been used in patients with respiratory failure, but the clinical benefit in patients with post-extubation respiratory failure (PERF) remains unclear [7]. This Korean study further went on to conclude that in PERF the use of HFNC is not inferior when compared to NIV in terms of patients requiring re-intubation and such patients had a shorter stay in the ICU and even better tolerated the HFNC [7].

Yang L et al. explored the feasibility of NIV and assessed the risk factors of NIV failure in patients with acute respiratory failure following cardiac surgery. The NIV failure group had a higher in-hospital mortality and longer stay in the intensive care unit (ICU). Most cases of NIV failure occurred within 1–48 h of the treatment. The main causes of early NIV failure were a weak cough reflex and/or excessive secretions and hemodynamic instability. A Sequential Organ Failure Assessment (SOFA) score ≥10.5, vasoactive-inotropic score ≥6, and pneumonia were predictors of NIV failure, whereas a body mass index (BMI) ≥25.0 kg/m^2 predicted NIV success [8].

To increase the success of weaning, the question of giving NIV to each patient after extubation comes to mind. However, NIV has been shown to be effective and successful only in the risky patient groups [9, 10]. It was observed that there was no decrease in re-intubation and mortality rates with NIV therapy in an unselected patient group. The risk factors predicted in the studies were defined as age over 65 years and having an underlying cardiac or respiratory disease. In two multicentric, randomized, and controlled trials, the positive effects of NIV treatment on re-intubation and mortality rates were shown immediately after planned extubation in selected patients [11, 12]. As a result, it is recommended to apply NIV only to selected, high-risk patients in order to prevent respiratory failure.

48.2 To Treat Acute Respiratory Failure After Extubation

Although there is not enough randomized controlled research in this subject, it is recommended not to use NIV in the treatment of patients with respiratory failure after extubation [13]. In this case, the individual and clinical characteristics of a patient and the experience of the center in NIV therapy are also important. As the number of COPD patients included in the research on this subject is low, this result may not be applicable for COPD patients.

48.3 To Facilitate Weaning

It is already known that NIV improves respiratory pattern and reduces inspiratory effort in patients intubated due to hypercapnic respiratory failure. It has been shown to be as effective as invasive mechanical ventilation to maintain adequate gas exchange in selected patients during weaning [14]. A meta-analysis evaluating data from 16 randomized controlled trials mostly composed of hypercapnic COPD patients showed that the rate of weaning failure was lower in the NIV group than in the conventional group [15]. Unlike hypoxemic patients, NIV is recommended to facilitate weaning from invasive ventilation in patients with hypercapnic respiratory failure.

On the other hand, NIV has been shown to be successful in a multicenter randomized controlled trial in comparison with standard oxygen therapy in patients with hypoxemic respiratory failure after abdominal surgery. It was also shown that the NIV group had a lesser rate of intubation, nosocomial infection, and duration of mechanical ventilation [16]. However, there are no adequate data to conclude on the success of NIV in hypoxemic patients.

According to the results of these researches, it is seen that there are factors that play a role in obtaining different results. Different results can be obtained in heterogeneous patient groups. In order to obtain more reliable results, studies

should be carried out which are as homogenous and as large as possible. NIV should be used especially in the weaning period of COPD patients. Better results were obtained especially in the early period before respiratory failure develops. It is noteworthy that low pressures are used in studies that failed NIV administration. The tidal volume generated by the applied pressure must be checked and required pressure for sufficient tidal volume must be ensured. Appropriate pressures should be adjusted according to the clinical evaluation of the patient and the results of gas exchange. There are significant differences between the duration of NIV therapy in the studies. Although there is no consensus on this issue, the duration of NIV should be sufficient according to the clinical condition of the patient. NIV application experience is an another important factor. The experience of the team members who applied NIV in the clinic will increase the success rate and the safety of the patient with early recognition of failure and taking precautions when needed. When NIV therapy is contemplated, selecting an appropriate interphase and ventilator mode should monitor the patient. Most importantly, all the equipment required for intubation of the patient should be readily available.

References

1. Béduneau G, Pham T, Schortgen F, et al. Epidemiology of weaning outcome according to a new definition. The WIND study. Am J Respir Crit Care Med. 2017;195:772–83.
2. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. Chest. 1997;112(1):186–92.
3. Mayordomo-Colunga J, Medina A, Rey C, et al. Predictores de éxito y de fracas en la ventilación no invasiva en la bronquiolitis aguda. An Pediatr (Barc). 2009;70(1):34–9.
4. Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. Eur Respir J. 2010;36:362–9.
5. Demoule A, Chevret S, Carlucci A, Kouatchet A, Jaber S, Meziani F, et al. Changing use of noninvasive ventilation in critically ill patients: trends over 15 years in francophone countries. Intensive Care Med. 2016;42:82–92.
6. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817–22.
7. Yoo J-W, et al. Clinical efficacy of high-flow nasal cannula compared to noninvasive ventilation in patients with post-extubation respiratory failure. Korean J Intern Med. 2016;31:82–8.
8. Yang L, et al. Risk factors for noninvasive ventilation failure in patients with post-extubation acute respiratory failure after cardiac surgery. J Thorac Dis. 2018;10(6):3319–28.
9. Su CL, Chiang LL, Yang SH, et al. Preventive use of noninvasive ventilation after extubation: a prospective, multicenter randomized controlled trial. Respir Care. 2012;57:204–10.
10. Jiang JS, Kao SJ, Wang SN. Effect of early application of biphasic positive airway pressure on the outcome of extubation in ventilator weaning. Respirology. 1999;4:161–5.
11. Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005;33:2465–70.
12. Ferrer M, Valencia M, Nicolas JM, et al. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006;173:164–70.
13. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi P Members of the Steering Committee, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Mehta S, Raoof S Members of the Task Force. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2):1602426.
14. Vitacca M, Ambrosino N, Clini E, et al. Physiological response to pressure support ventilation delivered before and after extubation in patients not capable of totally spontaneous autonomous breathing. Am J Respir Crit Care Med. 2001;164:638–41.
15. Burns KE, Meade MO, Premji A, et al. Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review. CMAJ. 2014;186:E112–22.
16. Jaber S, Lescot T, Futier E, et al. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery. JAMA. 2016;315:1345–53.

49 Multidisciplinary Approach to Noninvasive Ventilation (NIV) in Critical Care

Guy W. Soo Hoo

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Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
BiPAP	Bilevel positive airway pressure support
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPE	Cardiogenic pulmonary edema
ED	Emergency Department
HDU	High Dependency Unit
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive Care Unit
M–F	Monday–Friday
NCEPOD	National Confidential Enquiry into Patient Outcomes and Death
NEWS	National Early Warning Score
NIV	Noninvasive ventilation
OR	Odds ratio
UK	United Kingdom

49.1 Introduction

It has been over three decades since noninvasive positive pressure ventilation (NIV) delivered through a mask interface was introduced as an alternative mode of ventilatory support for those with acute respiratory distress and failure [1–3]. Since its entry into medical care, NIV has become the treatment of choice for a host of respiratory conditions, specifically acute exacerbations of chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary edema [4]. The list of conditions that can be successfully treated with NIV increases annually with increasing provider expertise and experience.

Patients were initially treated in closely monitored settings and initial experience was tempered by difficult application of therapy which often led to treatment failures. This limited its implementation in several locales, sometimes for years as healthcare providers sought to overcome the learning curve that accompanied NIV. This early difficulty also underscored the importance of a multidisciplinary approach to the application of NIV which differs from invasive mechanical ventilation. The providers involved with NIV are nursing, respiratory therapy, and physician staff and their roles are a little different when compared to patients treated with invasive ventilation. In the latter situation, the provider roles are well defined and usually do not overlap. With NIV, there is a need for more active multidisciplinary involvement by all parties to ensure the successful application of NIV. The primary focus of this review is the multidisciplinary aspects of care required for the successful application of NIV.

49.2 Methods

This review focuses on publications with publication dates between 2017 and 2019. A PUBMED search was conducted starting with the key words "multidisciplinary" and "noninvasive ventilation", and additional searches completed by adding the terms "nursing", "respiratory therapy", "healthcare providers", and "respiratory therapy providers". The search returned 1316 citations, but several citations were repeated with these multiple search strategies, and 907 more accurately reflects the number of citations with this search. Many of the citations dealt with invasive as opposed the noninvasive ventilation, as several were also consensus or guideline statements. The search did not identify any randomized trials or other interventional clinical trials on this subject. However, observational or retrospective studies were identified along with a few qualitative studies which addressed multidisciplinary aspects of care and comprise the bulk of this review. The review focused on the management of adult patients and reports in English. NIV use in neonatal patients and children were not included for review.

49.3 Multidisciplinary Elements of Care and Time Requirements

The successful application of NIV hinges on a comprehensive, multidisciplinary approach to therapy. It is instructive to review some of the early reports on NIV application to better appreciate the perspectives of each of the healthcare disciplines involved in management. The sentinel report about difficulty in patient management was from Chevrolet and colleagues published in 1991 [5]. Their primarily message involved the difficult and time-consuming nature of NIV and supported their experience with six prospectively evaluated patients. Several other issues may have clouded their experience. All of their patients had hypercapnic respiratory acidosis and were on the brink of respiratory failure and intubation. NIV was delivered via a nasal mask with volume cycled ventilators. Three had underlying restrictive physiology, one with neuromuscular weakness, one with severe pulmonary hypertension and fluid overload, and one with morbid obesity and obesity hypoventilation. Three had obstructive physiology, one with cystic fibrosis and the other two with advanced obstructive lung disease. Those with restrictive physiology were successfully treated, but those with obstructive physiology all failed and eventually required endotracheal intubation. The authors charted the time required at bedside and it averaged over 90% of their time for the failed patients compared to 40% for those successfully treated. High peak airway pressures (>30 cm H_2O) were noted for each patient who failed. Mouth leaks, patient ventilator discoordination, and pressure alarms were the main reasons required for the constant bedside presence by nursing. While this experience was attributed to the mode of ventilatory support (NIV), subsequent experience suggests some areas of application that could have been optimized, including the patient-mask interface (orofacial), type of ventilator (pressure cycled vs. volume), and the presence of respiratory therapy (not reported). Only one nurse was familiar with NIV prior to this reported trial and with training provided to other staff as they cared for the patient. In addition, patient selection may have also doomed therapy as those with obstructive physiology were also febrile and with significant secretions. In other words, the time-consuming aspect may not have been the ventilatory modality (NIV), but issues related to patient selection and methods of NIV application which have since improved.

In a prospective, randomized trial by Kramer and colleagues of 31 patients, the workload and perception of nurses and respiratory therapists were directly assessed during the trial [6]. NIV was delivered through a nasal mask with a relatively new ventilatory support device (bilevel positive airway pressure or BiPAP®, Respironics Inc.; Murrysville, PA) with average pressures after a day of use at 11.3 ± 0.9 cm H_2O. Both nursing and respiratory therapy spent around 100 min for the initial 8 h of treatment (~21%) and much less in the second 8 h, with respiratory therapy averaging 34 min (7%) and nursing 82 min (17%) of their time at the patient's bedside. The more important finding was that both respiratory and nursing spent comparable amounts of time with those who were invasively ventilated with similar levels of difficulty rating for both provider classes. Difficulty ratings were actually lower for those treated with NIV than invasive ventilation for both groups. These results can be attributed to several differences, starting with a different ventilatory support system, with lowered delivered peak airway pressures and technology, improved patient comfort, and acceptance of ventilatory support. In addition, there also seemed to be more training and greater familiarity with NIV by the front line healthcare providers.

A prospective observational trial by Nava and colleagues was undertaken to specifically address the actual workload and costs associated with NIV during the treatment of acute exacerbation of COPD [7]. Ten patients were treated with face mask NIV and pressure support ventilation and

were compared to six who require intubation and mechanical ventilation. The latter group was also paralyzed and sedated, and a stopwatch was used to record the actual time spent at the bedside by healthcare providers. This study included physicians, as well as nurses and respiratory therapists. They recorded workload for the first 48 h of ventilatory support. No differences were noted between NIV and intubated patient for either nursing or physicians, both groups spending about 14–18% of their time at the bedside. Respiratory therapists did spend more time in the first 6 h with NIV patients (~30%) compared to <10% with intubated patients, but over the course of treatment, workload decreased to be comparable to the intubated patients, comprising about 10% of their total time. The composite workload of all three groups was similar between NIV and intubated patients and the costs of treatment were also similar. After the initial 48 h, the investigators noted a further reduction in time at the bedside by both physicians and nurses with NIV patients, approaching 1 h/day, whereby physician and nursing time was stable for intubated patients at 2–4 h/day.

In a more recent study by Simonelli and colleagues, a physiotherapist (or respiratory therapist) focused cardiopulmonary rehabilitation unit in Italy reported their experience in 201 patients with chronic respiratory failure [8]. The physiotherapists spend an average of 17.2 ± 15.4 min on each session with each subject with more time spent for those with neuromuscular disease. They were able to achieve adequate training with an average of 8.2 ± 3.2 sessions (range 2–16), further supporting efficacy and minimal time requirements once staff involved with NIV are trained and comfortable with its application.

49.4 NIV Consensus Recommendations

Since these reports, issues involving excessive time or workload with NIV have faded but remain an important aspect of management. Consensus guidelines have continued to emphasize the importance of attention to technical issues [9]. The most frequent reasons for NIV failure remain excess mask leak, insufficient ventilatory support, and patient ventilator asynchrony, issues that were identified as causes of NIV failures since its initial application. These reflect issues that are best identified and managed at the bedside and require close attention by front line providers, specifically nursing and respiratory therapy staff. This further reinforces the need for close monitoring and a multidisciplinary approach to management.

In their guidelines on the ventilatory management of acute hypercapnic respiratory failure in adults, the British Thoracic Society/Intensive Care Society provides a framework for patient management to include immediate clinical assessment, an assisted ventilation plan, and recovery and discharge plans [9]. Included in their recommendations were identification of a specifically identified NIV treatment area, staffing levels with nursing assignments of one nurse for every two NIV patients, NIV protocols, designated lead of a core NIV multidisciplinary group, access to NIV technical support, audit mechanisms and regular staff education as well as training modules. The construct of the multidisciplinary team included physicians, nursing, and physiotherapists. It should be noted that in Europe, the physiotherapist provides the same role and function as the respiratory therapist in North America. For all intents and purposes, the position should be considered the same, despite some differences in the scope of practice.

49.5 NIV-Focused Care Audit

To further examine the status of NIV delivery, the British Thoracic Society proposed an audit of the status of NIV in the United Kingdom (UK), which was conducted by the Clinical Outcome Review Program and published by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in 2017 [10]. Through a combination of questionnaires and case reviews, the group analyzed 353 patients and 165 hospitals

who were treated with NIV. It is worthwhile to review their findings with respect to the multidisciplinary focus of this review and the findings fall into the following broad categories.

49.5.1 Staffing

A lead physician or "designated expert" in NIV available 24/7 is one of their guideline recommendations, but in over half (55%), this coverage was provided by the general medical staff. Only 23% had recommended coverage by a subspecialty respiratory consultant (pulmonary physician). In 75% of the hospitals, a respiratory consultant was available less than half of the time. With respect to nursing, less than half (49%) of the hospitals had recommended nursing ratios (1:2 NIV patients). Changes to ventilator settings were most commonly performed by the respiratory consultant, but in 20%, changes were made by medical trainees (resident physicians), more than half by nurses and in more than a third by the physiotherapist. Most hospitals (89%) did report annual training programs in NIV. A competency assessment for NIV was present in 82% of hospitals, but 38% permitted staff without NIV competency to supervise the care of NIV patients. In hospitals without a medical lead for NIV, nursing represented that lead in 44% and physiotherapy in 15%.

49.5.2 Protocol

With respect to local guidelines or protocol on the management of NIV patients, most facilities had guidelines with >90% having materials listing indications, contraindications, and escalation. Protocol or guidelines for weaning were present in 73%. A prescription form for the management of NIV patients was found in 69% and a specific observation chart in 83%. In addition to a protocol for treatment, a National Early Warning Score (NEWS) was also recommended to track patients which in turn would trigger alerts for deteriorating patients who may warrant escalation of care. They found that NEWS were not consistently documented in 47% of cases. In addition, an initial respiratory consultant was only called in 24% of their cases and 14% had no defined initial management plan on inappropriate plan. Eventually, 75% of patients had respiratory consultant review.

49.5.3 Outcomes

The overall success rate of NIV was 64%, with only 5% proceeding to intubation and mechanical ventilation, and 25% had treatment withdrawn. They reported mortality of 35%, with a mortality rate of 25% in those with COPD. Their reviewers cited the quality of NIV care as good in 27.5%, acceptable in 48.5%, but poor or unacceptable in 24%. There were opportunities for improvement in management noted in 60% of their cases.

49.5.4 Recommendations

The panel identified 21 recommendations, but the most important related to this review involve governance, treatment, and review of NIV care. First and foremost, there should be a clinical lead for NIV encompassing medical and nursing leadership. A minimal staffing ratio of one nurse to two NIV patients is recommended. Operational policies must be in place that address clinical areas of application, staff, escalation of treatment, documentation, and frequency of patient review. Staff must have minimal competency in NIV management and NIV management and care must be discussed daily with those with NIV expertise. Governance policies should include all sites of NIV application and all disciplines, specifically medical, nursing, and physiotherapy personnel. And lastly, NIV management to include mortality and quality of care should be audited and reviewed at least annually.

These recommendations were made to address issues identified in the British healthcare system, but these general principles are applicable to all healthcare systems and all areas where NIV is administered. These issues have been previously

noted to contribute to worsening outcomes in association with training, experience, and staffing [11–15], but this association, while intuitive can be difficult to demonstrate short of a focused audit as outlined in the NCEPOD report.

49.6 Multidisciplinary Issues

49.6.1 Location of Care

These and other issues have been the focus of recent observational or retrospective studies which form the remainder of this review. An analysis of ten Spanish units involved 387 patients with mixed results, but clearly success rates for NIV were lower (58% vs. 66%) when patients were treated in a ward setting where nursing and staffing ratios are lower than an intensive care unit (ICU), and issues with inadequate training were identified [16]. The emergency department (ED) had the greatest success (83%) despite a lower nursing ratio of 1:8–12, possibly related to closer overall monitoring in an ED setting.

Another observational study compared three models of care in Australian NIV patients (ward, specialized high dependency unit (HDU) and ICU) during 91 episodes of respiratory failure requiring NIV in three hospitals with established NIV experience [17]. It is noteworthy that all sites had a respiratory specialist whether nursing or physician background. No significant difference was noted in the groups with respect to demographics and severity of the respiratory illness. Nursing ratios were 1:4 and 1:8 for the ward, 1:2 for the HDU, and 1:1 for the ICU. Respiratory consultants were available for HDU and ICU patients on a daily basis, but thrice weekly for the ward patients. Correction of respiratory acidosis and overall outcomes were no different between any of the three units. However, the intubation rate was higher in the ICU patients (20%) vs. 0–2% for the other sites. This experience demonstrates that the location of NIV application may not matter in terms of outcomes, provided there are staff well trained in NIV patient management. Costs associated with ward care were less, but other issues with respect to severity of illness, patient preferences, and direction of care were not assessed as these may explain the differences in intubation rate.

49.7 Key Elements of NIV Administration

Operator-dependent factors, defined as inappropriate indications for NIV application, inadequate ventilator settings, inadequate patient reassessment, and titration of ventilatory support have been identified as a cause of NIV failure, in a retrospective review of 1095 patients treated in a Florida hospital [18]. The authors were unable to identify specific responsibility for these aspects of care, but these categories clearly implicate all those involved, including physicians, nursing, and respiratory therapy. The authors did not report a statistical analysis, but these categories which comprised 13–33% of the reasons for failure and failure of NIV was associated with a 22% mortality.

49.7.1 Protocols

Some of these identified deficiencies may be addressed with specific treatment protocols or dedicated treatment teams. Protocol management is not a new concept and was an integral part of patient management introduced in a prospective, randomized description of ward-based NIV care [19]. This was a crucial aspect of successful patient outcomes as the staffing ratio was as low as 1:13 and training was modest comprising of an initial 8 h and then monthly refresher sessions. There was standardized treatment, regular arterial blood gas determinations, and pre-established criteria for deterioration and intubation. They demonstrated a reduction in the number of patients meeting criteria for intubation with NIV (15% vs. 27%, $p < 0.02$) and hospital mortality (10% vs. 20%, $p = 0.05$), with the actual intubation rates lower (6% vs. 10%) and an extra 26 min of nursing time required during the first 8 h of care.

Protocols are an important aspect of management as they provide guidance during periods of deterioration where other members of the multidis-

ciplinary team may not be immediately available. The existence of protocols and training was one of the key issues identified as crucial for the success of NIV. As an extension of protocol management, a dedicated treatment team that is not restricted by the physical limitations of location is another model of multidisciplinary care that has been demonstrated to be effective at providing NIV.

49.8 NIV-Focused Treatment Teams

In a retrospective before and after review, a dedicated respiratory therapy team in a Swiss hospital managed a total of 126 ICU patients with COPD exacerbations [20]. Prior to the respiratory team, physicians and ICU nurses managed the patient, but this was left to trained respiratory therapists as the intervention under review. This relieved nursing staff of the NIV care of these patients. The dedicated NIV treatment team significantly increased NIV utilization (64–92%, $p < 0.01$). There was no difference in the severity of illness between the cohorts, but those treated with the dedicated NIV team had a decreased odds ratio for death or intubation (OR = 0.20; 95% CI 0.06–0.70) representing a 14.6% reduction in the absolute risk of death or intubation in those managed by the dedicated treatment team. This is a unique approach and addresses some of the nursing time commitment issues that may have limited NIV application.

In another cohort study from Switzerland, a multidisciplinary respiratory care team comprised of a pulmonologist and respiratory therapist focused on patients presenting with respiratory failure to the Emergency Department (ED) with a goal of "instantaneous" NIV support [21]. The team was operational only during typical administrative hours (M–F; 0800–1800) and in their cohort of 63 patients, the door to NIV time averaged 56 min (range 32–97 min). This experience was substantially shorter than NIV initiated outside their window which averaged 84 min (range 57–166 min). Their cohort had uniform improvement in cardiopulmonary parameters with NIV treatment. They reported an immediate failure rate of 2%, but over the hospitalization, mortality was 19%. While they were not able to correlate outcomes with the presence of a dedicated team, they provided a proof of concept of rapid initiation of NIV with a dedicated, trained NIV team. A summary of these treatment models is outlined in Table 49.1.

Table 49.1 Summary of multidisciplinary models of care

Reference	Location	Staff	Additional training	Guidelines	Impact
Plant et al. [19]	Ward	Nursing 1:13	8 h Monthly	Arterial blood gas Standard orders Criteria for escalation	Decreased intubation Decreased mortality
Parker et al. [17]	ICU	Nursing 1:1 Physician	None stated	Local	No differences
	HDU	Nursing 1:2 Respiratory nurse	None stated	Local	No differences
	Ward	Nursing Day: 1:4 Night: 1:8 Respiratory nurse	None stated	Local	No differences
Simonelli et al. [8]	Rehab ward	Physician Physiotherapist Nursing	2 h 15 days apprenticeship	Local	Increased efficiency
Horvath et al. [21]	ED	Physician Respiratory therapist	Local training	Local	More rapid NIV
Vaudan et al. [20]	ICU	Physician/nursing vs. Respiratory therapist	Local training	Local	Decreased intubation Decreased mortality Shorter length of stay

49.9 Nursing Care Issues

Most of the focus has been on respiratory therapy, with a relative paucity of investigations related to nursing issues. This has been outlined in a recent review and issues identified reinforce those previously highlighted [22]. These include the experience and skill of those administering NIV, mask leaks, patient-ventilator synchrony, and interface issues. Some areas not previously highlighted include patient discomfort, gastric distension, and local pressure ulcers associated with the mask and enteral feedings. They did allude to nursing requirements for a minority of patients, citing a nursing activity score that indicated about one-fourth of NIV patients would require a nursing ratio of 1:1. No clinical trials have addressed these issues and these represent opportunities for more nursing research.

49.10 Patient Care Perspectives

The other aspect of NIV that has long been neglected has been the perspective of the patient undergoing noninvasive ventilatory support. This is important given increasing focus on patient-centered care. The majority of the work in this area has been qualitative, involving structured interviews or questionnaires and mostly led by nursing. The investigations have focused on patient perspectives, and reasons behind acceptance and discontinuation of NIV. Jerpseth and colleagues focused on the experience of the patient with advanced COPD in Norway [23]. Part of the focus of these 12 interviews involved perception of their disease as well as experience after an illness that required NIV support. Feelings of isolation, dyspnea, and fragility were common themes. Patients viewed the mask NIV as both a savior and a burden, referring to the latter as a "life buoy". In addition to pain and claustrophobia, there were also expressions of hopelessness and loss of control. More importantly, subject often felt that they had been excluded from decision making and were left out of discussions of prognosis, death, and dying.

In another study of 12 patients from Japan, a mixed-methods approach was used to assess patient experience on NIV [24]. They first conducted semi-structured interviews and then used information identified from those interviews to assess the experience of 126 patients who were treated with NIV. They identified eight primary issues associated with NIV. Technical issues involved discomfort with the mask and air pressure and flow. From a subjective standpoint, subjects expressed relief of dyspnea with NIV, but also noted sleep deprivation as a prominent issue. They were often unable to visualize the need for NIV, but gradually came to acknowledge their need for NIV, relief of anxiety, and discomfort associated with nursing involvement as well as increased acceptance of NIV with self-directed measures.

In their analysis of 126 patients treated with NIV, they were able to separate their analysis between those successfully treated with NIV and those who either discontinued NIV or required intubation with NIV. One of their measures included a delirium score, the Intensive Care Delirium Screening Checklist (ICDSC) where a score of 3–5 is considered delirious. It is noteworthy those who stopped or "abandoned" NIV all had high scores ≥5. Those with lower scores and sleep deprivation were also more likely to stop NIV. Sleep deprivation was an especially important factor with an odds ratio (OR) of 72.36 (95% CI 9.07–577.16; $p < 0.001$) for abandonment of NIV. Mask discomfort generated an OR of 4.38 (95% CI 1.07–17.96; $p = 0.04$). The ICDSC score after 12 h of NIV had an OR of 1.62 (95% CI 1.11–2.37; $p = 0.013$). High oxygenation ratios ($PaO_2/FIO_2 > 192$) after 3 h of NIV were also associated with cessation of NIV (OR 1.01; 95% CI: 1.001–1.018; $p = 0.025$). When examining their NIV patients who were intubated, parameters that identified those converted from NIV to invasive ventilation were APACHE II scores (OR 1.10; 95% CI 1.005–1.227; $p = 0.040$), improved in dyspnea after 6 h (OR 0.272; 95%

CI: 0.076–0.976; $p = 0.046$); and a $PaO_2/FIO_2 < 120$ after 3 h of NIV (OR 0.987;95% CI 0.978–0.995; $p = 0.002$). In summary, increased severity of illness, ongoing dyspnea, suboptimal oxygenation, and mask discomfort are well recognized factors that contribute to the failure of NIV. In addition, sleep deprivation and delirium are also risk factors that predict patient cessation of NIV. These latter two elements have not been well recognized and are important clinical features that may often be first noted by nurses and other bedside healthcare providers. These certainly represent opportunities to improve and optimize NIV delivery.

49.11 NIV Providers and Patient Perceptions

In a further analysis of multidisciplinary aspects of NIV, a questionnaire survey of 32 French and Belgian ICUs of a total of 311 ICU physicians, 752 nurses, 396 patients, and 145 relatives revealed marked differences in perceptions of NIV among both healthcare providers, patients and their families [25]. Of note, less than half (45%) reported written guidelines on NIV use. There was discordance in willingness to administer NIV between physicians (64%) and nurses (32%), with those with a higher case volume, more willing to administer NIV. Individual perception of NIV competency was identified as independent factors for NIV use among both physicians and nurse. However, negative perceptions still exist with notations of "care for a NIV patient is excessively time-consuming", "it is an aggressive device", "it makes patients suffer", and "feeling of regret in relation to NIV". Among patients and relatives, anxiety (37% and 45% respectively) were the most common responses. Dyspnea, long duration of NIV, and need to have someone bedside were independent risk factors for anxiety. In summary, the most noteworthy findings of this questionnaire are the discrepant perceptions of efficacy between physicians and nurses, patients and their relatives. A great portion of nursing staff felt NIV was traumatic and stressful to patients. Others have noted differences in expectations between physicians and other healthcare providers, specifically respiratory therapists in NIV efficacy and outcomes, and therefore this discordance between physicians and nurses, patients and their relatives has been previously noted and is not totally unexpected [26]. However, this is especially noteworthy given this study is from a region where there is a relatively high use of NIV, especially when compared to the United States. This report also suggests that there may be a less than optimal multidisciplinary approach to the care of these patients and identifies an opportunity for improvement with additional NIV training and education.

Another questionnaire survey of 407 Spanish nurses and physicians highlighted gaps in knowledge and management issues with respect to noninvasive ventilation [27]. It is noteworthy that the overall percentage of correct responses was only 50%. The authors demonstrated nurses had less knowledge than physicians about NIV with average scores of 3.27 ± 0.5 vs. 2.62 ± 0.5, difference 0.65; 95% CI: 0.48–0.82, $p < 0.01$ (lower scores with greater knowledge). Mask and patient-ventilator synchronization were the most commonly cited issues, with no differences noted between nurses or physicians. The results also highlight the need for more education and training.

49.12 Conclusions

It has been well recognized that NIV has required a multidisciplinary effort to achieve optimal outcomes. This primarily involves three groups of healthcare providers, physicians, nurses, and respiratory therapists (physiotherapists in some countries). What was once very laborious and time-consuming has turned into a first-line intervention for most patients with acute exacerbations of COPD and cardiogenic pulmonary edema. But the success of NIV still depends on the multidisciplinary cooperation between all three disciplines.

Table 49.2 Multidisciplinary recommendations for NIV infrastructure and patient management (adapted from NCEPOD report [10])

Clinical lead
Physician
Nursing
NIV training/expertise
Operational policy
Identify appropriate clinical area
Minimal staff competency and training
Specialty training/expertise in NIV
Staffing ratios (recommended nurse: NIV patient 1:2)
Escalation procedures
Escalation of care (ICU)
Appropriateness of invasive ventilation
Limits of treatment
Step down procedures
Standard documentation
Vital signs (hourly until stable) and charting
Ventilator support and settings: standardized protocol adjustments
Frequency of review
Review of care with specialty consultant within 14 h and daily
Transition of care
Post-hospitalization
Home NIV
Governance of NIV unit
Multidisciplinary (medical, nursing, respiratory therapy)
Locations (Emergency Department, Ward, Step down, and ICU level)
Records
Database of NIV-treated patients
Annual audits of care
Morbidity and mortality review
Quality improvement

NIV training and education, explicit guidelines on patient management, including guidelines for escalation and termination of support are important aspects of care. Dedicated staff with specific expertise in NIV are important and in addition to clinical leads, a focused team of specialized healthcare providers may also translate into clinical benefit. Attention to detail is another important factor in NIV and refers to close bedside care and management, especially with respect to problems associated with the mask, ventilator, and patient-ventilator coordination. These issues have been previously cited as part of the essential components for an optimal NIV and are further summarized in Table 49.2. Less recognized features that impact NIV include patient identified issues of sleep deprivation, delirium, hopelessness, anxiety, and depression. Figure 49.1 provides a framework for the understanding of these multidisciplinary relationships and the central relationship to the patient. In addition to close working relationships, training and education are also essential components. These all represent areas that are amenable to a multidisciplinary approach to improve quality of care, which would translate into improved patient care and outcomes.

49.12.1 Learning Points

1. Multidisciplinary care is crucial for optimal delivery of NIV.
2. Training, education, protocols, and guidelines are important parts of multidisciplinary care.
3. Dedicated NIV treatment teams may be a treatment model.
4. Patient perspectives on NIV have not previously been well appreciated.

49.12.2 Critical Points

1. Multidisciplinary care remains suboptimal in many areas.
2. If providers are adequately trained, patient outcomes may not differ with location of care.
3. Discordance between perceptions and expectations of NIV exist.
4. Sleep deprivation and delirium are common and may be unrecognized in NIV patients.

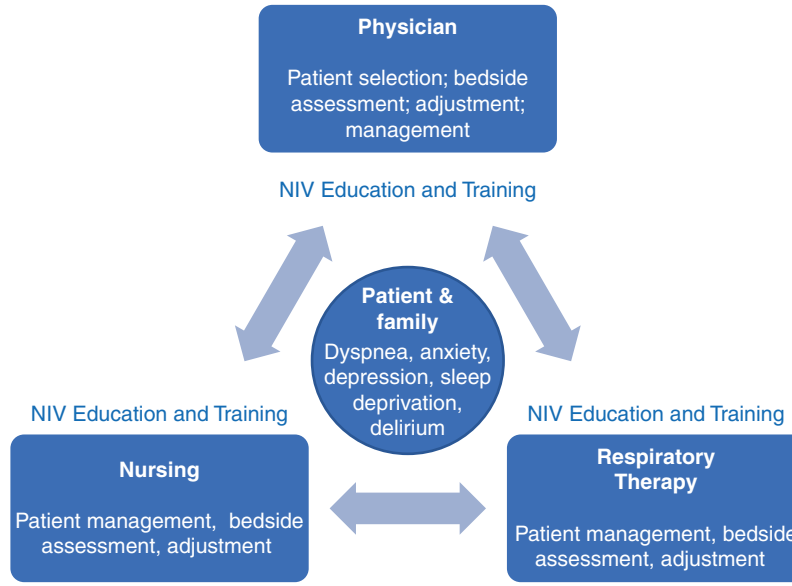

Fig. 49.1 Multidisciplinary relationship and roles of healthcare providers centered around patient-focused issues. The figure highlights the continuous interaction and interdependence of each discipline with each other and the domains of their focus. The patient is central to management and key patient issues are listed

References

1. Meduri GU, Conoscenti CC, Menashe P, et al. Noninvasive face mask ventilation in patients with acute respiratory failure. Chest. 1989;95:865–70.
2. Brochard L, Isabey D, Piquet J, et al. Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. N Engl J Med. 1990;323:1523–30.
3. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333:817–22.
4. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. Lancet. 2009;374:250–9.
5. Chevrolet JC, Jolliet P, Abajo B, et al. Nasal positive pressure ventilation in patients with acute respiratory failure: difficult and time-consuming procedure for nurses. Chest. 1991;100:775–82.
6. Kramer N, Meyer TJ, Meharg J, et al. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med. 1995;151:1799–806.
7. Nava S, Evangelisti I, Rampulla C, et al. Human and financial costs of noninvasive mechanical ventilation in patients affected by COPD and acute respiratory failure. Chest. 1997;111:1631–8.
8. Simonelli C, Paneroni M, Vitacca M. An implementation protocol for noninvasive ventilation prescription: the physiotherapist's role in an Italian hospital. Respir Care. 2013;58:662–8.
9. Davidson AC, Banham S, Elliott M, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl 2):ii1–ii35.
10. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD). Inspiring change: a review of the quality of care provided to patients receiving acute non-invasive ventilation. 2017. pp. 1–116. https://www.nceod.org.uk/2017report2/downloads/InspiringChange_FullReport.pdf. Accessed 15 Apr 2019.
11. Dres M, Tran TC, Aegerter P, et al. Influence of ICU case-volume on the management and hospital outcomes of acute exacerbations of chronic obstructive pulmonary disease∗. Crit Care Med. 2013;41:1884–92.
12. Mehta AB, Douglas IS, Walkey AJ. Hospital noninvasive ventilation case volume and outcomes of acute exacerbations of chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2016;13:1752–9.
13. Ozsancak UA, Sidhom SS, Khodabandeh A, et al. Use and outcomes of noninvasive positive pressure ventilation in acute care hospitals in Massachusetts. Chest. 2014;145:964–71.
14. Scala R, Corrado A, Confalonieri M, Marchest S, et al. Increased number and expertise of Italian respiratory high-dependency care units: the Second National Survey. Respir Care. 2011;56:1100–7.
15. Soo Hoo GW, Santiago S, Williams AJ. Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: determinants of success and failure. Crit Care Med. 1994;22:1253–61.

16. Raurell-Torreda M, Argilaga-Molero E, Colomer-Plana M, et al. Optimising non-invasive mechanical ventilation: which unit should care for these patients: a cohort study. Aust Crit Care. 2017;30:225–33.
17. Parker K, Perikala V, Aminazad A, et al. Models of care for non-invasive ventilation in the acute COPD comparison of three tertiary hospitals (ACT3) study. Respirology. 2018;23:492–7.
18. Bhatti H, Ramdass A, Cury JD, et al. Operator dependent factors implicated in failure of non-invasive positive pressure ventilation (NIPPV) for respiratory failure. Clin Respir J. 2017;11:901–5.
19. Plant PK, Owen J, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. Lancet. 2000;355:1931–5.
20. Vaudan S, Damian R, Beuret P, et al. Impact of a dedicated noninvasive ventilation team on intubation and mortality rates in severe COPD exacerbations. Respir Care. 2015;60:1404–8.
21. Horvath CM, Brutsche MH, Schoch OD, et al. NIV by an interdisciplinary respiratory care team in severe respiratory failure in the emergency department limited to day time hours. Intern Emerg Med. 2017;12:1215–23.
22. Bambi S, Mati E, De Felippis C, et al. Noninvasive ventilation: open issues for nursing research. Acta Biomed. 2017;88:32–9.
23. Jerpseth H, Dahl V, Nortvedt P, et al. Older patients with late-stage COPD: their illness experiences and involvement in decision-making regarding mechanical ventilation and noninvasive ventilation. J Clin Nurs. 2018;27:582–92.
24. Murata H, Inoue T, Takahashi O. What prevents critically ill patients with respiratory failure from using non-invasive positive pressure ventilation: a mixed-methods study. Jpn J Nur Sci. 2017;14:297–310.
25. Schmidt M, Boutmy-Deslandes E, Perbet S, et al. Differential perceptions of noninvasive ventilation in intensive care among medical caregivers, patients and their relatives: a multicenter prospective study—the PARVENIR study. Anesthesiology. 2016;124:1347–59.
26. Bierer GB, Soo Hoo GW. Noninvasive ventilation for acute respiratory failure: a national survey of Veterans Affairs hospitals. Respir Care. 2009;54:1313–20.
27. Raurell-Torreda M, Argilaga-Molero E, Colomer-Plana M, et al. Nurses' and physician' knowledge and skills in non-invasive ventilation: equipment and contextual influences. Enferm Intensiva. 2019;30:21–32.

Noninvasive Ventilation for High-Risk Endotracheal Intubation

50

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50.1 Introduction

Endotracheal intubation is an integral component of critical care. Nevertheless, critically ill patients may suffer life-threatening complications, especially when intubation is considered difficult. Intubation is considered difficult if it requires multiple attempts or techniques or prolonged time [1]. Classically, difficult intubation is thought to be related to poor visualization during laryngoscopy or difficulty passing the endotracheal tube. Difficult intubation, when defined as requiring three or more attempts or lasting more than 10 min using conventional laryngoscopy,

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occurs in approximately 10% of intensive care unit (ICU) intubations [2].

A broader definition of difficult intubation should also include challenges that are not directly related to laryngoscopy or passage of the endotracheal tube. Difficult intubation should also include the physiologic challenges of critically ill patients due to poor cardiopulmonary reserve [3]. Significant respiratory impairment, structural heart disease, systemic vasoplegia, acidosis, and pulmonary vascular disease are common in critically ill patients and increase the risk of complications. Severe hypoxemia (defined as $SpO_2 < 80\%$) is the most common complication and occurs in up to 28% of ICU intubations [4]. Hypotension is also quite common, found in 9–25% of ICU intubations [4–6]. These complications and cardiac arrest occur more often in critically ill patients compared with those intubated for elective anesthesia.

Noninvasive ventilation (NIV) has traditionally been used to prevent the need for invasive mechanical ventilation. Nevertheless, NIV can be helpful in the process of transition to invasive mechanical ventilation and endotracheal intubation itself, and maintaining positive pressure ventilator support with NIV throughout the intubation process may reduce the risk of complications. While the benefits of NIV in transition to mechanical ventilation can be applied to a broad range of clinical scenarios where difficult airway may be anticipated, patients in hypoxemic respiratory failure who are treated with and fail noninvasive ventilation (NIV) are at particularly high risk for peri-intubation complications and mortality as removing NIV to facilitate endotracheal intubation may result in alveolar derecruitment and reduced spontaneous minute ventilation [7]. Therefore, this chapter will discuss the theoretical benefits of NIV use in the transition to mechanical ventilation and review current evidence for its use in different clinical settings.

50.2 Benefits of NIV in Endotracheal Intubation

The physiologic benefits of NIV prior to and during intubation are similar to that of its use for other indications. NIV augments ventilation and oxygenation. PEEP improves alveolar recruitment and helps maintain upper airway patency. It can also provide some insight into the patient's hemodynamic response to positive pressure ventilation. For intubation, NIV can increase the time before oxyhemoglobin desaturation and reduce the risk of significant hypoxemia. It can further facilitate concomitant bronchoscopic intubation during spontaneous ventilation with the use of mild sedation. This may further reduce the risk of peri-intubation worsening of hypoxemia, hypoventilation, and hypotension. We think this technique is particularly useful when intubating patients with poor cardiopulmonary reserve, such as those with pulmonary arterial hypertension with right ventricular dysfunction. Intubating patients with decompensated right ventricular failure may be particularly risky given the potential for systemic vasodilation and elevation of pulmonary vascular resistance.

50.2.1 Ventilation

Apnea during elective intubation for general anesthesia is generally tolerated. The increase in $PaCO_2$ is approximately 3–4 mmHg/min. $PaCO_2$ rises more quickly in patients with increased metabolic rate, which is common in critically ill patients due to fever, tissue injury, or systemic inflammation. NIV can improve alveolar gas exchange and decrease the work of breathing by improving tidal volumes [8]. One case series suggests that NIV can be used to maintain sufficient ventilation during deep sedation for procedural anesthesia [9].

50.2.2 Oxygenation

After induction of anesthesia and neuromuscular blockade, patients become apneic and their lungs recoil to functional residual capacity (FRC). Oxygen transport continues as the residual oxygen in alveolar air at FRC diffuses into pulmonary capillary blood. The time to arterial desaturation during apnea depends on the volume of alveolar air at FRC, the alveolar partial pres-

sure of oxygen as well as total oxygen consumption and the quantity and distribution of pulmonary blood flow. Supine positioning, central obesity, and parenchymal lung disease may decrease FRC and lead to rapid desaturation. Denitrogenation/pre-oxygenation and apneic oxygenation can increase the time before desaturation [10, 11]. Nevertheless, patients with oxygen saturation less than or equal to 93% during pre-oxygenation tend to desaturate to less than 90% during intubation [12].

Using NIV for pre-oxygenation may result in less desaturation compared with standard denitrogenation with spontaneous breathing of pure oxygen. Positive pressure ventilation can recruit atelectatic lung and increase the FRC, thus reducing the shunt fraction. Reduced work of breathing may also reduce oxygen consumption. Improved alveolar ventilation can also result in increased alveolar oxygen content by washing out CO_2 and nitrogen. Multiple studies have shown that NIV compared to standard pre-oxygenation can reduce the risk of significant hypoxemia during intubation.

NIV has also been used in place of apneic oxygenation during the intubation process. It has been used with a nasal interface to support bronchoscopic intubation using light or moderate sedation in particularly high-risk patients. This method, described in Fig. 50.1, allows for continued ventilation, maintenance of PEEP and minimization of atelectasis, maintenance of FRC, and maintenance of airway patency throughout the intubation process.

50.2.3 Upper Airway Patency

Sedation and paralytics typically used for induction decrease pharyngeal muscle tone and may lead to upper airway obstruction. This may in turn result in difficulty with ventilation and oxygenation during preoxygenation or after a failed attempt at intubation. NIV can help keep the upper airway patent during bronchoscopic intubation [13]. NIV may also be useful in situations where reduced upper airway patency is the reason for intubation. For example, NIV may be used as a bridge to intubation in situations of an edematous airway causing post-extubation stridor or in the setting of angioedema. The application of NIV may reduce the severity of upper airway obstruction by stenting the airway open while equipment for intubation is gathered and medical management is being administered.

50.2.4 Hemodynamics

Hypotension is a frequent complication of endotracheal intubation in critically ill patients [4–6, 14]. NIV, as with any positive pressure ventilation, can have complex effects on hemodynamics, which can often result in unpredictable

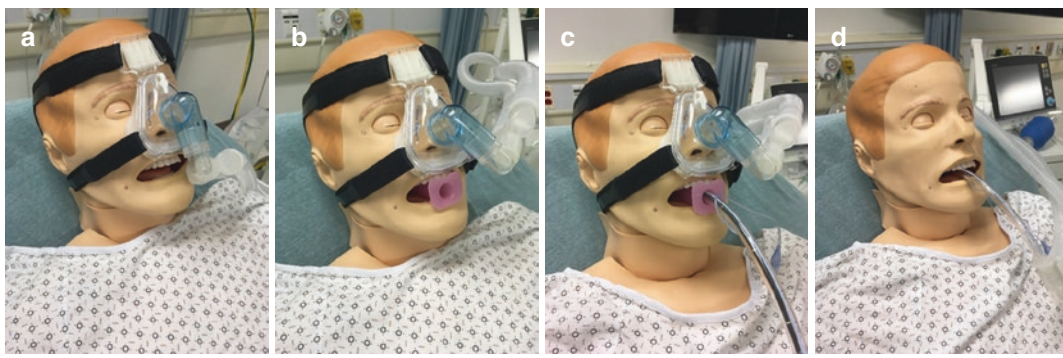

Fig. 50.1 (**a**) Patient on noninvasive ventilation via nasal delivery system, (**b**) Williams airway inserted to assist with awake bronchoscopy, (**c**) once bronchoscope enters the trachea, the pre-loaded endotracheal tube can be advanced into the airway, (**d**) noninvasive ventilation, Williams airway, and bronchoscope removed leaving only the endotracheal tube

outcomes in critically ill patients. NIV applies positive intrathoracic pressure, which may reduce venous return to the right heart [15]. To a lesser extent, NIV tends to reduce the effective left ventricular afterload, which can be helpful in decompensated left heart disease. NIV can also unload the respiratory muscles, which may result in lower oxygen consumption and thus circulatory demand.

NIV can have dual effects on pulmonary vascular resistance. In patients with significant atelectasis, positive pressure can recruit atelectatic lung units and as a result reduce pulmonary vascular resistance [16, 17]. There is however an inflection point at which further increases in pressure results in alveolar overdistension and further transmission of this pressure to the pulmonary vasculature, resulting in increased pulmonary vascular resistance [16, 18, 19]. Patients with pulmonary vascular disease may have noncompliant pulmonary vasculature. In these patients, hyperinflation may result in a more pronounced increase in resistance. Moreover, small increases in pulmonary vascular resistance in these patients may more readily result in decompensated right heart failure.

The use of NIV prior to intubation may help unmask the sometimes unpredictable effect of positive pressure ventilation on hemodynamics. This may allow for further hemodynamic optimization prior to sedation and intubation. NIV can also be used to support awake bronchoscopic intubation with the use of minimal sedation to prevent significant hemodynamic perturbations in patients with poor circulatory reserve, such as those with underlying pulmonary arterial hypertension [20].

50.3 Procedures

Varying approaches in using NIV during intubation have been described. A traditional approach used NIV as a method for pre-oxygenation up until laryngoscopy. This approach allows patients who fail NIV to undergo intubation without the need to transition to bag-valve-mask ventilation prior to intubation. Compared to pre-oxygenation with non-rebreathing bag-valve-mask ventilation, NIV has been shown in small randomized studies to result in improved pre-oxygenation and lower rates of severe peri-intubation hypoxemia [21, 22]. Both full face mask and nasal mask have been used; however, some evidence favors the nasal mask interface, which has been shown in a randomized study to result in better ventilation in generally anesthetized patients [23]. This may be due to nasal mask appliance creating a gradient between the nasopharynx and oropharynx, pushing the soft palate and tongue forward and thus preventing upper airway obstruction. A full-face mask appliance, on the other hand, does not create a pressure gradient between the nasopharynx and oropharynx, and as a result may not as effectively keep the tongue and soft palate from obstructing the upper airway.

More novel and less well-studied strategy is the extension of the use of NIV continuously throughout the intubation process either with bronchoscopic intubation or direct or video laryngoscopy. This strategy, based on the nasal application of NIV, has theoretical advantages for patients who are severely hypoxemic, may not tolerate lying supine, may have a difficult airway, and/or have a limited cardiopulmonary reserve. Studies describing and supporting the various ways to intubate with the support of NIV are limited to case series and case reports (Table 50.1).

Most of the reported use of NIV has been with bronchoscopic intubation [13, 20, 24–27]. Our approach uses a nasal mask NIV interface, semi-recumbent or upright positioning, use of an intubating airway (i.e., Williams airway), mild to moderate sedation, and topical local anesthetic (i.e., lidocaine) applied to the upper airway (Fig. 50.1) [24]. Adequate topical anesthesia typically requires high concentrations of lidocaine (4% or 5% lidocaine). An important

Table 50.1 Summary of studies on intubation technique with the support of NIV

Author	Intubation technique	Patient characteristics and intubation conditions	Findings
Aoyama et al. [26]	Fiberoptic intubation with continuous positive pressure ventilation via laryngeal mask airway ($n = 40$) vs. intubating laryngeal masks ($n = 20$) vs. endoscopy mask (Patil mask, $n = 20$).	Elective surgery patients. Standard anesthetic induction used.	Endoscopy mask was superior to laryngeal mask airway interfaces for delivering adequate tidal volumes, but it also tends to insufflate the stomach more.
Nafeh et al. [27]	Fiberoptic intubation through a Boussignac valve attached to a face mask while delivering continuous oxygen at 30 L/min in 11 severely obese patients.	Elective surgery patients. General anesthesia initiated only upon intubation.	PEEP of 7.5 cm water achieved with 30 L/min oxygen. None of the severely obese patients experienced desaturation during intubation.
Rothfleisch et al. [13]	Fiberoptic nasotracheal intubation supported by concomitant CPAP (20 cm water) applied to the contralateral nare via nasal pillow in an obese patient.	Emergent intubation for hypoxemic respiratory failure associated with altered mentation.	Images of the hypopharynx showed improved upper airway patency with the application of 20 cm water CPAP.
Wong et al. [11]	Bronchoscopic intubation through intubating laryngeal mask airway (air-Q) with BiPAP applied (with topical anesthetic) in a patient with severe obstructive sleep apnea. Before placement of laryngeal mask airway, he was supported with BiPAP via face mask.	Emergent intubation for hypoxemic respiratory failure for a patient with severe obstructive sleep apnea. The patient was kept awake for the intubation.	SpO_2 of 97% or above was maintained throughout the intubation process.
Barjaktarevic and Berlin [25]	Bronchoscopic intubation supported by nasal BiPAP in 10 patients who failed NIV. After application of topical anesthetic, intubating (Williams) airway was placed in the oropharynx. Bronchoscopic intubation was performed through intubating airway.	Emergent intubation for hypoxemic respiratory failure. In addition to topical anesthetic, mild to moderate sedation was used.	Mean decrease in SpO_2 was 4.7 ± 3.1%. Hypotension was the most common complication (33%). Only one intubation attempt was required for each of the 10 patients.
Cataldo et al. [28]	Nasal BiPAP supported direct or video laryngoscopic intubation in 3 patients in acute respiratory failure.	Emergent intubation for acute respiratory failure. Anesthetic induction and paralytics were used.	Use of nasal NIV to maintain oxygenation and ventilation during the "apneic period" after anesthetic induction is feasible. Nasal NIV can also be used with direct or video laryngoscopy.

(continued)

Table 50.1 (continued)

Author	Intubation technique	Patient characteristics and intubation conditions	Findings
Johannes et al. [20]	Bronchoscopic intubation supported by nasal BiPAP ($n = 4$) or HFNC ($n = 5$) in 9 patients with right heart failure associated with pulmonary hypertension. Topical anesthetic, intubating (Williams) airway, and mild to moderate sedation were used.	Emergent intubation for acute respiratory failure. Patients had pulmonary hypertension based on elevated RVSP (55–165 mmHg) and RV dysfunction on echocardiography.	All intubations were successful with the first attempt. One patient had significant desaturation during intubation (SpO_2 decrease of >10%). Hypotension was the most common post-intubation complication. Maximal decrease in MAP in the first hour after intubation was 11.2 ± 13.4 mmHg. Catecholamine support was initiated or escalated in 8 of the 9 patients within 1 h of intubation.

component of this approach is keeping the patient awake yet cooperative with the procedure and maintaining spontaneous breathing. In addition to the typical advantages of NIV for intubation discussed in this chapter, this strategy confers other theoretical benefits. Maintaining spontaneous breathing during intubation with the use of mild to moderate sedation leverages the ventilatory support that NIV provides and may result in improved tidal volumes and minute ventilation. It avoids the risk of insufficient ventilation and oxygenation often seen after anesthetic induction in patients with a difficult airway, especially in case of a failed intubation attempt. This strategy also allows for more flexibility in patient position during intubation—intubation can be performed in the supine, semi-recumbent, and upright positions. Lastly, this strategy may help minimize hemodynamic perturbations often seen during conventional anesthetic induction, with hypoventilation and hypoxemia during intubation, and with the transition from negative pressure ventilation to positive pressure ventilation. This last theoretical advantage may be particularly important for patients with poor cardiopulmonary reserve, such as patients with decompensated pulmonary arterial hypertension, for whom endotracheal intubation may be particularly risky. We have described a case series of using NIV-supported bronchoscopic intubations in patients with pulmonary arterial hypertension suffering from acute respiratory failure [20].

The use of nasal NIV to support intubation with direct or video laryngoscopy has been described in three cases by Cataldo and colleagues [28]. In these cases, NIV is used for preoxygenation and to support oxygenation and ventilation after anesthetic induction and prior to intubation. One potential concern with this approach is that the bulk of the nasal mask appliance may interfere with the procedural mechanics of and obscure visualization during direct laryngoscopy. Cataldo and colleagues contend in their report that the additional bulk of the nasal mask is not prohibitive to laryngoscopy, even direct laryngoscopy. Regardless, this approach is likely best tolerated using a standard anesthetic induction (instead of using mild to moderate sedation). It likely would be faster to set up and complete compared to a bronchoscopic approach. It would however not have the benefit of keeping the patient awake and spontaneously breathing and of positional flexibility inherent with bronchoscopic intubation.

It is important to note that high-flow nasal cannula (HFNC) has also emerged as an effective pre-oxygenation tool [29]. Similar to NIV, HFNC has been shown in randomized controlled studies to result in improved oxygenation and lower rates of severe hypoxemia during intubation compared to bag-valve-mask ventilation. Moreover, HFNC

can also be used for apneic oxygenation throughout the intubation process. HFNC has also been used in combination with NIV to allow for apneic oxygenation once the NIV interface is removed for laryngoscopy.

50.4 Limitations of Noninvasive Ventilation During Intubation

The use of NIV to support intubation can increase the complexity of airway management plans. Proper training with the techniques and equipment and having defined back-up plans are important to avoid complications. Setting up NIV for patients not already on it prior to intubation may require additional time, which may preclude consideration for NIV if the patient is decompensating rapidly. Further, pressure settings and mask fit need to be optimized to ensure adequate tidal volumes and minute ventilation, to minimize airway obstruction, to unload the respiratory muscles, and to minimize discomfort.

Some patients may not tolerate NIV due to patient-ventilator asynchrony or noncompliance with the mask interface or poor mask seal otherwise. Excess airway secretions or vomiting may also preclude the use of NIV prior to and during intubation.

Bronchoscopic intubation supported by NIV requires much more time to prepare for and to perform. It may not be an appropriate intubation approach for a patient who is rapidly decompensating. The patient needs to be able to tolerate NIV, the mask interface, and bronchoscopy with mild to moderate sedation for this procedure to be performed successfully. As such, patients need to be selected carefully.

50.5 Conclusions

50.5.1 Learning Points

- NIV use in transition to invasive mechanical ventilation—during the preparation for intubation and endotracheal intubation itself—may help mitigate the intubation risk in anticipated difficult airway scenarios.
- NIV can be used as a tool for pre-oxygenation and has been shown to result in lower risk of severe peri-intubation hypoxemia.
- NIV can be used to support the entirety of intubation, especially in particularly high-risk intubations, such as for patients with severe hypoxemia, a difficult airway, or poor cardiopulmonary reserve.

50.5.2 Critical Points

- Familiarization with the use of NIV and its associated equipment is important prior to applying it for intubation.
- Careful patient selection is crucial, especially if bronchoscopic intubation with mild sedation is being considered.

50.5.3 Key Summary

- NIV can be useful to support endotracheal intubation in the ICU with the potential to improve peri-intubation oxygenation, ventilation, and airway patency. In combination with bronchoscopic intubation with the use of only mild sedation with the maintenance of spontaneous breathing, NIV can facilitate intubation for exceptionally high-risk patients, such as those with a difficult airway, with severe hypoxemia, and/or poor cardiopulmonary reserve.

References

1. Henderson JJ, Popat MT, Latto IP, et al. Difficult Airway Society guidelines for management of the unanticipated difficult intubation. Anaesthesia. 2012;67(4):452.
2. De Jong A, Molinari N, Terzi N, et al. Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. Am J Respir Crit Care Med. 2013;187(8):832–9.

3. Choudhury A, Gupta N, Magoon R, et al. Airway management of the cardiac surgical patients: current perspective. Ann Card Anaesth. 2017;20(Suppl):S26–35.
4. Jaber S, Amraoui J, Lefrant JY, et al. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Crit Care Med. 2006;34(9):2355–61.
5. Griesdale DE, Bosma TL, Kurth T, et al. Complications of endotracheal intubation in the critically ill. Intensive Care Med. 2008;34(10):1835–42.
6. Simpson GD, Ross MJ, McKeown DW, et al. Tracheal intubation in the critically ill: a multi-centre national study of practice and complications. Br J Anaesth. 2012;108(5):792–9.
7. Barjaktarevic I, Esquinas AM, West FM, et al. Noninvasive ventilation in difficult endotracheal intubation: systematic and review analysis. Anaesthesiol Intensive Ther. 2017;49(4):294–302.
8. Kallet RH, Diaz JV. The physiologic effects of noninvasive ventilation. Respir Care. 2009;54(1):102–15.
9. Strayer RJ, Caputo ND. Noninvasive ventilation during procedural sedation in the ED: a case series. Am J Emerg Med. 2015;33(1):116–20.
10. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. Ann Emerg Med. 2012;59(3):165–75.
11. Wong DT, Wang J, Venkatraghavan L. Awake bronchoscopic intubation through an air-Q(R) with the application of BIPAP. Can J Anaesth. 2012;59(9):915–6.
12. Davis DP, Hwang JQ, Dunford JV. Rate of decline in oxygen saturation at various pulse oximetry values with prehospital rapid sequence intubation. Prehosp Emerg Care. 2008;12(1):46–51.
13. Rothfleisch R, Davis LL, Kuebel DA, et al. Facilitation of fiberoptic nasotracheal intubation in a morbidly obese patient by simultaneous use of nasal CPAP. Chest. 1994;106(1):287–8.
14. Perbet S, De Jong A, Delmas J, et al. Incidence of and risk factors for severe cardiovascular collapse after endotracheal intubation in the ICU: a multicenter observational study. Crit Care. 2015;19:257.
15. van den Berg PCM, Jansen JRC, Pinsky MR. Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. J Appl Physiol (1985). 2002;92(3):1223–31.
16. Roos A, Thomas LJ, Nagel EL, et al. Pulmonary vascular resistance as determined by lung inflation and vascular pressures. J Appl Physiol. 1961;16:77–84.
17. Simmons DH, Linde LM, Miller JH, et al. Relation between lung volume and pulmonary vascular resistance. Circ Res. 1961;9:465–7.
18. Hughes JM, Glazier JB, Maloney JE, et al. Effect of lung volume on the distribution of pulmonary blood flow in man. Respir Physiol. 1968;4:58–72.
19. Vieillard-Baron A, Bouferrache K, Charron C. Right ventricular function evaluation in acute respiratory distress syndrome: back to the future. Crit Care Med. 2010;38(9):1909–10.
20. Johannes J, Berlin DA, Patel P, Schenck EJ, et al. A technique of awake bronchoscopic endotracheal intubation for respiratory failure in patients with right heart failure and pulmonary hypertension. Crit Care Med. 2017;45(9):e980–4.
21. Baillard C, Fosse JP, Sebbane M, et al. Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. Am J Respir Crit Care Med. 2006;174(2):171–7.
22. Baillard C, Prat G, Jung B, et al. Effect of preoxygenation using non-invasive ventilation before intubation on subsequent organ failures in hypoxaemic patients: a randomised clinical trial. Br J Anaesth. 2018;120(2):361–7.
23. Oto J, Kimball WR, Wang J, et al. Continuous positive airway pressure and ventilation are more effective with a nasal mask than a full face mask in unconscious subjects: a randomized controlled trial. Crit Care. 2013;17(6):R300.
24. Ma KC, Chung A, Aronson KI, Krishnan JK, et al. Bronchoscopic intubation is an effective airway strategy in critically ill patients. J Crit Care. 2017;38:92–6.
25. Barjaktarevic I, Berlin D. Bronchoscopic intubation during continuous nasal positive pressure ventilation in the treatment of hypoxemic respiratory failure. J Intensive Care Med. 2015;30(3):161–6.
26. Aoyama K, Yasunaga E, Takenaka I, et al. Positive pressure ventilation during fibreoptic intubation: comparison of the laryngeal mask airway, intubating laryngeal mask and endoscopy mask techniques. Br J Anaesth. 2002;88(2):246–54.
27. Nafeh S, Danielou E, Calenda E, et al. Fiberoptic tracheal intubation through a Boussignac valve to maintain continuous oxygenation during intubation in severely obese patients: 11 cases. J Clin Anesth. 2011;23(4):345–6.
28. Cataldo S, Pedro M, Lokhandwala B. The nasal oxygenation and ventilation of the airway (NOVA) technique, a new and safer approach to airway management in the critical ill patient. SOJ Anesthesiol Pain Manag. 2014;1(2):1–4.
29. Miguel-Montanes R, Hajage D, Messika J, et al. Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. Crit Care Med. 2015;43(3):574–83.

Part IV

Neonatology-Pediatric

Maria Cristina Mondardini
and Fabio Caramelli

CPAP in Neonates: Current Methods and Further Improvements

51

Charles Christoph Roehr

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51.1 Background: Noninvasive Respiratory Support for Neonates

51.1.1 From Breathing Liquid to Air: Conditioning the Lungs and Respiratory Aparatus

In utero, the foetus breathes. Pulmonary fluid is secreted by the alveolar epithelium and moves from the lungs to the amniotic cavity by breath-like motions [1]. The glottis controls the amount of fluid released from the lungs, thus regulating the intra-alveolar pressure before birth [2]. The presence of positive intrapulmonary pressure is a physiologic stimulus, essential for normal fetal lung development [3]. Likewise, fetal breathing movements are essential for preparing the respiratory musculature and the pulmonary tissue for their functions after birth [4].

51.1.2 The Significance of Establishing the Functional Residual Capacity and Tidal Volume at Birth

Recapitulating the physiology of cardiopulmonary transition at birth helps to understand the importance of providing adequate respiratory support from birth [5]. At birth, the lungs transition from a fluid-secreting organ to being the primary organ of gas exchange. In order to establish the capacity of gas exchange, the fluid-filled airways need to be cleared of lung fluid immediately [6, 7]. The first breaths facilitate airway fluid clearance, primarily as a result from transepithelial pressure gradients generated during inspiration. When breathing is established successfully, a sufficient functional residual capacity (FRC) will have been generated, and regular breathing commences [8]. The biochemical properties of surfactant aid improving lung compliance by preventing end-expiratory alveolar collapse and maintaining FRC [9, 10]. Failure to clear the terminal gas exchange units can lead to respiratory distress and ultimately respiratory failure [11]. The application of positive end-expiratory pressure (PEEP) reduces the pressure gradient for airway liquid re-entry and helps establish and maintain FRC [8, 12]. Term infants generate an FRC of approx. 30 ml/kg and tidal volume (V_t) of approx. 5 ml/kg within minutes of birth [4].

51.1.3 Treating Respiratory Distress by Applying Noninvasive Positive End-Expiratory Pressure

It is well described that mechanical ventilation (MV) represents a significant contributing factor for developing BPD [12]. This is due to the early infliction of volutrauma, barotrauma, atelectotrauma, and biotrauma on the developing lungs [13]. Parallel to the initial BPD description by Northway and colleagues [14], Gregory and co-workers described the positive properties of using positive end-expiratory in the treatment of neonatal respiratory distress [15]. In their seminal study, authors documented a significant reduction in mortality from respiratory distress syndrome (RDS) in 20 infants with respiratory distress (birth weights between 930 and 3830 g), treated with CPAP, which at the time was applied via a head box [15]. From then on a multitude of nasal CPAP devices and other forms of noninvasive respiratory support (NIV) were introduced to neonatal care [16]. However, intubation and MV remained the standard treatment for RDS until the superior value of CPAP over MV was established through large randomised controlled trials, summarised in a comprehensive meta-analysis by Fischer and Bührer [17]. Consequently, the paradigm of invasive respiratory support changed to offering noninvasive support for newborn infants with signs of RDS [18, 19].

51.2 Current Methods and Further Improvements of Noninvasive Respiratory Support for Newborn Infants

To review the latest evidence from clinical trials and upcoming developments in neonatal NIV, we performed a comprehensive electronic search of the database of the National Center for Biotechnology Information, PubMed® (US National Library of Medicine, 8600 Rockville Pike, Bethesda MD, 20894 USA) [20]. Search words included the *wild card* neonat∗, newborn, neonate, CPAP, and noninvasive ventilation. The last date of search update was 04/05/2019. The search was filtered by adding clinical trial (publication type) and publication date/year (01/01/2017–01/05/2019). The initial search revealed >800 hits; by adding the filter *publication date*, 50 clinically relevant publications were identified. By the use of the filter *publication type: clinical trial*, the results were further reduced to seven relevant citations, one of which was a study protocol [21–27].

51.2.1 Continuous Positive Airway Pressure

One of the many challenges in providing continuous positive airway pressure (CPAP) is the regular occurrence of nasal trauma. Surveying a unit with high familiarity in CPAP use for newborn infants, Fischer and co-workers found a 40% rate of nasal mucosal irritation or more serious forms of nasal trauma stemming from pressure effects of CPAP devices [28]. Thus, various measures to prevent nasal skin breakdown have been reported as anecdotal reports, but little actual clinical research has been conducted [29]. Following the publication of a systematic review on nasal injury in preterm infants receiving NIV, Imbulana and colleagues decided to research the value of barrier dressing to reduce nasal injury in preterm infants receiving treated with CPAP [21]. In their single centre, randomised controlled trial (RCT), the authors studied infants of <30 weeks of gestation and/or with birth weight <1250 g receiving CPAP. Infants were randomly allocated to receive either a hydrocolloid nasal barrier dressing during CPAP or no barrier dressing. The primary outcome was the incidence of any nasal injury during CPAP support, until the infant was both >30 weeks of postmenstrual age and >1250 g, unless CPAP therapy was stopped earlier. Nasal injury was regularly assessed by bedside nurses using a standardised form. Of the 108 enrolled preterm infants, 53 infants received CPAP with barrier dressing and 55 infants in the no barrier group. Infants in the barrier group had significantly lower rates of nasal injury compared with the no barrier group: 18 of 53 (34%) vs. 31 of 55 (56%), respectively (p = 0.02). The authors assessed a number needed to treat (NNT) of five infants requiring treatment to prevent one episode of nasal injury. Thus, the authors conclude that prophylactic use of a nasal barrier dressing, applied within 48 h of commencing treatment with CPAP, reduces nasal injury in very preterm or very low birth weight infants [21].

In another very recent study concerning CPAP, Amatya and co-workers studied the most successful strategy for weaning infants off nasal CPAP [22]. Based on the observation that such strategies are neither well defined nor uniformly practised, the objective of this study was to determine whether gradual weaning of nasal CPAP pressure was more successful than sudden weaning off nasal CPAP to room air. For this, the authors conducted a single-centre RCT in a maximum-level neonatal intensive care unit on 70 preterm neonates, born between 26 and 32 weeks' gestation and requiring nasal CPAP for at least 48 h. Neonates stable on nasal CPAP in air (0.21 FiO_2) and 5 cm H_2O of positive end-expiratory pressure were randomised to the gradual wean group (reduction in pressure by 1 cm H_2O every 8 h until 3 cm H_2O was reached) or to sudden wean group (singular transition from CPAP to no respiratory support/air). The primary outcome was success at the first trial to wean to air. Secondary outcomes were number of attempts

and weight and postmenstrual age (PMA) at the time of successful weaning. Total number of days on nasal CPAP and length of stay (LOS) in the hospital were also compared between groups. The authors found that of the 70 infants included in the study, 35 were randomised to sudden group and 33 infants to gradual group. In sudden and gradual groups, 14 and 22 infants, respectively, were weaned successfully in the first attempt (p = 0.03). Characteristics of the infants who were successfully weaned were a PMA of 32.7 ± 1.7 weeks vs. 33.1 ± 2.4 weeks (p = 0.39) PMA and at a weight of 1651 ± 290 g vs. 1589 ± 398 g (p = 0.46) in the sudden and gradual groups, respectively. The total number of days on NCPAP was 27 ± 19 days vs. 32 ± 24 days (p = 0.38), and LOS was 63 ± 25 days vs. 63 ± 22 days (p = 0.99) in the sudden and gradual groups, respectively. The authors concluded that the gradual weaning method was more successful as compared to sudden weaning method in the initial trial off nasal CPAP. In their study, there was no difference in the PMA, weight at the time of successful weaning, total days on nasal CPAP, and LOS between the two groups [22].

The question whether nasal CPAP is best delivered by nasal mask or by nasal prong has long been debated. Investing themselves in a study to compare the efficacy and safety of CPAP delivered using nasal masks with binasal prongs, Chandrasekaran et al. randomly allocated 72 neonates between 26 and 32 weeks' gestation to receive bubble CPAP by either nasal mask (n = 37) or short binasal prongs (n = 35). The primary outcomes were mean FiO_2 requirement at 6, 12, and 24 h of CPAP initiation and the area under curve (AUC) of FiO_2 against time during the first 24 h (FiO_2). Secondary outcomes were the incidence of CPAP failure and nasal trauma. The FiO_2 requirements at 6, 12 and 24 h (mean (SD), 25 (5.8) vs. 27.9 (8); 23.8 (4.5) vs. 25.4 (6.8) and 22.6 (6.8) vs. 22.7 (3.3)) as well as FiO2 AUC0–24 (584.0 (117.8) vs. 610.6 (123.6)) were similar between the groups. There was no difference in the incidence of CPAP failure (14% vs. 20%; relative risk 0.67; 95% confidence interval 0.24–1.93). The incidence of severe nasal trauma was lower with the use of nasal masks (0% vs. 31%; $p < 0.001$). Authors concluded that nasal masks appeared to be as efficacious as binasal prongs in providing CPAP and that masks were associated with lower risk of severe nasal trauma [23] (Table 51.1).

Table 51.1 Advantages and disadvantages of CPAP therapy (modified from Ref. [16])

Advantages	Disadvantages
Increases functional residual capacity and tidal volume	Skin excoriation and nasal damage are commonly encountered and may give rise to bacterial infection, in particular by coagulase-negative staphylococci
Stabilises upper airway and chest wall stability and aids alveolar distension	Air may escape into the stomach, causing gaseous distension (CPAP belly syndrome)
Improves pulmonary compliance and reduces work of breathing	Increased intrathoracic pressure may reduce venous return to the right heart and reduce cardiac output
Reduces the alveolar-arterial oxygen pressure gradient	Lung overinflation decreases tidal volume and may increase pCO_2 and the dead-space fraction
Reduces intrapulmonary shunting	High CPAP can lead to lung overinflation, decreased compliance, and increased work of breathing
Reduces apnoea	

Traditionally, nasal CPAP is being applied at pressures between 4 and 8 cm H_2O with sufficient results. Recently, Mukerji and colleagues sought to evaluate physiological cardiorespiratory implications of high pressures (>8 cm H_2O) on CPAP in preterm neonates. In a feasibility trial, 15 preterm neonates at postmenstrual age ≥32 weeks on CPAP 5 cm H_2O were studied. The mean GA, age at study, and weight of subjects were 27.4 (2.6) weeks, 58.5 (35.5) days, and 2.3 (0.6) kg, respectively. The CPAP pressures were increased by 2 cm H_2O increments up to 13 cm H_2O. At each increment, cardiac output, electrical diaphragmatic (Edi) activity, and clinical cardiorespiratory parameters were measured. Predefined cut-off values for changes in cardiorespiratory parameters were used as termination criteria. The median (IQR) time at each CPAP increment was 10 (5, 20) min. Cardiac outputs

(ml/kg/min) at 5, 7, 9, 11, and 13 cm H_2O were not different at 295, 290, 281, 286, and 292 min, respectively ($p = 0.99$). Edi values demonstrated a trend towards decline at 9 cm H_2O before rising again. No other cardiorespiratory parameters were different across CPAP levels; no subject met termination criteria. The authors concluded that high CPAP levels were well tolerated for short durations. Further physiological and clinical research is required on safety/efficacy, particularly in neonates with more severe lung disease, as well as its impact over longer durations [30].

Similarly, Martherus and co-workers compared two different strategies of respiratory support at birth in a retrospective, matched pair analysis between the University of Leiden Medical Centre, The Netherlands, and the University Medical Centre of Cologne, Germany. The objective was to compare the centres' two strategies: (a) Leiden, low pressure, CPAP 5–8 cm H_2O and/or positive pressure ventilation (PPV) and FiO_2 0.3–1.0 ($n = 27$); or (b) Cologne, high pressure, CPAP 12–35 cm H_2O, no PPV, and FiO_2 0.3–0.4 ($n = 27$). The conclusion was that when comparing the two strategies in infants <28 weeks' gestation, results from both centres indicate that such infants can be supported noninvasively at birth with either higher or lower pressures, and whilst higher-pressure support may require less oxygen, it does not eliminate the need for oxygen supplementation. Obviously, further studies need to examine the effect of high pressures and pressure titration in the delivery room [31].

51.2.2 Early Nasal CPAP from Birth

O'Donnell et al., using video recordings of preterm infants at birth, proved that approx. 80% of extremely low gestational age newborn (ELGAN, birth weight <1000 g) indeed show spontaneous breathing [32]. Thus, routine intubation of even the most immature infants would interfere with their physiological foetal-neonatal transition. Since 2008, several large-scale clinical trials have compared the use of invasive to noninvasive respiratory support of breathing of VLBWI and ELGANs from birth. Meta-analyses of these studies have shown significant positive impact on survival and overall pulmonary outcomes with no added negative effects in the non-pulmonary outcomes in the noninvasively managed patients; according to Fischer and Bührer, the NNT to save one VLBW infants from death or BPD is 35 (Fig. 51.1) [17]. Follow-up studies of preterm infants treated with CPAP from birth compared to those routinely ventilated showed that pulmonary function was significantly improved at term equivalent age [33]. Non-ventilated infants had significantly higher respiratory compliance, lower elastic work of breathing, and, consequently, improved respiratory rate and minute ventilation [33].

However, whilst these results were encouraging, CPAP failure following initial stabilisation can be as high as 50%, depending on the gestational age investigated [34]. Over the past years, investigators predominantly compared T-piece devices to other manual ventilation devices, mostly self-inflating bags (SIB) [35]. For reasons of their superior in vitro performance in controlling peak inspiratory pressure and to some extent the tidal volume, as much as their relative stability even under conditions of mask leak [36], T-piece devices have been the preferred devices to use during foetal-to-neonatal stabilisation [37]. In a recent in vivo, animal study by Thio and colleagues, the T-piece device was considered the 'gold standard' and compared to a selection of four commercially available SIBs, operated at a constant gas flow of 8 l/min. Peak inspiratory pressure inflations of 30 cm H_2O, combined with set PEEP of 5, 7, and 10 cm H_2O, were delivered at rates of 20, 40, and 60/min. These combinations were repeated without gas flow. Authors measured mean PEEP, maximum and minimum PEEP, and its difference (PEEP reduction). A total of 3288 inflations were analysed. The mean PEEP delivered by all SIBs was lower than set PEEP ($p < 0.001$), although some differences were <0.5 cm H_2O. In 55% of combinations, the presence of gas flow resulted in increased PEEP delivery (range difference 0.3–2 cm H_2O). The mean PEEP was closer to set PEEP with faster inflation rates and higher set

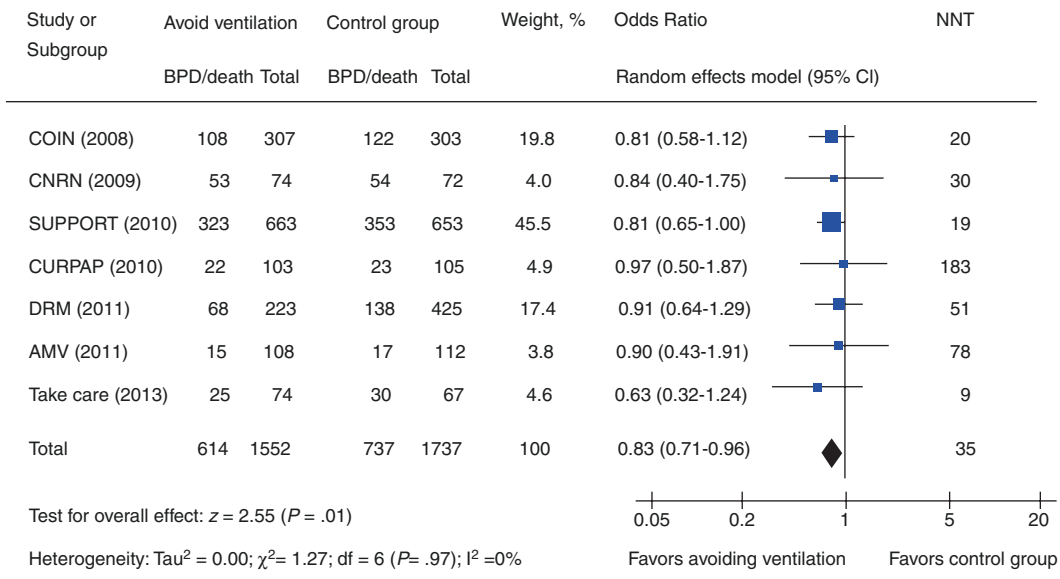

Fig. 51.1 Forest plot comparison of death or bronchopulmonary dysplasia (BPD), or both, at 36 weeks' corrected gestation; death; and BPD at 36 weeks' corrected gestation. Nasal CPAP, continuous positive airway pressure. (Extracted from Ref. [17])

PEEPs. The mean (SD) PEEP reductions were 3.9 (1.6), 8.2 (1.8), 2 (0.6), and 1.1 (0.6) cm H_2O with the four investigated SIBs, whereas it was 0.5 (0.2) cm H_2O with the T-piece. Authors concluded that PEEP delivery with SIBs depended on the set PEEP, inflation rate, device model, and gas flow. At recommended inflation rates of 60/min, some devices may deliver PEEP close to the set level, although the reduction in PEEP could make some SIBs potentially less effective for lung recruitment than a T-piece device [38].

Apart from T-piece devices and SIBs, a few other devices have been used to stabilise infants in the DR. A recent study by Donaldsson and colleagues introduced a novel resuscitation device which promises reduced work of breathing (WOB). Authors hypothesised that their device, used with nasal prongs or face mask as interfaces, would impose less work of breathing (iWOB) and thus could improve infant outcome. Presenting data from a benchtop study, authors describe the in vitro performance of the new system and present a clinical feasibility trial of initial stabilisation of preterm infants [24]. A mechanical lung model was used to determine iWOB at increasing levels of CPAP. The clinical feasibility trial included 36 infants (27–34 weeks of gestation), randomised into three groups, comparing the T-piece device, the new system with face mask, or the new system with prongs. Collected data included data on handling and safety, time to stable breathing, and need for positive pressure ventilation and intubation. The authors found that in the mechanical lung model, the new system reduced iWOB with 91.5% (mask) and 86.6% (medium prongs) compared with T-piece at 4 cm H_2O CPAP ($p < 0.001$). Presenting data of a feasibility trial in 45 patients studied in the DR with the use of the new device or T-piece resuscitator, authors found less convincing results. Donaldsson et al. provided data on 36 late preterm infants, treated at birth with either CPAP via a T-piece (n=12) or via the new system. The new system was used with masks and nasal prongs (12 per group). No issues were described concerning the handling of the new system. Clinically, more pneumothoraces were seen in the group receiving support with the new system and nasal prongs. However, due to the small patient numbers in each group, no meaningful conclusions regarding the clinical benefit or harm of the new system over CPAP should be drawn [24]. More studies will be required to establish if this new device will

contest the T-piece devices as the most appropriate DR manual ventilation device.

51.2.3 New Insights on the Use of Nasal High-Flow Nasal Cannula Therapy, Compared to CPAP

The application of medical gases at high-flow rates via small nasal cannulae as another form of noninvasive, continuous distending pressure has steadily found its way into the respiratory management of neonates [39]. With nasal high-flow therapy (nHFT) or high-flow nasal cannula (HFNC), which is often likened to CPAP, heated and humidified gas at flow rates between 2 and 8 l/min is applied to the nares via tiny, low diameter nasal cannulae [40]. However, compared to the nasal interfaces used with CPAP, which as outlined above can be applied through masks, tightly fitted binasal prongs, or even pharyngeal tubes, the cannulae used in nHFT are much smaller and, possibly for this reason, appear to be tolerated much better than conventional CPAP applications. According to recent meta-analyses and the Cochrane review by Wilkinson et al., nHFT can be considered equally efficacious as nasal CPAP when used for secondary respiratory support, following extubation, in preventing infants from re-intubation but not for primary respiratory support of lower gestational age infants [41]. nHFT was further found to cause far less nasal trauma and fewer pneumothoraces than nasal CPAP therapy [41]. However, although there currently may not be enough evidence to support nHFT use as primary therapy for infants with RDS from birth, data from units with long experience in the use of nHFT have reported very satisfactory results when employing nHFT as primary and secondary respiratory support, as recently published by Zivanovic et al. [42].

51.2.4 Studies Expected for Immediate Publication

One already much debated trial comes from an Australian multicentre collaboration on the use of nHFT in non-tertiary units. Publicised under the slightly dubious acronym, the HUNTER trial is a large, multicentre RCT comparing nHFT to nasal CPAP as first-line respiratory support for preterm infants in non-tertiary units. One already much debated trial comes from an Australian multicentre collaboration on the use of nHFT in non-tertiary units. Announced as the HUNTER trial, this large, multicentre, non-inferiority RCT compares nHFT to nasal CPAP as first-line respiratory support for late preterm infants born in non-tertiary units. The primary outcome was treatment failure within 72 h of randomisation. Treatment failure is determined by lack of oxygenation, significant apnoea, poor blood gasses, or as per the clinical decision of the attending team that urgent intubation and mechanical ventilation or transfer to a tertiary NICU, is required. Secondary outcomes include incidence of pneumothorax requiring drainage, duration of respiratory support, supplemental oxygen and hospitalisation, costs associated with hospital care, cost-effectiveness, parental stress and satisfaction, and nursing workload. The trial results have been published as abstracts and oral presentations but not yet in printed form. According to the investigators, nHFT was inferior to nasal CPAP, when employed at non-tertiary centres [27].

51.3 Further New and Upcoming Developments

51.3.1 Studies Comparing CPAP to Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation (NIPPV) describes the nasal application of intermittent peak inspiratory pressure (PIP) inflations at pressures similar to those applied during conventional ventilation. The assumption is that the PIP applied to the nasopharynx corresponds to an equal distending pressure at the distal airways. Consequently, the result would be an elevated mean airway pressure, which augments and maintains the tidal volume and supports spontaneous breathing whilst protecting the airways from collapse during apnoea [39]. Several studies suggest

that NIPPV, in particular when synchronised (SNIPPV) with the infants' spontaneous breaths, reduces inspiratory effort and optimised tidal volume and improves carbon dioxide exchange in prematurely born infants [43].

51.3.2 Clinical Applications of Noninvasive Positive Pressure Ventilation

Indications for using neonatal NIPPV include primary and secondary respiratory support, scenarios where higher mean airway pressure than CPAP may be required, or where significant apnoea of prematurity (AOP) places the infant at risk for MV. At present, there is a paucity of data to recommend the optimal PIP level, optimal delta PIP/PEEP (delta p), inspiratory time, or respiratory rate. Studies further differ regarding the level of applied PEEP (5–8 cm H_2O) and PIP (10–20 cm H_2O), the delta p between pressures (0–3 cm H_2O), inspiratory time (0.3–1 s) and any given backup. In practice, an invasive ventilation mode is chosen on the ventilator (IMV, SIMV, etc.), and intermittent positive airway pressure (IPPV) is applied via the patient interface (mask, nasal, or pharyngeal prong), or special commercial devices with Bi-PAP or Si-PAP modes can be chose to achieve the same effect [44].

51.3.3 Non-synchronised and Synchronised NIPPV

Investigating whether using NIPPV for treating AOP was superior over other forms of noninvasive respiratory support, Gizzi et al. investigated the effects of flow-SNIPPV, NIPPV, and nCPAP on the rate of AOP, bradycardia, and gas exchange in preterm infants. In their study, SNIPPV seemed more effective than non-synchronised NIPPV and nCPAP in reducing the incidence of AOP, bradycardia, and desaturation episodes in preterm infants [45]. As many of the latest generation of mechanical ventilators now offer synchronisation of NIPPV, results from further studies on the efficacy of synchronised NIPPV, preferably performed with comparable protocols and devices, are awaited. Despite initial promising data, according to recent surveys, NIPPV has not yet been widely embraced in clinical practice as the method of first choice [46].

51.3.4 Nasal High-Frequency Oscillation Ventilation

Similar to NIPPV, pharyngeal or nasal application of high-frequency oscillation ventilation (nHFOV) has found its way in to neonatal care and, in 2015, was employed in less than a quarter of European NICUs [47]. Only one recent, medium-scale (n = 76) prospective clinical trial on nHFOV has recently been published [48]. Whilst the results from Zhu et al. indicate that nHFOV, compared to nCPAP, effectively reduced the need for MV in preterm infants with moderate to severe RDS without an increase in adverse effects and had positive effects on CO_2 clearance, the study's methodology has also been criticised, and further trials are awaited [49].

51.3.5 What Will Be the Upcoming Developments? A Glimpse at the Future

Looking into the future, it is obvious that much more research is needed to define the most suitable respiratory support mode for individual patients, in a specific clinical care setting, meeting the needs and expectations of the patients' family. Whilst nasal CPAP remains the best researched and accepted form of NIV, use of higher CPAP settings may well prove beneficial in future studies. Likewise, simpler forms of support like nHFT might be easier to employ, also possibly at higher settings, both as primary and as secondary forms of noninvasive respiratory support. Conversely, support modes involving higher levels of technology, like NIPPV or SNIPPV, wherever feasible and affordable, may offer significant advantages over nCPAP alone and will be measured against CPAP in upcoming studies.

A balance will need to be struck between the most effective care packages to ensure not only survival but also intact survival, aiming at obtaining the best possible long-term outcomes [50]. Thus, more research into these modes is required to prevent ventilation, minimise oxygen exposure, and, consequently, reduce death and BPD. More needs to be learnt regarding which would be the most suitable mode of support for infants of specific gestational ages, for disease entities, and for stages of disease progression. The use of noninvasive respiratory support techniques and surfactant replacement therapy has so far only been investigated for nCPAP. The combination of supportive treatments, like caffeine, vitamin A, systemic or inhaled corticosteroids, or physiotherapy with noninvasive respiratory support, is also widely under-researched and would warrant more attention in future research.

To conclude, whilst CPAP has very much become the first choice of respiratory support of newborn infants, increased attention will need to be paid to identify the optimal mode of NIV for individual patients, recognizing their disease progression based on the individual pathophysiology.

References

1. Polglase GR, Wallace MJ, Grant DA, Hooper SB. Influence of fetal breathing movements on pulmonary hemodynamics in fetal sheep. Pediatr Res. 2004;56:932–8.
2. Crawshaw JR, Kitchen MJ, Binder-Heschl C, Thio M, Wallace MJ, Kerr LT, Roehr CC, Lee KL, Buckley GA, Davis PG, Flemmer A, Te Pas AB, Hooper SB. Laryngeal closure impedes non-invasive ventilation at birth. Arch Dis Child Fetal Neonatal Ed. 2018;103:F112–9.
3. Hooper SB, Te Pas AB, Kitchen MJ. Respiratory transition in the newborn: a three-phase process. Arch Dis Child Fetal Neonatal Ed. 2016;101:F266–71.
4. Vyas H, Field D, Milner AD, Hopkin IE. Determinants of the first inspiratory volume and functional residual capacity at birth. Pediatr Pulmonol. 1986;2:189–93.
5. Hooper SB, Harding R. Fetal lung liquid: a major determinant of the growth and functional development of the fetal lung. Clin Exp Pharmacol Physiol. 1995;22:235–47.
6. Siew ML, Wallace MJ, Allison BJ, Kitchen MJ, te Pas AB, Islam MS, Lewis RA, Fouras A, Yagi N, Uesugi K, Hooper SB. The role of lung inflation and sodium transport in airway liquid clearance during lung aeration in newborn rabbits. Pediatr Res. 2013;73:443–9.
7. Karlberg P. The adaptive changes in the immediate postnatal period, with particular reference to respiration. J Pediatr. 1960;56:585–604.
8. Siew ML, Te Pas AB, Wallace MJ, Kitchen MJ, Lewis RA, Fouras A, Morley CJ, Davis PG, Yagi N, Uesugi K, Hooper SB. Positive end-expiratory pressure enhances development of a functional residual capacity in preterm rabbits ventilated from birth. J Appl Physiol (1985). 2009;106:1487–93.
9. Jobe AH. Lung maturation: the survival miracle of very low birth weight infants. Pediatr Neonatol. 2010;51:7–13.
10. Curstedt T, Halliday HL, Hallman M, Saugstad OD, Speer CP. 30 years of surfactant research - from basic science to new clinical treatments for the preterm infant. Neonatology. 2015;107:314–6.
11. Edwards MO, Kotecha SJ, Kotecha S. Respiratory distress of the term newborn infant. Paediatr Respir Rev. 2013;14:29–36.
12. Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, Epstein MF, Fitzhardinge PM, Hansen CB, Hansen TN, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics. 1987;79:26–30.
13. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med. 2007;357:1946–55.
14. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med. 1967;276(7):357–68.
15. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK. Treatment of the idiopathic respiratory-distress syndrome with continuous positive airway pressure. N Engl J Med. 1971;284:1333–40.
16. Roehr CC, Schmalisch G, Khakban A, Proquitté H, Wauer RR. Use of continuous positive airway pressure (CPAP) in neonatal units—a survey of current preferences and practice in Germany. Eur J Med Res. 2007;12:139–44.
17. Fischer HS, Bührer C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. Pediatrics. 2013;132:e1351–60.
18. Polin R, Committee on Fetus and Newborn; American Academy of Pediatrics. Respiratory support in preterm infants at birth. Pediatrics. 2014;133:171–4.
19. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Visser GH, Halliday HL. European consensus guidelines on the management of respiratory distress syndrome - 2016 update. Neonatology. 2017;111:107–25.
20. Phillips RS. Accessing electronic information for clinical decisions. Arch Dis Child. 2000;83(5):373–74. https://www.ncbi.nlm.nih.gov/pubmed/. Accessed 5 May 2019.

21. Imbulana DI, Owen LS, Dawson JA, Bailey JL, Davis PG, Manley BJ. A randomized controlled trial of a barrier dressing to reduce nasal injury in preterm infants receiving binasal noninvasive respiratory support. J Pediatr. 2018;201:34–39.e3.
22. Amatya S, Macomber M, Bhutada A, Rastogi D, Rastogi S. Sudden versus gradual pressure wean from nasal CPAP in preterm infants: a randomized controlled trial. J Perinatol. 2017;37:662–7.
23. Chandrasekaran A, Thukral A, Jeeva Sankar M, Agarwal R, Paul VK, Deorari AK. Nasal masks or binasal prongs for delivering continuous positive airway pressure in preterm neonates-a randomised trial. Eur J Pediatr. 2017;176:379–86.
24. Donaldsson S, Drevhammar T, Taittonen L, Klemming S, Jonsson B. Initial stabilisation of preterm infants: a new resuscitation system with low imposed work of breathing for use with face mask or nasal prongs. Arch Dis Child Fetal Neonatal Ed. 2017;102:F203–7.
25. Roberts KD, Brown R, Lampland AL, Leone TA, Rudser KD, Finer NN, Rich WD, Merritt TA, Czynski AJ, Kessel JM, Tipnis SM, Stepka EC, Mammel MC. Laryngeal mask airway for surfactant administration in neonates: a randomized, controlled trial. J Pediatr. 2018;193:40–46.e1.
26. Latremouille S, Al-Jabri A, Lamer P, Kanbar L, Shalish W, Kearney RE, Sant'Anna GM. Heart rate variability in extremely preterm infants receiving nasal CPAP and non-synchronized noninvasive ventilation immediately after extubation. Respir Care. 2018;63:62–9.
27. Manley BJ, Roberts CT, Arnolda GRB, Wright IMR, Owen LS, Dalziel KM, Foster JP, Davis PG, Buckmaster AG. A multicentre, randomised controlled, non-inferiority trial, comparing nasal high flow with nasal continuous positive airway pressure as primary support for newborn infants with early respiratory distress born in Australian non-tertiary special care nurseries (the HUNTER trial): study protocol. BMJ Open. 2017;7(6):e016746.
28. Fischer C, Bertelle V, Hohlfeld J, Forcada-Guex M, Stadelmann-Diaw C, Tolsa JF. Nasal trauma due to continuous positive airway pressure in neonates. Arch Dis Child Fetal Neonatal Ed. 2010;95:F447–51.
29. Imbulana DI, Manley BJ, Dawson JA, Davis PG, Owen LS. Nasal injury in preterm infants receiving non-invasive respiratory support: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2018;103:F29–35.
30. Mukerji A, Wahab MGA, Mitra S, Mondal T, Paterson D, Beck J, Fusch C. High continuous positive airway pressure in neonates: a physiological study. Pediatr Pulmonol. 2019;54:1039. https://doi.org/10.1002/ppul.24312.
31. Martherus T, Oberthuer A, Dekker J, Kirchgaessner C, van Geloven N, Hooper SB, Kribs A, Te Pas AB. Comparison of two respiratory support strategies for stabilization of very preterm infants at birth: a matched-pairs analysis. Front Pediatr. 2019;7:3.
32. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ. Crying and breathing by extremely preterm infants immediately after birth. J Pediatr. 2010;156:846–7.
33. Roehr CC, Proquitté H, Hammer H, Wauer RR, Morley CJ, Schmalisch G. Positive effects of early continuous positive airway pressure on pulmonary function in extremely premature infants: results of a subgroup analysis of the COIN trial. Arch Dis Child Fetal Neonatal Ed. 2011;96:F371–3.
34. Fuchs H, Lindner W, Leiprecht A, Mendler MR, Hummler HD. Predictors of early nasal CPAP failure and effects of various intubation criteria on the rate of mechanical ventilation in preterm infants of <29 weeks gestational age. Arch Dis Child Fetal Neonatal Ed. 2011;96:F343–7.
35. Hawkes CP, Ryan CA, Dempsey EM. Comparison of the T-piece resuscitator with other neonatal manual ventilation devices: a qualitative review. Resuscitation. 2012;83:797–802.
36. Hartung JC, te Pas AB, Fischer H, Schmalisch G, Roehr CC. Leak during manual neonatal ventilation and its effect on the delivered pressures and volumes: an in vitro study. Neonatology. 2012;102:190–5.
37. Roehr CC, O'Shea JE, Dawson JA, Wyllie JP. Devices used for stabilisation of newborn infants at birth. Arch Dis Child Fetal Neonatal Ed. 2018;103:F66–71.
38. Thio M, Dawson JA, Crossley KJ, Moss TJ, Roehr CC, Polglase GR, Davis PG, Hooper SB. Delivery of positive end-expiratory pressure to preterm lambs using common resuscitation devices. Arch Dis Child Fetal Neonatal Ed. 2019;104:F83–8.
39. Owen LS, Manley BJ, Davis PG, Doyle LW. The evolution of modern respiratory care for preterm infants. Lancet. 2017;389:1649–59.
40. Roehr CC, Yoder BA, Davis PG, Ives K. Evidence support and guidelines for using heated, humidified, high-flow nasal cannulae in neonatology: Oxford Nasal High-Flow Therapy Meeting, 2015. Clin Perinatol. 2016;43:693–705.
41. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev. 2016;2:CD006405.
42. Zivanovic S, Scrivens A, Panza R, Reynolds P, Laforgia N, Ives KN, Roehr CC. Nasal high-flow therapy as primary respiratory support for preterm infants without the need for rescue with nasal continuous positive airway pressure. Neonatology. 2019;115:175–81.
43. Ferguson KN, Roberts CT, Manley BJ, Davis PG. Interventions to improve rates of successful extubation in preterm infants: a systematic review and meta-analysis. JAMA Pediatr. 2017;171:165–74.
44. Mahmoud RA, Roehr CC, Schmalisch G. Current methods of non-invasive ventilatory support for neonates. Paediatr Respir Rev. 2011;12:196–205.
45. Gizzi C, Montecchia F, Panetta V, et al. Is synchronized NIPPV more effective than NIPPV and NCPAP in treating Apnoea of prematurity (AOP)? A randomised crossover trial. Arch Dis Child Fetal Neonatal Ed. 2015;100:17–23.
46. Bresesti I, Zivanovic S, Ives KN, Lista G, Roehr CC. National surveys of UK and Italian neonatal

units highlighted significant differences in the use of non-invasive respiratory support. Acta Paediatr. 2019;108:865–9.
47. Fischer HS, Bohlin K, Bührer C, Schmalisch G, Cremer M, Reiss I, Czernik C. Nasal high-frequency oscillation ventilation in neonates: a survey in five European countries. Eur J Pediatr. 2015;174:465–71.
48. Zhu XW, Zhao JN, Tang SF, Yan J, Shi Y. Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with moderate-severe respiratory distress syndrome: a preliminary report. Pediatr Pulmonol. 2017;52:1038–42.
49. Fischer HS, Rimensberger PC. Early noninvasive high-frequency oscillatory ventilation in the primary treatment of respiratory distress syndrome. Pediatr Pulmonol. 2018;53:126–7.
50. Zivanovic S, Roehr CC. One step further toward defining the optimal respiratory care package for neonates: interventions to successfully extubate preterm infants. JAMA Pediatr. 2017;171:120–1.

52 CPAP in Perioperative Respiratory Complications in Children: When and Where

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Abbreviations

BIPAP	Bi-level positive airway pressure
CPAP	Continuous positive airway pressure
NIV	Noninvasive ventilation
OSA	Obstructive sleep apnea
PICU	Pediatric intensive care unit
PPCs	Postoperative pulmonary complications

Nowadays, the development of lung injury caused by endotracheal tubes and invasive mechanical ventilation has led clinicians to opt for noninvasive ventilation (NIV) in patients who have indications [1]. The delivery of positive airway pressure to the lungs via an interface constitutes the basis of NIV. There are two main modes of NIV in children: continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BIPAP). Indications of NIV include upper airway obstructions (e.g., vocal cord dysfunction, laryngomalacia), chronic respiratory failure (e.g., neuromuscular disease, cerebral palsy), and control of breathing abnormalities (e.g., central apnea, central hypoventilation) [2, 3].

CPAP was first used in the treatment of premature neonates with respiratory distress syndrome in the early 1970s, and it has continued to be used in different indications. These indications include asthma, bronchiolitis, pediatric acute respiratory syndrome, cystic fibrosis, obstructive sleep apnea (OSA), neuromuscular disorders, and cardiac disease [4]. However, currently, CPAP can be used prophylactically for upper airway complications that may occur during the surgery and anesthesia of patients with or without the above-listed diseases, except for the curative treatment of these diseases. When the literature is examined, it is noteworthy that CPAP

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is more commonly used after extubation in the postoperative period.

In this paper, we aimed to evaluate postoperative CPAP usage by considering articles that discuss when and where to use CPAP in the pediatric population and were published in the last 2 years. Although CPAP can be used for laryngospasm treatment immediately after extubation, generally in the postoperative period, the use of CPAP is related to respiratory complications after adenotonsillectomy or tonsillectomy; cardiac, hepatic, and laparoscopic surgeries; and tracheocutaneous fistula repair [5–10]. In the following, postoperative pulmonary complications (PPCs) will be examined under separate headings for each surgery.

52.1 Adenotonsillectomy or Tonsillectomy

Tonsillectomy or adenotonsillectomy is one of the most common surgical interventions in childhood, and the majority of these patients constitute children with OSA [11]. The incidence of pediatric OSA ranges from 1% to 5%. Adenotonsillar hypertrophy is an important factor in the etiology of pediatric OSA, and accordingly, adenotonsillectomy is considered a first-line treatment for these patients [12]. Another treatment of choice for OSA is the use of CPAP, which is used by some patients with OSA preoperatively. The aim of CPAP usage is to provide airway patency by preventing airway collapse [4].

It should not be forgotten that adenotonsillectomy in pediatric patients with OSA is associated with an increased risk of PPCs [12]. In pediatric patients who underwent adenotonsillectomy, PPCs after surgery range from 1.4% to 5%. These complications can be listed as follows: pulmonary edema, laryngospasm, bronchospasm, hypoxemia, hypercapnia, and apnea exacerbation events [13]. In the following studies, these complications and the importance of CPAP are discussed.

In a retrospective cohort study that investigated 167 pediatric patients in total who underwent adenotonsillectomy due to OSA, it was reported that 143 of 167 patients required postoperative monitoring. However, only 6 of 143 (4.2%) of these patients had PPCs including bronchospasm (2), laryngospasm (2), severe hypoxemia (1), and reintubation (1), and 66% of these complications were seen in the immediate (<12 h) postoperative period. Furthermore, the authors reported that patients who have a preoperative Apnea-Hypopnea Index of >44 are at a high risk in terms of respiratory complications [13]. In a similar study, it was stated that a weight under 18 kg is associated with an increased risk of respiratory complications after tonsillectomy [11]. Shamil et al. evaluated the effect of a nasal decongestant on PPCs after adenotonsillectomy. They reported in this preliminary study that three patients in the control group required major medical intervention: transfer to pediatric intensive care unit (PICU) and the need for noninvasive ventilation [12]. In another retrospective study related to PPCs, the authors reported that 26.8% (n = 36) of pediatric patients after adenotonsillectomy were admitted to the PICU. Various respiratory interventions were applied to these patients. The use of CPAP constituted 5.5% of these applications. In addition, CPAP was used by 2.9% of non-PICU patients [14].

Recently, Buzi et al. presented a more robust study in terms of the advantages of CPAP usage. The above studies are mostly focused on the risk of PPCs and on treatment protocols. However, this study aimed not only to determine of the risks of complication but also to evaluate the effective treatment processes. In a retrospective study that included 69 pediatric patients who had undergone tonsillectomy, the need for NIV (CPAP, BIPAP, or both) among these patients was evaluated in the postoperative period. The authors reported that 59 patients were treated with CPAP, 16 patients with BIPAP, and 9 patients with both CPAP and BIPAP in the first postoperative 6 days. The NIV therapies for 40 patients were started in the first 24 h postoperatively, and all NIV therapies were performed for an average of 3.85 days. Indeed, the use of NIV after tonsillectomy seems a controversial issue. In these patients, practitioners have two major drawbacks

about NIV usage: postoperative hemorrhage and subcutaneous emphysema in the neck and chest as a result of air entering into the dissection plane due to pressure. Regardless, the authors argued that NIV can be an alternative method to invasive ventilation [6].

52.2 Abdominal Surgery

Pulmonary atelectasis after abdominal surgery is a common postoperative complication, which occurs due to cephalic displacement of the diaphragm and muscle paralysis, and as a result, reduced lung compliance, the deterioration of arterial oxygenation, and lung injury may occur. In the postoperative period, pulmonary atelectasis can be treated with invasive ventilation or NIV. However, invasive ventilation has some disadvantage, such as prolonged mechanical ventilation and hospitalization and an increased risk of ventilator-associated pneumonia [7, 8]. In this context, the use of CPAP improves oxygenation, decreases the work of breathing and oxygen consumption, and reduces the likelihood of postoperative reintubation, thus playing a key role in preventing PPCs [7].

Chiusolo et al. investigated the CPAP usage in pediatric patients after liver transplantation. In a retrospective observational study that included 119 recipients, the risk factors of CPAP usage were evaluated in the postoperative period. CPAP by helmet or oxygen by venture mask was performed after extubation in the PICU. As a result, they said that a weight of <11 kg, PaO_2/FiO_2 of <380 before extubation, positive fluid balance of >148 mL/kg, and the use of vasopressors in the intraoperative period are the decisive criteria for CPAP application in pediatric patients developing acute respiratory failure after liver transplantation in the PICU [7]. In a randomized double-blinded controlled study conducted by Abdel Ghaffar et al., the authors reported that the application of early post-extubation CPAP improves oxygenation in the first 12 h after pediatric laparoscopic surgery [8].

52.3 Cardiac Surgery

PPCs are largely responsible for morbidity and mortality in patients undergoing cardiac surgery, and their incidence rate varies from 6% to 76%. In these patients, CPAP is one of the recommended methods for preventing PPCs and improving functional respiratory capacity and gas exchange [9].

In a randomized controlled study with 50 pediatric patients who had undergone cardiac surgery, CPAP was performed twice daily for 30 min on postoperative days 1–5, except in patients in the control group, and respiratory parameters were evaluated. The results from this study suggest that CPAP was effective in improving peak expiratory flow on postoperative day 1; however, CPAP did not reduce the length of stay in the intensive care unit and hospital [9]. A retrospective observational study conducted in the PICU evaluated pediatric patients between the ages of 3 days and 16 years requiring NIV after cardiac surgery. The authors noted that CPAP is the most used NIV mode, with an increased success rate in NIV usage and a decreased need for invasive mechanical ventilation [15].

52.4 Tracheocutaneous Fistula Repair

In contrast to the abovementioned advantages of CPAP, the use of NIV after pediatric tracheocutaneous fistula repair may lead to respiratory problems. Pediatric patients who have a long duration of tracheostomy and who are of a younger age at the time of tracheostomy carry the risk of persistent tracheocutaneous fistula after decannulation. However, these patients may be in need of NIV usage even after tracheocutaneous fistula repair due to existing comorbidities, and this situation is associated with PPCs. One hundred eight pediatric patients after tracheocutaneous fistula repair were closely followed in the PICU, and planned (CPAP or BIPAP) and unplanned (bag-valve-mask ventilation) NIV was performed. This retrospective study showed that the use of NIV in

these patients (especially unplanned NIV) might increase the rates of subcutaneous emphysema, pneumomediastinum, and pneumothorax. Therefore close monitoring of these patients should be conducted [10].

In summary, the success of NIV requires overcoming respiratory distress without the need for invasive techniques. Thus, a more comfortable way of solving possible respiratory problems related to patients can be achieved. For CPAP usage, the first step is to determine the indication area accurately. In this context, CPAP is more applicable to patients transferred to the intensive care unit in the postoperative period. The presence of exiting diseases among patients is important, which may affect the success of CPAP. Practitioners should be aware of the difficulties associated with surgery during the use of CPAP after surgical procedures. It is important to know the uses and limitations of CPAP to reduce patient risks and increase success.

References

1. Macintyre NR, Nava S, Diblasi R, et al. Respiratory care year in review 2010: Part 2. Invasive mechanical ventilation, noninvasive ventilation, pediatric mechanical ventilation, aerosol therapy. Respir Care. 2011;56(5):667–80.
2. Amin R, Al-Saleh S, Narang I. Domiciliary noninvasive positive airway pressure therapy in children. Pediatr Pulmonol. 2016;51(4):335–48.
3. Grychtol R, Chan EY. Use of non-invasive ventilation in cerebral palsy. Arch Dis Child. 2018;103(12):1170–7.
4. Fedor KL. Noninvasive respiratory support in infants and children. Respir Care. 2017;62(6):699–717.
5. Baker PA, Navaratnarajah J, Black AE. Assessment and management of the predicted difficult airway in babies and children. Anaesth Intensive Care Med. 2015;16(12):622–31.
6. Buzi A, Coblens OM, MacGillivray M, et al. The use of noninvasive positive pressure ventilation following pediatric tonsillectomy. Otolaryngol Head Neck Surg. 2017;157(2):297–301.
7. Chiusolo F, Fanelli V, Ciofi Degli Atti ML, et al. CPAP by helmet for treatment of acute respiratory failure after pediatric liver transplantation. Pediatr Transplant. 2018;22(1)
8. Abdel-Ghaffar HS, Youseff HA, Abdelal FA, et al. Post-extubation continuous positive airway pressure improves oxygenation after pediatric laparoscopic surgery: a randomized controlled trial. Acta Anaesthesiol Scand. 2019;63(5):620–9.
9. Silva CR, Andrade LB, Maux DA, et al. Effectiveness of prophylactic non-invasive ventilation on respiratory function in the postoperative phase of pediatric cardiac surgery: a randomized controlled trial. Braz J Phys Ther. 2016;20(6):494–501.
10. Smith JD, Thorne MC, Thatcher AL. Positive airway pressure ventilation and complications in pediatric tracheocutaneous fistula repair. Laryngoscope. 2020;130(1):E30–4.
11. Julien-Marsollier F, Salis P, Abdat R, et al. Predictive factors of early postoperative respiratory complications after tonsillectomy in children with unidentified risks for this complication. Anaesth Crit Care Pain Med. 2018;37(5):439–45.
12. Shamil E, Rouhani MJ, Panayi AC, et al. Investigating the effect of a nasal decongestant on post-adenotonsillectomy respiratory complications in 25 paediatric patients with obstructive sleep apnoea: a pilot study. J Laryngol Otol. 2019;133(2):110–4.
13. Marrugo Pardo G, Romero Moreno LF, et al. Respiratory complications of adenotonsillectomy for obstructive sleep apnea in the pediatric population. Sleep Disord. 2018;2018:1968985.
14. Arambula AM, Xie DX, Whigham AS. Respiratory events after adenotonsillectomy requiring escalated admission status in children with obstructive sleep apnea. Int J Pediatr Otorhinolaryngol. 2018;107:31–6.
15. Fernandez Lafever S, Toledo B, Leiva M, et al. Noninvasive mechanical ventilation after heart surgery in children. BMC Pulm Med. 2016;16(1):167.

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53.1 Introduction

Acute respiratory failure (ARF) is one of the leading causes of morbidity and mortality in children. Traditionally invasive mechanical ventilation (IMV) is used for treatment of severe ARF, but endotracheal intubation (ETI) is associated with complications like upper airway injuries, ventilator-associated pneumonias, etc. Delivery of mechanical ventilation through noninvasive route (NIV) has been currently emerging as a first-line strategy as it is associated with a reduction in intubation rate [1, 2]. NIV refers to the technique of supporting respiration using a machine and interface without the need for intubation of the trachea. The main advantage of NIV is that it can be used on demand (Table 53.1). However, NIV is less efficient than IMV because of unavoidable air leaks and associated difficulties for continuous use. The prompt recognition of early predictors of NIV failure is crucial for the safety of patients. This chapter gives a brief summary of the indications and implementation of NIV in children with ARF.

53.2 Physiology and Types of NIV

NIV improves oxygenation and ventilation by recruiting more alveoli, improving airflow, decreasing work of breathing, and stenting upper airways. More details of mechanism of action are dependent on the type of NIV used. Basic types of NIV include positive pressure ventilation (BiPAP and CPAP) and negative pressure ventilation. Even though HFNC is not categorized as NIV, there has been robust use of HFNC in children with respiratory distress due to various etiologies (Fig. 53.1).

53.2.1 Continuous Positive Airway Pressure (CPAP)

CPAP provides a constant positive pressure throughout the entire respiratory cycle while the patient is breathing spontaneously. CPAP improves airflow, stents upper and central airways, decreases the load of inspiratory muscles, and recruits collapsed alveoli, thus improving oxygenation [3].

53.2.2 Bi-Level Positive Airway Pressure (BiPAP)

BiPAP delivers positive pressure in two levels. Apart from baseline expiratory positive pressure (EPAP), this device also gives inspiratory positive pressure (IPAP) greater than EPAP called delta P, which is the expanding pressure translated into tidal volume. BiPAP breaths are either triggered by the patient occurring synchronous with patient breath or delivered mandatorily as preset on the machine irrespective of patient's breathing. BiPAP is helpful in hypoventilation, so improving both hypercarbia and hypoxemia [4].

Table 53.1 Advantages of NIV over invasive mechanical ventilation

Decrease in rate of endotracheal intubation and mechanical ventilation
Preservation of spontaneous respiration
Preservation of airway protective reflexes like coughing and sneezing
Children can continue to speak
Oral feeding is possible, depending on clinical situation
Reduced risk of nosocomial infections
Decreased need for sedation

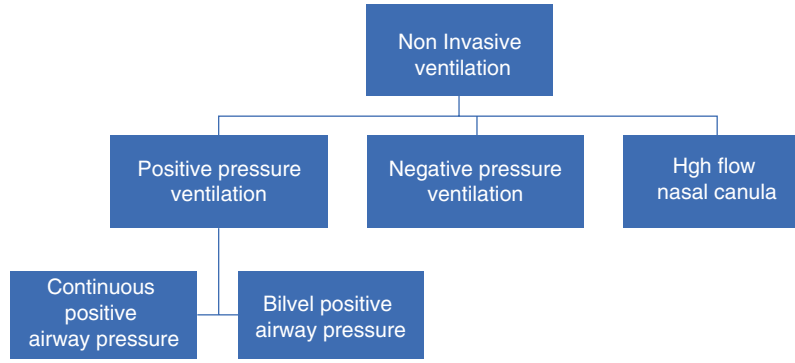

Fig. 53.1 Types of NIV

53.2.3 High-Flow Nasal Cannula (HFNC)

There has been a rise in use of HFNC recently across neonatal and pediatric intensive care units. HFNC delivers heated, humidified air/oxygen mixture to the patient through special nasal prongs. The high amount of oxygen air gas flow decreases the nasopharyngeal dead space. The Fraction of inspired oxygen (Fio_2) level could be modified to maintain optimum PaO_2 or SaO_2 keeping it at minimum required. Often, HFNC is enough to manage the respiratory symptoms but at times is used to bridge higher level of respiratory support including invasive mechanical ventilation. HFNC often will be able to generate a PEEP ranging from 2 to 5 cm H_2O in newborns and children depending upon the amount of flow [5, 6]. HFNC is not effective to treat hypoventilation.

53.2.4 Negative Pressure Ventilation

The third system is negative pressure ventilation, historically delivered by a large negative pressure chamber (iron lung or tank ventilator) but in more recent decades via smaller systems such as the cuirass. The cuirass is a plastic shell that encases the ribs and delivers either mono- or biphasic ventilator support through negative pressure. These devices have the ability to provide continuous negative pressure to the chest, similar to CPAP. It also can be set in the control mode to deliver biphasic pressure, negative pressure to augment inspiration, and positive pressure to facilitate exhalation. Lastly, it can provide rapid alternating positive and negative pressure to the chest as physiotherapy to aid in secretion clearance, similar to cough assist. Commonly used pressures and settings for NPV use in children were described [7].

53.2.5 Indications of NIV in Acute Respiratory Failure

NIV is indicated for impending or established respiratory failure due to various conditions. Table 53.2 lists the common indications for NIV in acute setting. In children with ARF, it is used as therapy until the acute illness improves or as a treatment modality to prevent endotracheal intubation.

53.3 NIPPV Use for Acute Respiratory Failure in Specific Clinical Conditions

53.3.1 Asthma

Studies have shown that in children with status asthmaticus, when used with short-acting beta-2 agonists, NIPPV is well tolerated and shows greater improvement in asthma score respiratory rate and reduced oxygen concentration as com-

Table 53.2 Indications of NIV in ARF in children

Restrictive disease
Neuromuscular diseases
Scoliosis (post-surgery)
Lower airway obstruction
Bronchiolitis
Asthma
Upper airway obstruction
Pierre Robin syndrome
Treacher Collins syndrome
Craniosynestosis
Upper airway malformations
Storage disease
Neonates
Delivery room management
Respiratory distress syndrome
Post extubation management
Parenchymal disease
Community acquired pneumonia
Acute CF exacerbation
Others
Pulmonary cardiogenic oedema
Acute chest syndrome
Post-operative respiratory failure
Ventilator weaning
Storage diseases

pared to standard treatment [8, 9]. However, recent systematic reviews caution that the current data are not yet conclusive, especially regarding the ability of NIV to prevent ETI/IMV; further high-quality research is needed [10]. The use of HFNC in the management of pediatric status asthmaticus has been associated with significantly reduced work of breathing, RR, and expiratory time [11, 12]. HFNC's ability to effectively improve the expiratory time may decrease dynamic hyperinflation in patients with obstructive lung disease, such as asthma.

53.3.2 Bronchiolitis

HFNC oxygen therapy has become a reasonable alternative to NIV for the treatment of acute bronchiolitis [13]. In a RCT comparing the outcomes of infants with bronchiolitis treated with low-flow oxygen or HFNC, showed that there was a reduced need for escalation of care among the group receiving HFNC [14, 15].

Pederson et al. reported in a study that nasal CPAP (nCPAP) [16]. Nasal CPAP was reported to be more effective than HFNC as initial supportive treatment for infants with moderate to severe bronchiolitis [15, 16]. Howerver large, multicenter database study of PICU patients with bronchiolitis who received either HFNC or NPPV as their initial mode of respiratory support found that treatment with NPPV was associated with a higher subsequent use of IMV, even after adjusting for illness severity and the presence of significant comorbidity [17]. Observational studies showed that after the introduction of HFNC as the standard approach for oxygen therapy in intensive care, the intubation rates decreased to less than 10% from originally greater than 30% [1]. HFNC use is increasing, and it seems to be useful as first-line therapy in the emergency room and in the pediatric ward to prevent PICU admission, but it is not clear yet if it is equivalent to noninvasive ventilation (NIV). NIV use in bronchiolitis is well established, mainly in continuous positive airway pressure mode in moderate and severe bronchiolitis. A prospective interventional trial would be required to establish superiority of HFNC or NPPV in reducing the need for IMV. The trend is to offer respiratory support such as HFNC therapy outside high dependency or intensive care, reducing health-care costs and potentially further reducing the need for invasive ventilation. There will always remain a selective high-risk subgroup of infants with bronchiolitis who are more likely to not benefit from NIV or HFNC therapy.

53.3.3 Pediatric ARDS

Early identification and optimal management are crucial in pediatric ARDS to improve short-term and long-term outcomes. The Pediatric Acute Lung Injury Consensus Conference Group published recommendations on managing ARDS in 2015 [18]. They stated that the use of NIV mild ARDS is beneficial; however worsening of the

disease or severe disease warrants endotracheal intubation (ETI) and Invasive mechanical ventilation (IMV). NIV should be instituted in the appropriate ICU settings monitored by highly trained staff. Evidences also showed high failure rate of NIV in pediatric ARDS [2, 19]. So, as of now, there are no conclusive guidelines on the use of NIV in ARDS as more study results are awaited on this topic.

53.3.4 Neonatal Respiratory Distress Syndrome (RDS)

Recent update from European consensus guidelines on management of neonatal RDS [20] has recommended the use of CPAP via mask or nasal prongs with starting pressure from 6 to 8 cm H_2O to stabilize a spontaneously breathing preterm babies at risk of RDS, rather than intubation in the delivery room to reduce risk of BPD. High flow nasal canula was found to be inferior to CPAP as aprimary mode of respiratrory support for infants more than 28 weeks of gestation in the delivery room setting [21]. CPAP with early rescue surfactant is considered optimal management for babies with RDS.

53.3.5 Pneumonia

Mechanical respiratory support is an integral part of management of children with acute pneumonia with severe respiratory distress and impending or established respiratory failure. There have been growing evidence to support the use of NIV in children with acute pneumonia. A prospective randomized trial from Chile showed [22] that NIV improved hypoxemia and the signs and symptoms of acute respiratory failure in children with pneumonia. An RCT comparing bubble CPAP, low-flow oxygen, and HFNC in children less than 5 years of age with acute pneumonia showed improved outcomes with bubble CPAP [23]. A prospective observational clinical study conducted in Portugal found that pneumonia was one of the independent risk factors associated with NIV failure in children [24]. In short, NIV may be very useful in pediatric acute pneumonia as an early treatment option or in non-severe cases.

53.3.6 Postoperative and Post-extubation Respiratory Support

NIV is an appealing option for reducing reintubation rates following surgery or invasive ventilation episodes. A small randomized study of NIV versus oxygen therapy in young children post-extubation failed to show any statistically significant reduction in reintubation rate with NIV [25]. In preterm infants, a randomized study showed equivalent levels of treatment failure (34.2% vs. 25.8%) for re-intubation prevention post-extubation using HFNC or CPAP [26]. NIV is used in many centers to support children with neuromuscular or chronic respiratory disease pre- and post-major surgery (e.g., scoliosis repair, but evidence relating to this practice is currently limited) [27].

53.3.7 Acute on Chronic Respiratory Failure in Neuromuscular Disorders

NIV may be used to treat acute respiratory failure or may be used as a primary intervention in the treatment of chronic hypoventilation in patients with neuromuscular disease. Piastra et al. [28] reported that NIV can be routinely attempted in pediatric patients with neuromuscular disease to avoid or delay invasive ventilation with an artificial airway. The combination of MIE with NIV has recently been recommended for the effective control of airway secretions and prevention of NIV failures, particularly when treating ARF episodes in NMD patients [29]. The timing of initiating NIV treatment is important. A case report suggests that an early implementation of combined NIV/MIE on type II spinal muscular atrophy (SMA) children with acute respiratory failure

(ARF) may eliminate the need for intubation and shorten the length of hospital stay [30]. The Cochrane database review in 2017 [31] found no randomized trials on which to elaborate evidence-based practice for the use of noninvasive versus invasive mechanical ventilation. It reflects the need of new randomized trials to compare NIV with invasive ventilation in acute neuromuscular respiratory failure.

53.3.8 Cardiac Disease

Noninvasive ventilation (NIV) is increasingly being used in ARF, after cardiac surgery for congenital heart disease. Positive airway pressure may reduce pulmonary vascular resistance if it achieves appropriate alveolar recruitment and it diminishes left ventricle afterload by increasing transmural pressure. On the other hand, it decreases right ventricle preload, and it increases its afterload. In pediatric patients with heart disease, the overall success rate of NIV following extubation was found to be 77.8% when used prophylactically or when acute respiratory failure was noted [32]. A study reported 85% success rate with use of NIV after heart surgery resulting in lesser need for IMV. CPAP was the most common modality, and the "nasopharyngeal tube" was the most common interface in the study with the use of bi-level ventilation increasing in latter part of the study [33].

53.3.9 Others

Other indications for NIV in pediatric acute settings include, but not limited to interhospital transport [34], cystic fibrosis pulmonary exacerbation [35, 36] (PMID, 8218802), children with burns [37], acute respiratory distress in children with central nervous system disorders [38], and acute chest syndrome in sickle cell disease [39]. One other report includes the use of NIV in conjunction with extracorporeal CO_2 removal as a bridging therapy before lung transplant in a case of bronchiolitis obliterans with refractory respiratory failure [40].

53.4 Clinical Management of NIV

53.4.1 Choice of Ventilator

In a setting of acute respiratory failure, there are options to use two types of ventilators: ICU ventilators with NIV mode which use high-pressure compressed air and oxygen and portable ventilators (can also be used at home) which use room air or compressed air. There are various types of modes available by which a patient could be ventilated depending on underlying respiratory pathology for example continious pressure via CPAP mode, Bilvel pressure, Pressure control modes (SIMV pressure control or pressures support or Volme control/volume support modes) as well there are newer modalities with Volume target modes (example Average volume – assured pressure support (AVAPS) or volume target pressure support modes). The ventilator should be able to synchronize with the child's breathing pattern, which requires the ability to adjust the inspiratory and expiratory trigger sensitivities, the pressurization rate, the inspiratory time, the backup respiratory rate, and the tidal volume. It is ideal that ventilator should have the ability to compensate for unintentional leaks as it is a cause of patient ventilator asynchrony. Some intensive care ventilation systems provide the ability to use neurally adjusted ventilatory assist (NAVA), which may improve synchronization of supported breaths to patient effort, using monitoring of electrical impulses from the diaphragm. In the NAVA, the ventilator detects the contraction signal of the aperture by the EMG electrode located in the lower esophagus and controls the ventilator, flow, volume, and pressure without delay. These electrical impulses from diaphragm help in maintaining ventilator patient synchrony, and they are unaffected by system leaks [41, 42].

53.4.2 Initiation/Settings/Monitoring of NIV

The choice of type of NIV depends upon the patient characteristics and disease severity. Before initiation of NIV, the medical team needs to do a

thorough assessment of the clinical severity and underlying etiology of respiratory failure. Initial assessment should also include relevant imaging, chest X-ray, and lab testing like electrolytes and blood gases. Absolute contraindications of NIV include cardiopulmonary arrest, coma, severely decreased level of consciousness, inability to protect airway, inability to fit interface or mask, facial deformity, trauma or burns, and undrained pneumothorax. Relative contraindications include hemodynamic instability, vasopressors, recent airway or upper GI surgery, active upper GI bleeding, inability to cooperate, excessive secretions, and cyanotic congenital heart disease [43].

Non Invasive ventilation is usually initiated with low settings and then titrated according to clinical, radiological, and laboratory improvement and, most importantly, patient tolerance. Refer to Table 53.3 for NIV settings. HFNC or CPAP can be used in hypoxemic respiratory failure, but hypercapnic respiratory failure needs the use of Bil-level ventilation mode. The initial settings for CPAP include physiological values (3–5 cm H_2O) and then are titrated up according to clinical response. The use of Bilevel ventilation includes selecting a mode (S,T, or S/T mode), Setting Titrating IPAP from 6–12 cm H_2O, EPAP of 5–8 cm H_2O, and backup rate according to the age of the patient (initial rate ranging from 4 to 10/min) [43]. The delta P (IPAP-EPAP) is an important parameter which determines the amount of tidal volume delivered and varies according to the underlying respiratory condition. If more lung or chest expansion is required (i.e., ARDS, neuromuscular weakness), increased delta P will be required. Secondary settings are available depending on device that may include the trigger sensitivity, the rise time, the breath transition cycle, and a gradual pressure ramp time, could be adjusted to maximize patient's comfort. In general, the difference between inspiratory and expiratory pressure should be at least 6–8 cm H_2O to have a VT of 6–10 mL/kg of ideal body.

Table 53.3 : Initial settings for different types of NIV

Settings	HFNC	CPAP	BiLevel (BiPAP)
Flow (L/min)	x		
CPAP (+cm H_2O)		x	
IPAP (+cm H_2O)			x
EPAP (+cm H_2O)			x
Back up rate (/min)			x
Rise time (s)		x	x
Ramp (min)		x	x
FiO_2 (as needed)	x	x	x

Oxygen can be supplemented to maintain desired saturation. Selection of an appropriate interface is crucial to begin NIV. Often, more than one type of face mask may need to be tried to find the best fit for the child. Close cardiorespiratory monitoring is important for successful maintenance of NIV. Monitoring includes heart rate, respiratory rate, SaO_2, FiO_2, and blood pressure. Blood gases and/or chest X-ray need to be repeated as indicated to know the respiratory status. SaO_2 and blood gases are also helpful in down titrating settings to avoid hyperventilation. Mask fitting and ventilator-patient synchrony need to be periodically assessed for successful continuation of NIV. Light sedation in the ICU may improve synchrony, decrease leak, and improve overall tolerance of NIV. In case of worsening of underlying condition or failure of NIV, patient may need ETI and IMV.

53.4.3 Interface

Initiation and maintenance of NIV in children are challenging, especially small children and infants. Children are generally uncomfortable with the interface and airflow. The ideal interface should be small with minimal dead space, causing minimal leaks, lightweight, easy to fit and remove, nontraumatic, manufactured with nonallergenic material, cheap and having an appropriate and well-adapted headgear that confers stability preventing movement or dislocation of the interface in order to minimize leaks [44]. The first response to anything introduced on the face will be to remove it in a conscious child. It takes a great effort from the intensive care team to work with the child to get used to the interface. Sometimes, switching between interfaces is required to find the best fit for the patient.

Table 53.4 Different types of patient interfaces

Type	Explanation	Advantage	Disadvantage	Used with
Nasal prongs	Special cannula inserted into the nostrils	Less anxiety, no irritation to the eyes, minimal contact	Increased leak, irritation in the nostrils, not effective in nasal obstruction	HFNC
Nasal mask	Mask covering only the nose	No risk of aspiration, allows coughing, eating, easy fitting, low risk of claustrophobia and gastric distension	Leak, skin erosion, not effective in nasal obstruction	CPAP, BiPAP
Oronasal mask	Cover nose and mouth	Less leak, improved ventilation and gas exchange	Risk of aspiration, claustrophobia, gastric distension, limit eating and talking, pressure sore	CPAP, BiPAP
Full face mask	Cover the whole face	More effective ventilation, less leak	Anxiety, less tolerated by small children, aspiration, gastric distension	CPAP, BiPAP
Helmet	Cover head and all or part of neck, no contact with face	Allows eating, coughing and talking, no pressure ulcers, better tolerated	Higher dead space, difficult humidification, claustrophobia, noise	CPAP, BiPAP

Table 53.4 gives details about various interfaces used, advantages, and challenges. The choice of interface is determined by patient's age, facial morphology of patient, the type of circuit, and ventilatory mode. Interfaces can be vented or non-vented, i.e., with or without intentional leaks. In the ICU settings, most patients are placed on NIV with closed double-limb circuits that are supported by non-vented masks. Portable home ventilators and CPAP devices use a single-limb circuit with vented interfaces [45]. Skin injury to the face is a common issue with any of the interface. The ICU team needs to carefully monitor for facial skin injuries. The patient will be unable to tolerate NIV with facial discomfort or skin injury. Children are at greater risk of skin injury during NIV than adults [46]. Skin breakdown can be prevented or managed by alternating two or more types of masks to switch the pressure points.

53.4.4 Predictors of Success/Failure

The likelihood of success or failure of NIV depends on multiple factors, including the underlying medical conditions, severity and type of the respiratory failure, the timing of starting NIV, and the level of experience of the care team. Indeed, a reduction in respiratory rate after 1–6 h is clearly associated with NIV success. The independent predictors of NIV failure including pH less than 7.25 after 1–2 h of NIV, ventilation-perfusion impairment, higher pediatric risk of mortality score (PRISM), lower respiratory rate, decrease in early therapy and the presence of ARDS, higher pediatric logistic organ dysfunction score, FiO_2 >80%, and higher mean airway. An increase in FiO_2, a FiO_2 of >0.8, or a decrease in PaO_2/FiO_2 after 1 h of NIV therapy and poor tolerance to interface is associated with a higher risk of intubation, mean airway [19, 47, 48]. Predictors of HFNC failure in bronchiolitis include increased PCO_2, failure to reduce RR or normalize HR, and failure to decrease FiO_2 less than 0.5 in the first 1–2 h.

53.4.5 Complications

NIV and HFNC are generally safe modalities, but complications are well documented. Complications associated with NIV are most often seen in the most fragile patients; they include gastric distention, aspiration, pneumothorax, and pressure ulcerations. Pressure ulcer-

ations have been reported in 4–27% of children [49]. The skin breakdown is more severe with oronasal masks and bridge of the nose is most vulnerable for severe break down, skin ulcerations can be minimized by careful evaluation at regular intervals to identify early signs of potential breakdown, and maintaining normal skin hydration is an important intervention for protecting skin tissue integrity. Gastric distention can be minimized by all patient receiving NIV gastric tubes in place to vent excess air from the stomach. Aspiration precautions involve paying close attention to feeding schedules, elevation of the head of the bed, positioning of the patient, careful suctioning procedures to reduce gagging and emesis, and close patient monitoring. Nasal dryness and congestion could be minimized with humidification.

HFNC therapy is well tolerated, therefore reducing the need for sedation. Complications reported by the use of HFNC oxygen therapy are rare and similar to those reported with CPAP and bi-level vent, including gastric insufflation, eye irritation, inability to continuously monitor capnography, and air leak (e.g., pneumothorax, pneumomediastinum). The successful use of these therapies relies upon appropriate case selection and the presence of expert staff, trained to closely monitor the child and the equipment and to modify settings and interfaces accordingly.

53.5 Summary

NIV has shown significant promise for the management of acute respiratory failure in infants and children and may be used safely and effectively with careful patient selection, meticulous monitoring, and ongoing care by a well-trained team. The studies have shown that NIV is a good choice of respiratory support in acute bronchiolitis, status asthmaticus, and mild to moderate pneumonia. The careful selection of patient and appropriate delivery modality and the interface along with close cardiorespiratory and blood gas monitoring over the first 2 h are integral to success. If there is worsening of clinical status, the escalation to invasive ventilation via endotracheal intubation should be considered immediately. As health-care providers, we must recognize key differences in the operation of various devices to safely set up, control, and manage the patient.

References

1. Ganu SS, Gautam A, Wilkins B, Egan J. Increase in use of non-invasive ventilation for infants with severe bronchiolitis is associated with decline in intubation rates over a decade. Intensive Care Med. 2012;38(7):1177–83.
2. Wolfler A, Calderini E, Iannella E, et al. Evolution of noninvasive mechanical ventilation use: a cohort study among Italian PICUs. Pediatr Crit Care Med. 2015;16(5):418–27.
3. Pavone M, Verrillo E, Caldarelli V, Ullmann N, Cutrera R. Non-invasive positive pressure ventilation in children. Early Hum Dev. 2013;89(Suppl 3):S25–31.
4. Waldhorn RE. Nocturnal nasal intermittent positive pressure ventilation with bi-level positive airway pressure (BiPAP) in respiratory failure. Chest. 1992;101(2):516–21.
5. Spence KL, Murphy D, Kilian C, McGonigle R, Kilani RA. High-flow nasal cannula as a device to provide continuous positive airway pressure in infants. J Perinatol. 2007;27(12):772–5.
6. Spentzas T, Minarik M, Patters AB, Vinson B, Stidham G. Children with respiratory distress treated with high-flow nasal cannula. J Intensive Care Med. 2009;24(5):323–8.
7. Hassinger AB, Breuer RK, Nutty K, Ma CX, Al Ibrahim OS. Negative-pressure ventilation in pediatric acute respiratory failure. Respir Care. 2017;62(12):1540–9.
8. Basnet S, Mander G, Andoh J, Klaska H, Verhulst S, Koirala J. Safety, efficacy, and tolerability of early initiation of noninvasive positive pressure ventilation in pediatric patients admitted with status asthmaticus: a pilot study. Pediatr Crit Care Med. 2012;13(4):393–8.
9. Thill PJ, McGuire JK, Baden HP, Green TP, Checchia PA. Noninvasive positive-pressure ventilation in children with lower airway obstruction. Pediatr Crit Care Med. 2004;5(4):337–42.
10. Silva PDS, Barreto SS. Noninvasive ventilation in status asthmaticus in children: levels of evidence. Rev Bras Ter Intensiva. 2015;27(4):390–6.
11. Baudin F, Buisson A, Vanel B, Massenavette B, Pouyau R, Javouhey E. Nasal high flow in management of children with status asthmaticus: a retrospective observational study. Ann Intensive Care. 2017;7(1):55.

12. Hess DR. Aerosol therapy during noninvasive ventilation or high-flow nasal cannula. Respir Care. 2015;60(6):880–891; discussion 891–3.
13. McKiernan C, Chua LC, Visintainer PF, Allen H. High flow nasal cannulae therapy in infants with bronchiolitis. J Pediatr. 2010;156(4):634–8.
14. Franklin D, Babl FE, Schlapbach LJ, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. N Engl J Med. 2018;378(12):1121–31.
15. Milési C, Essouri S, Pouyau R, et al. High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). Intensive Care Med. 2017;43(2):209–16.
16. Pedersen MB, Vahlkvist S. Comparison of CPAP and HFNC in management of bronchiolitis in infants and young children. Children (Basel). 2017;4(4):28.
17. Clayton JA, McKee B, Slain KN, Rotta AT, Shein SL. Outcomes of children with bronchiolitis treated with high-flow nasal cannula or noninvasive positive pressure ventilation. Pediatr Crit Care Med. 2019;20(2):128–35.
18. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16(5):428–39.
19. Muñoz-Bonet JI, Flor-Macián EM, Brines J, et al. Predictive factors for the outcome of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med. 2010;11(6):675–80.
20. Sweet DG, Carnielli V, Greisen G, et al. European Consensus Guidelines on the management of respiratory distress syndrome - 2019 update. Neonatology. 2019;115:432–50.
21. Roberts CT, Owen LS, Manley BJ, Frøisland DH, Donath SM, Dalziel KM, et al.; HIPSTER Trial Investigators. Nasal high-flow therapy for primary respiratory support in preterm infants. N Engl J Med. 2016;375(12): 1142–51.
22. Yañez LJ, Yunge M, Emilfork M, et al. A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med. 2008;9(5):484–9.
23. Chisti MJ, Salam MA, Smith JH, et al. Bubble continuous positive airway pressure for children with severe pneumonia and hypoxaemia in Bangladesh: an open, randomised controlled trial. Lancet. 2015;386(9998):1057–65.
24. Abadesso C, Nunes P, Silvestre C, Matias E, Loureiro H, Almeida H. Non-invasive ventilation in acute respiratory failure in children. Pediatr Rep. 2012;4(2):e16.
25. Fioretto JR, Ribeiro CF, Carpi MF, et al. Comparison between noninvasive mechanical ventilation and standard oxygen therapy in children up to 3 years old with respiratory failure after extubation: a pilot prospective randomized clinical study. Pediatr Crit Care Med. 2015;16(2):124–30.
26. Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2013;369(15):1425–33.
27. Khirani S, Bersanini C, Aubertin G, Bachy M, Vialle R, Fauroux B. Non-invasive positive pressure ventilation to facilitate the post-operative respiratory outcome of spine surgery in neuromuscular children. Eur Spine J. 2014;23(Suppl 4):S406–11.
28. Piastra M, Antonelli M, Caresta E, Chiaretti A, Polidori G, Conti G. Noninvasive ventilation in childhood acute neuromuscular respiratory failure: a pilot study. Respiration. 2006;73(6):791–8.
29. Chen TH, Hsu JH, Wu JR, et al. Combined noninvasive ventilation and mechanical in-exsufflator in the treatment of pediatric acute neuromuscular respiratory failure. Pediatr Pulmonol. 2014;49(6):589–96.
30. Chen TH, Hsu JH, Jong YJ. Noninvasive airway approaches for acute neuromuscular respiratory failure in emergency departments. Pediatr Pulmonol. 2017;52(10):E55–7.
31. Luo F, Annane D, Orlikowski D, et al. Invasive versus non-invasive ventilation for acute respiratory failure in neuromuscular disease and chest wall disorders. Cochrane Database Syst Rev. 2017;12:CD008380.
32. Gupta P, Kuperstock JE, Hashmi S, et al. Efficacy and predictors of success of noninvasive ventilation for prevention of extubation failure in critically ill children with heart disease. Pediatr Cardiol. 2013;34(4):964–77.
33. Fernández Lafever S, Toledo B, Leiva M, et al. Noninvasive mechanical ventilation after heart surgery in children. BMC Pulm Med. 2016;16(1):167.
34. Cheema B, Welzel T, Rossouw B. Noninvasive ventilation during pediatric and neonatal critical care transport: a systematic review. Pediatr Crit Care Med. 2019;20(1):9–18.
35. Fauroux B, Burgel PR, Boelle PY, et al. Practice of noninvasive ventilation for cystic fibrosis: a nationwide survey in France. Respir Care. 2008;53(11): 1482–9.
36. Sprague K, Graff G, Tobias DJ. Noninvasive ventilation in respiratory failure due to cystic fibrosis. South Med J. 2000;93(10):954–61.
37. Smailes ST. Noninvasive positive pressure ventilation in burns. Burns. 2002;28(8):795–801.
38. Falsaperla R, Elli M, Pavone P, Isotta G, Lubrano R. Noninvasive ventilation for acute respiratory distress in children with central nervous system disorders. Respir Med. 2013;107(9):1370–5.
39. Heilbronner C, Merckx A, Brousse V, et al. Early noninvasive ventilation and nonroutine transfusion for acute chest syndrome in sickle cell disease in children: a descriptive study. Pediatr Crit Care Med. 2018;19(5):e235–41.
40. Moscatelli A, Ottonello G, Nahum L, et al. Noninvasive ventilation and low-flow veno-venous extracorporeal carbon dioxide removal as a bridge to lung transplantation in a child with refractory hypercapnic respiratory failure due to bronchiolitis obliterans. Pediatr Crit Care Med. 2010;11(1):e8–12.

41. Ferreira JC, Diniz-Silva F, Moriya HT, Alencar AM, Amato MBP, Carvalho CRR. Neurally adjusted ventilatory assist (NAVA) or pressure support ventilation (PSV) during spontaneous breathing trials in critically ill patients: a crossover trial. BMC Pulm Med. 2017;17(1):139.
42. Longhini F, Pan C, Xie J, et al. New setting of neurally adjusted ventilatory assist for noninvasive ventilation by facial mask: a physiologic study. Crit Care. 2017;21(1):170.
43. Viscusi CD, Pacheco GS. Pediatric emergency noninvasive ventilation. Emerg Med Clin North Am. 2018;36(2):387–400.
44. Mortamet G, Amaddeo A, Essouri S, Renolleau S, Emeriaud G, Fauroux B. Interfaces for noninvasive ventilation in the acute setting in children. Paediatr Respir Rev. 2017;23:84–8.
45. Essouri S, Chevret L, Durand P, Haas V, Fauroux B, Devictor D. Noninvasive positive pressure ventilation: five years of experience in a pediatric intensive care unit. Pediatr Crit Care Med. 2006;7(4):329–34.
46. Fauroux B, Lavis JF, Nicot F, et al. Facial side effects during noninvasive positive pressure ventilation in children. Intensive Care Med. 2005;31(7):965–9.
47. Dohna-Schwake C, Stehling F, Tschiedel E, Wallot M, Mellies U. Non-invasive ventilation on a pediatric intensive care unit: feasibility, efficacy, and predictors of success. Pediatr Pulmonol. 2011;46(11):1114–20.
48. Bernet V, Hug MI, Frey B. Predictive factors for the success of noninvasive mask ventilation in infants and children with acute respiratory failure. Pediatr Crit Care Med. 2005;6(6):660–4.
49. Fedor KL. Non invasive respiratory support in infantsand children. Respirar Care. 2017;62:699–717.

54 Home Noninvasive Mechanical Ventilation in Pediatric Patients: Current Characteristics and Practical Advice

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Abbreviations

BPAP	Bilevel positive airway pressure
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
IPAP	Inspiratory positive airway pressure
NIV	Noninvasive ventilation
NMD	Neuromuscular diseases
OSAS	Obstructive sleep apnea syndrome
S/T	Spontaneous/timed
SMA	Spinal muscular atrophy

54.1 Introduction

In recent years, the number of children who need long-term mechanical ventilation has increased. Long-term mechanical ventilator support at home can be performed via tracheostomy or noninvasively with an interface. Noninvasive ventilation (NIV) has become more preferable as long-term supportive therapy in recent years, and use of invasive ventilation via tracheostomy has decreased [1]. The main reasons for this are the technological advances in NIV treatment as well as interfaces which have facilitated the use of this treatment in children, and NIV became an acceptable alternative to tracheostomy for clinicians and families. Increased survival of children with complex underlying disease and shift in healthcare from hospital to home-based care were contributing factors to increased use of home NIV in children [2]. Long-term NIV has been used in many different diseases that cause chronic respiratory pump failure. Airway disorders, neuromuscular disorders, and central nervous system disorders are main conditions that cause respiratory insufficiency or sleep disordered breathing in infants and children [3]. Main purposes of NIV in these children are to overcome upper airway obstruction, control hypoventilation, reduce the work of breathing, manage central apneas, improve sleep consolidation, and improve gas exchange [4]. There are two main types of NIV: continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP). CPAP provides constant single-level pressure throughout the entire breath cycle and aims to prevent upper airway collapse and increase the cross-sectional area of airways [5]. BPAP generates inspiratory pressure on continuous airway pressure during every inspiration to augment patient's own respiratory effort [6] (Fig. 54.1).

54.2 Methodology

To identify all of the current concepts and up-to-date notions in long-term pediatric noninvasive ventilation, we screened the review articles in the last 5 years for the articles and data about long-term/home/domiciliary/chronic use of noninvasive ventilation in pediatric patients [2, 4, 6–8]. After defining the subjects and suitable subject headings for indications, equipment, technical issues, ventilation logic and strategies, organization, and complications, we searched PubMed for each of these concepts to list the studies that are relevant from the aspect of contributing with new clinical data and that are carried out within the last 2 years which is the scope of this yearbook.

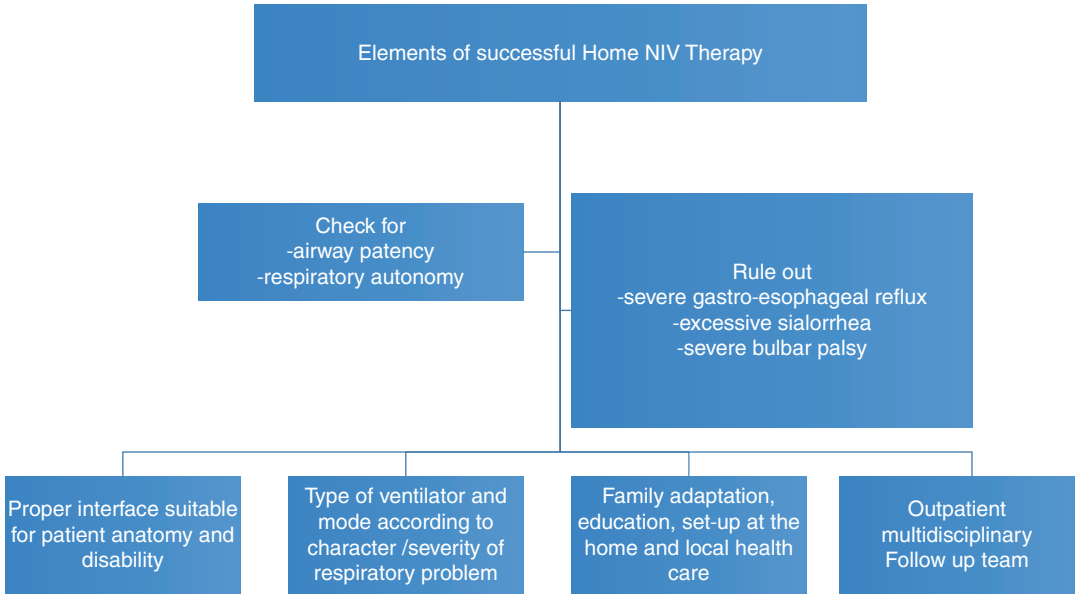

Fig. 54.1 Summary (diagnosis-treatment)

54.2.1 Patient Selection

Disequilibrium in the respiratory balance is the main indication for NIV. The load imposed on the respiratory system, the capacity of respiratory muscles, and the central drive are components of respiratory balance. In previous reviews, 73 medical conditions were defined to require NIV in disease course [2]. NIV indication is not based on the presence of a particular disease but is dependent on the type and severity of the respiratory failure caused by this disease [7]. Most common diseases reported to require long-term NIV are obstructive sleep apnea syndrome (OSAS), spinal muscular atrophy (SMA), neuromuscular diseases (NMD), upper airway disorders, and pulmonary parenchymal diseases [2].

It is important to emphasize that not all children are proper candidates for home NIV treatment. For NIV treatment a child should be able to protect upper airway patency and should have respiratory autonomy. NIV may be contraindicated in children with significant gastroesophageal reflux, excessive sialorrhea, and severe bulbar palsy because of risk of aspiration. Management of secretions is very important in children that are candidates for NIV. Besides frequent suctioning, pharmacological and surgical treatment options must be considered in children with excessive secretion. Children requiring NIV more than 16 h/day are not ideal candidates because of skin breakdown and facial developmental problems. Inability to tolerate NIV or to find adequate interface may be another contraindication for NIV usage. Caregivers who are frequently parents should undergo formal education and should be evaluated in terms of competence and compliance [4].

There is no validated criterion for timing of initiation of long-term NIV in children. Long-term NIV may be indicated because of failure to wean a patient off from noninvasive ventilation in pediatric intensive care unit, or home NIV treatment may be initiated with a planned procedure due to the foreseen disease course in NMD [1]. Ikeda et al. compared patients with non-neuromuscular diseases to those with neuromuscular diseases and found that the latter group had significantly more planned initiations and less frequent use of oxygen [1]. Long-term NIV may

also be initiated in case of nocturnal hypoventilation and in patients with a high apnea-hypopnea index in polysomnography [3]. In the study by Amaddeo et al., the researchers found that in clinical practice, CPAP/NIV was initiated mostly in subacute and chronic setting with most patients having an association of several abnormal gas exchange or sleep study parameters [6]. The effectiveness and benefits of the initiation criteria need to be studied.

54.3 Equipment and Settings

Home NIV system consists of the following components: ventilation machine, ventilation interface, expiratory system, and humidification system.

54.3.1 Ventilator

Clinicians should ensure that the prescribed ventilator is approved for children. Many devices are not able to generate small volumes reliably especially for younger children. Triggering ventilator may be very difficult for children with muscle weakness, and trigger system in ventilator must be pediatric specific. Sensitive trigger is essential to adapt patient to ventilator without significant increase in work of breathing. Devices with pressure presets are more useful to adapt variable breathing patterns of children and should be preferred rather than devices with volume presets. Alarm limits of devices must be adjustable for pediatric patients [7].

54.3.2 Interfaces

There are different types of interfaces: nasal prongs, nasal mask, oronasal mask, full-face mask, and the helmet. The helmet is not suitable for home NIV. These interfaces come in different shapes and sizes and are made of different materials [9]. Proper interface selection is a very important decision affecting NIV success in children. Interface represents the main connection between the ventilator and the patient, so patient's preferences should be considered [8]. The choice of interface is chosen according to patient's age, weight, and skull and facial anatomy, nasal obstruction, presence of mouth breathing, ventilator mode, and the patient's tolerance with the interface and ability to remove the interface unaided [6]. Choice of interface may be challenging in children with facial or skull deformity or asymmetry. The appropriate properties can be listed as good adhesion, easy to fit and remove, light weight, non-traumatic, cheap, low resistance to airflow, minimal dead space and minimal leak, and having appropriate and well-adapted headgear. Interfaces can be vented or non-vented. Non-vented interfaces are commonly used in intensive care unit with conventional ventilators and double-limb respiratory circuits. Most of home CPAP or BPAP devices use vented interfaces with single-limb circuit. Appropriate selection of device, mask, circuit, and device settings are critical for NIV success. The choice between vented and non-vented masks is based on the type and severity of the respiratory failure, ventilator mode, the experience of the medical team, and patient compliance. The headgear has crucial importance, and most important characteristics of a headgear are its suitable size, its stability, and its easiness to fit and remove.

54.3.2.1 Nasal Interface

Nasal masks cover only the nose, and the mouth remains uncovered. Nasal masks offer greater patient comfort because they allow coughing, eating, and talking and are easy to fit. Nasal masks have low risk of claustrophobia, aspiration, and gastric distention. These masks are available in different sizes for different ages. Mouth leaks and nasal obstruction are disadvantages for nasal masks, and there is a risk of skin ulcers for the nasal mask, even if it is less than the oronasal mask [4].

54.3.2.2 Nasal Prongs

Nasal prongs or pillows occlude the outer part of the nostrils. This interface is comfortable and well tolerated by children. Nasal prongs are com-

mercially available only for older children and adolescents. The use of high pressure with nasal prongs is usually not tolerated, and efficacy decreases in case of mouth breathing.

Rojas et al, reported 94% successful implementation rate for nasal NIV with a nasal RAM cannula in the outpatient home setting in 18 children. They list the indications as CPAP/BPAP masks intolerability (11%), dyspnea secondary to chest wall weakness (38%), and tracheostomy avoidance (50%). The authors report significant decrease in CO_2 levels and conclude that this interface may prove to be a feasible and safe treatment alternative. Larger studies in different patient groups are needed to validate the feasibility, but it is worth mentioning among the alternatives [10].

54.3.2.3 Oronasal Masks

Oronasal masks cover both the mouth and nose. This interface minimizes unintentional leak from the mouth. Oronasal mask can be used in case of nasal obstruction and significant mouth breathing. Oronasal masks have been shown to be more effective in improving gas exchange and minute ventilation. Oronasal masks limit eating and talking because of mouth coverage. Oronasal masks have higher risk of claustrophobia, aspiration, and gastric distention. These masks may cause skin ulcers secondary to pressure particularly in patients with long-term need. In the event of device malfunction, it is very difficult for children with muscle weakness to remove the oronasal mask, and this situation may cause asphyxia and/or aspiration [4]. Midface hypoplasia is another risk for especially long-term use of oronasal mask.

54.3.2.4 Full-Face Mask

This interface covers the eyes, nose, and mouth. When using full-face mask, mask-fit pressure is spread over a larger surface beyond the nose area, and this results in lower risk of skin ulcer and patients feel more comfortable. Larger volume of full-face mask may prevent carbon dioxide elimination because ratio between the tidal volume and the volume of interface is important for carbon dioxide rebreathing [9].

Appropriate selection of interface should be done by well-educated and experienced medical team. Medical team must be aware of the different interfaces available and should be ready and willing to try alternatives if one interface fails.

54.3.3 Expiratory System

Home NIV devices are usually used with vented interfaces and single-limb circuits. The position and type of exhalation openings is important for carbon dioxide (CO_2) elimination [8]. There are open-outlet expiratory system and controlled exhalation valve system. In the case of double-limb circuit, controlled exhalation valve system can be integrated to ventilator machine, but in single-limb respiratory circuit, the valve should be placed closer to the patient side [8]. In the open-outlet system, an opening adjacent to patient (on mask or circuit) serves to wash out expired CO_2. In this case efficient positive end-expiratory pressure should be applied; otherwise there will be risk of carbon dioxide rebreathing of patient from tubing system. In hypoxic patients, controlled valve system must be preferred because the use of an open-valve system is associated with a markedly lower concentration of inhaled oxygen fraction [8].

54.3.4 Humidification and Warming

Humidification is not absolutely necessary for adult patients on home NIV, but pediatric patients usually require humidification. Most of the pediatric patients requiring home NIV are NMD patients in whom secretion management is a major problem. Without humidification, secretion management in these patients becomes difficult because of thick secretions. Dry mouth and nasal mucosa are problems that lead to patient discomfort and NIV failure because of increased resistance. Active humidification system with water passover humidifiers must be preferred in children because of minimal dead space and advantage of warm air.

54.4 Ventilator Settings

54.4.1 CPAP

The CPAP pressure provides a constant single-level pressure throughout the entire breathing cycle, and CPAP is proven to be efficacious in children with upper airway obstruction. In infants with severe upper airway obstruction, it is recommended to set highest CPAP level which is tolerated by patient because it is shown that setting CPAP pressure according to noninvasive variables such as sufficient gas exchange and decrease in respiratory and heart rate underestimate the optimum CPAP level by a mean of 2 cm H_2O [11].

54.4.2 BPAP

54.4.2.1 Mode

Spontaneous Mode
In this mode, each breath is initiated by the patient and expiratory and inspiratory support pressures are set, and there is no backup rate. This mode is not commonly used in children, but this can be useful for adolescents with obesity hypoventilation and OSAS.

Spontaneous/Timed Mode
In spontaneous/timed (S/T) mode, a backup rate is added to spontaneous mode, and the device starts to deliver breath when the patient's spontaneous respiratory rate decreases below the set backup rate. An inspiratory time is set, and this time is applied to all spontaneous and timed breaths in some devices and applied to only timed breaths in some devices. It is recommended to set backup rate closer to physiological respiratory rate during sleep.

54.5 Pressure Settings

Inspiratory positive airway pressure (IPAP) is the pressure that is delivered during inspiratory phase of breath. Expiratory positive airway pressure (EPAP) is the pressure delivered throughout the entire breath.

54.5.1 Rate

The rate represents the number of device breaths to be delivered per minute. In spontaneous/timed mode, set rate shows the minimum number of breaths that will be delivered by machine in case the patient's spontaneous respiratory rate falls below the backup rate.

54.6 Inspiratory Time

This represents the time in seconds in which the patient will receive IPAP. Depending on the device, inspiratory time can be applied either to all spontaneous and timed breaths or just timed breaths.

54.7 Sensitivity

Sensitivity represents the effort that must be generated by patient either to initiate a breath (trigger) or to terminate a breath (cycle). Both trigger and cycle sensitivity can be set to improve the patient-device synchrony. Sensitive trigger is necessary to adapt children to ventilator without increase in the work of breathing. The ventilator should be approved for children, and children with muscle weakness have difficulty in triggering breathing even in ventilators approved for children.

During BPAP, IPAP that is delivered during inspiration can be set according to either the target volume or target pressure. In volume-targeted, ventilation device provides a fixed volume throughout a given time span. Strict delivery of a preset volume is an advantage of this mode. But this mode is not able to adapt to the physiological changes of patient, and compensation of leaks is not possible which leads to insufficient volume delivery to patient [12]. In pressure-targeted mode, airflow is adjusted to generate fixed positive pressure during a given time span. This mode

is able to compensate unintentional leaks, and synchrony between device and patient improves because of variation of flow on a breath-to-breath basis. Because of their adaptation to variable respiratory patterns of children, devices with pressure presets are almost always more suitable for children [13].

Patient's underlying disease and type of respiratory insufficiency and indication of NIV are important for medical team while setting up BPAP. In children with NMD, goal of NIV is usually delivery of sufficient tidal volume, and this goal is achieved with low IPAP in most of patients, and these patients do not require high EPAP either, because they usually have a patent airway. S/T mode must be preferred in patients with NMD, and backup rate close to physiological respiratory rate during sleep should be set because of risk of inability of patients triggering the device for breath initiation [6]. It is important to set higher EPAP pressures in patients with anatomical or functional airway obstruction. Higher IPAP may be required in patients with restrictive lung problem such as pulmonary parenchymal disease, chest wall deformity, or scoliosis.

NIV treatment in children in acute settings and in long-term use is usually a challenging situation, and besides device and interface choice, settings of device should be set and adapted individually considering clinical benefit and compliance of the patient.

54.8 Organization of Home NIV

NIV in children is technically challenging especially in patients requiring long-term support and whose treatment will continue at home. NIV treatment is almost always initiated in hospital, and goals of hospital admission are to determine the needs of the patient; to adapt the patient to NIV treatment; to identify the best ventilator, mode, interface, and settings for patient; to follow the short-term beneficial effects of NIV on the patient; and to train the caregiver of the patient. Training of caregivers is crucial, and caregivers should be evaluated in terms of their competence and compliance. Lack of sufficient caregiver support may be a relative contraindication for home NIV treatment. Caregivers are not only trained about how to put on interface and device; they must also be trained about different problems that they may encounter at home. Secretion management is one of main problems in pediatric patients requiring home NIV treatment, and caregivers should be aware of this situation and must be trained for physiotherapy, postural drainage, and suctioning [7]. Caregivers should have training about action plan that they will apply in emergency situations. Home care system must be informed about individual features of NIV therapy and needs of patient and family before the discharge of the patient.

Admitting the patient to hospital is the common practice while starting NIV therapy. Since this causes shortage of hospital beds and economic constraints, there is a tendency to start NIV with an outpatient program. Amaddeo et al. report successful implementation of CPAP in a group of patients who had persistent OSAS, age >6 months, stable condition, and family agreeing with a regular follow-up [14]. They found a very good compliance rate of 87%, and the therapy was successful from the aspect of OSAS treatment and gas exchange. The strategy, however, is shown to be feasible and effective in selected patients with OSAS. Further studies are needed to define other patient groups in which this practice can be encouraged.

The underlying diseases that cause chronic respiratory failure in children are generally complex and usually connected to multiple disabilities which require multidisciplinary medical team follow-up. Children on home NIV therapy must be followed by multidisciplinary medical team concerning course of underlying disease, infection prophylaxis, adequate nutrition, mechanical ventilation assessment, and pulmonary physiotherapy.

In their study which evaluates the use of a stability guideline in long-term ventilator-dependent children discharging to home, Hanks et al. reviewed the use of an institutional guideline based on expert opinion which was used for patients who were first discharged home on mechanical ventilation. They demonstrated a low

utilization rate [15]. Guidelines like these can improve the patient experience and success rate as well as decrease failure and complication rate. The effect should be studied in further studies, and we predict similar guidelines will become widely used in time since the practice of home NIV is growing around the world.

54.9 Follow-Up

There are no validated guidelines for long-term follow-up of children undergoing home NIV therapy. Timing of follow-up visits is usually individualized depending on the age and medical condition of the child [6]. The first ventilation check-up must be organized within 1–3 months of NIV initiation [7]. Modification of ventilator settings or interface should be performed under the supervision of a physician. Since patients who receive NIV treatment at home are followed by many departments, the patient should be evaluated by all following departments during the same hospital visit.

54.10 Complications of Home NIV Therapy

54.10.1 Skin Ulcer

Skin erythema/ulcer is a common complication especially in patients using nasal and oronasal masks. The injury ranges from transient erythema to skin necrosis [16]. Preventing development of skin ulcer can be achieved by using different mask compositions, careful skin care and dressings, increasing the ventilator free time, alternating interfaces, and reminding caregivers not to seal mask too tightly.

54.10.2 Midface Hypoplasia

This is a specific complication seen in pediatric patients who started treatment at a very young age. Younger children undergoing home NIV therapy must be evaluated regularly in terms of maxillomandibular growth.

54.10.3 Nosebleeds and Nasal Congestion

High pressurized airflow may cause drying of nasal mucosa, and this can lead to nose bleeding or nasal congestion. Use of a humidification system may reduce this complication. Nasal congestion secondary to acute illness may reduce the effectiveness of NIV with nasal mask and lead to patient discomfort; patient may require alternate oronasal mask during this illness period.

54.10.4 Eye Irritation

Eye irritation appears usually secondary to improper fit of mask which is leading to air leak toward eyes. Proper fit of mask and frequent control of the mask position will overcome this complication.

54.10.5 Rebreathing

Rebreathing of patient's exhaled gases can occur in case of larger mask use and low EPAP presets. To avoid rebreathing, the smallest and best fitting mask must be used, and higher EPAP must be set in case of open-outlet exhalation system use.

54.10.6 Gastric Distention and Gastroesophageal Reflux

NIV therapy may cause gastric distention and increase the existing reflux and feeding intolerance. This complication can be treated by gastrostomy or nasogastric tube. NIV must be avoided in case of ongoing emesis. During the initiation of NIV, feeding can be held and reintroduced cautiously after tolerance of NIV.

54.10.7 Pneumothorax

Patients with pulmonary parenchymal disease such as cystic fibrosis have increased risk of pneumothorax. Careful pressure settings and

avoidance of higher pressures in risky patients and regular physical examination with X-ray will reduce the occurrence of pneumothorax.

54.10.8 Cardiac Side Effects

Elevation of intrathoracic pressure secondary to NIV therapy may reduce cardiac output because of decrease of venous return. This situation may cause significant clinical problem in hypovolemic states and in patients with congenital heart disease. NIV must be initiated cautiously in patients with underlying congenital heart disease especially single ventricle disorders.

54.10.9 Weaning

Children requiring long-term NIV should be evaluated regularly for tolerance and efficacy and also the need to continue NIV. Mastouri et al. in their retrospective cohort of patients with long-term NIV treatment who were eventually weaned defined the underlying disorders, weaning criteria, and clinical outcomes [17]. Discontinuation of NIV was authorized when their preset criteria were fulfilled. Forty percent of the patients could be weaned after surgery, 57% had spontaneous improvement, and another 3% were transitioned to oxygen therapy. Bronchopulmonary dysplasia, Pierre Robin syndrome, laryngomalacia, laryngeal paralysis, and Prader-Willi syndrome were the underlying diagnosis in patients who had spontaneous improvement, with the longest duration of CPAP being observed in patients with achondroplasia.

In long-term clinical follow-up, 35 patients with craniofacial or upper airway malformations had a second sleep study, and 7 (20%, 12% of the whole group) patients had a relapse of their OSAS after discontinuation of CPAP. The authors conclude weaning in children treated with long-term NIV is possible but is highly dependent on the underlying disorder. The relapse of previous conditions in some of the patients after weaning underlines that long-term follow-up by specialists both during therapy and after discontinuation of NIV is necessary in children with associated disorders (Table 54.1).

54.11 Final Conclusions

54.11.1 Learning Points

Noninvasive ventilation (NIV) has become more preferable as long-term supportive therapy in recent years. The main reasons for this are the

Table 54.1 Summary of best clinical/bench trials

Study, year	Design	No of patients	Main results	Conclusions
Ikeda et al., 2018 [1]	Retrospective review of records	53	Planned implementation and continuation rate was high among neuromuscular disorders	Long-term NIV is possible in multiple disabilities but particularly challenging in degenerative diseases
Rojas et al., 2017 [10]	Retrospective case series	18	Successful implementation in 94% significant decrease in arterial $PaCO_2$	May prove feasible alternative for mask intolerance and tracheostomy avoidance
Amaddeo et al., 2018 [14]	Prospective enrollment of selected patients in outpatient program, retrospective study	31	27 patients with good compliance and resultant good CPAP efficacy (for OSAS and gas exchange)	Initiating CPAP outpatient is feasible and effective in selected patients
Mastouri et al., 2017 [17]	Retrospective cohort follow-up of children who were weaned from long-term NIV	213	58 children weaned, longest duration in achondroplasia. 35 patitents with malformations had a second sleep study; 7 had a relapse of OSAS	Weaning in long-term NIV is dependent on the underlying disorder. Weaning failure can be seen in children with associated disorders

technological advances in NIV treatment as well as new interfaces.

- Patients are usually admitted to hospital when implementing home NIV therapy, but it is possible to commence this therapy in outpatient clinic in certain patient groups like OSAS patients.
- Patients, families, and institutions can benefit from the use of a guideline or routine checklist to be applied before discharging the patient (Table 54.2).

54.11.2 Critical Points

- The patient population and diversity of underlying diagnoses are growing as the equipment and experience on home NIV grow and healthcare shifts from hospital- to home-based care.
- For some selected patient groups, it can be possible and even better to start the treatment in outpatient circumstances.
- There is a need for institutional protocols, increased compliance to them, and regular follow-up visits and evaluations of both the therapy success and ongoing need for therapy for this patient population.

Table 54.2 Main conclusions/future perspective

– Some of the patient groups and diagnoses which were regarded as not compatible with noninvasive ventilation are now successfully managed long term by noninvasive ventilation
– The increasing number of patients and confidence in therapy has become possible by improvements in equipment and growing experience of healthcare staff
– Patient selection, targets of therapy, proper interface and device, assessment of home conditions, and capacity of the family and local healthcare system are all important components of therapy success. NIV can be implemented in outpatient clinic for some patient groups
– More studies on effects of discharging guidelines and follow-up protocols should be carried out to increase therapy success

54.11.3 Key Summary

When implementing home NIV treatment, not only underlying diagnosis but also the feasibility of the treatment at home should be taken into consideration. The discharge protocol and follow-up plan should be outlined and carried out according to the needs of the patient and the family to increase compliance.

References

1. Ikeda A, Tsuji M, Goto T, et al. Long-term home non-invasive positive pressure ventilation in children: results from a single center in Japan. Brain Dev. 2018;40(7):558–65.
2. Castro-Codesal ML, Dehaan K, Featherstone R, et al. Long-term non-invasive ventilation therapies in children: a scoping review. Sleep Med Rev. 2018;37:148–58.
3. Amaddeo A, Moreau J, Frapin A, et al. Long term continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) in children: initiation criteria in real life. Pediatr Pulmonol. 2016;51(9):968–74.
4. Amin R, Al-Saleh S, Narang I. Domiciliary noninvasive positive airway pressure therapy in children. Pediatr Pulmonol. 2016;51(4):335–48.
5. Chiang J, Amin R. Respiratory care considerations for children with medical complexity. Children (Basel). 2017;4(5)
6. Amaddeo A, Frapin A, Fauroux B. Long-term noninvasive ventilation in children. Lancet Respir Med. 2016;4(12):999–1008.
7. Windisch W, Geiseler J, Simon K, et al. German National Guideline for treating chronic respiratory failure with invasive and non-invasive ventilation - Revised edition 2017: Part 2. Respiration. 2018;96(2):171–203.
8. Windisch W, Geiseler J, Simon K, et al. German National Guideline for treating chronic respiratory failure with invasive and non-invasive ventilation: Revised edition 2017 - Part 1. Respiration. 2018;96(1):66–97.
9. Mortamet G, Emeriaud G, Jouvet P, et al. [Noninvasive ventilation in children: do we need more evidence?]. Arch Pediatr. 2017;24(1):58–65.
10. De Jesus Rojas W, Samuels CL, Gonzales TR, et al. Use of nasal non-invasive ventilation with a RAM cannula in the outpatient home setting. Open Respir Med J. 2017;11:41–6.

11. Khirani S, Ramirez A, Aloui S, et al. Continuous positive airway pressure titration in infants with severe upper airway obstruction or bronchopulmonary dysplasia. Crit Care. 2013;17(4):R167.
12. Fauroux B, Leroux K, Desmarais G, et al. Performance of ventilators for noninvasive positive-pressure ventilation in children. Eur Respir J. 2008;31(6):1300–7.
13. Essouri S, Nicot F, Clement A, et al. Noninvasive positive pressure ventilation in infants with upper airway obstruction: comparison of continuous and bilevel positive pressure. Intensive Care Med. 2005;31(4):574–80.
14. Amaddeo A, Frapin A, Touil S, et al. Outpatient initiation of long-term continuous positive airway pressure in children. Pediatr Pulmonol. 2018;53(10):1422–8.
15. Hanks J, Carrico CA. Evaluating the use of a stability guideline for long-term ventilator-dependent children discharging to home: a quality improvement project. J Pediatr Health Care. 2017;31(6):648–53.
16. Fauroux B, Lavis JF, Nicot F, et al. Facial side effects during noninvasive positive pressure ventilation in children. Intensive Care Med. 2005;31(7):965–9.
17. Mastouri M, Amaddeo A, Griffon L, et al. Weaning from long term continuous positive airway pressure or noninvasive ventilation in children. Pediatr Pulmonol. 2017;52(10):1349–54.

55 Noninvasive Ventilation in Paediatric Neuromuscular Disorders

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Abbreviations

BAE	Bronchopulmonary adverse event
BIPAP	Bi-level positive airway pressure
CPAP	Continuous positive airway pressure
CPF	Cough peak flow
DMD	Duchenne muscular dystrophy
EPAP	Expiratory positive airway pressure
FEV1	Forced expiratory volume in 1 s
FRC	Functional residual capacity
FVC	Forced vital capacity
IFR	Inspiratory flow reserve
IPAP	Inspiratory positive airway pressure
LRTI	Lower respiratory tract infection
MEP	Maximal expiratory pressure
MIC	Maximal insufflation capacity
MI-E	Mechanical insufflation-exsufflation
MIP	Maximum inspiratory pressure
NH	Nocturnal hypoventilation
NIV	Noninvasive ventilation
NMDs	Neuromuscular disorders
OSA	Obstructive sleep apnoea
PEEP	Positive end-expiratory pressure

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PEF	Peak expiratory flow
PIP	Positive inspiratory pressure
QOL	Quality of life
RCT	Randomised controlled trial
REM	Rapid eye movement
RNA	Ribonucleic protein
RSV	Respiratory syncytial virus
SDB	Sleep disordered breathing
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SNIP	Sniff nasal inspiratory pressure
VC	Vital capacity
XLMTM	X-Linked myotubular myopathy

55.1 Introduction

Neuromuscular disorders (NMDs) are clinically and genetically heterogeneous conditions with muscle weakness presenting at variable age groups. Muscle weakness can affect the respiratory function and airway protection through reduced tone. There can be additional factors like problems with clearance of secretions and scoliosis affecting respiratory function. The muscle weakness often leads to restrictive respiratory deficiency, reducing the vital capacity (VC), total lung capacity, and functional residual capacity [1, 2]. The respiratory deterioration is insidious, and early detection of nocturnal hypoventilation (NH) is crucial as it can be treated by prompt noninvasive ventilation (NIV) reducing its progression to daytime hypercapnia [3, 4] or clinical symptoms of hypoventilation [1, 5, 6].

Antisense nucleotide, nusinersen, is available in certain countries for treatment of spinal muscular atrophy (SMA) type 1, 2, and 3 related to SMN1 gene mutation. Patients previously dying before the age of 2 years due to respiratory failure are now showing clinically improved survival and motor function following the introduction of nusinersen. Gene therapy trials are under way for SMA type 1 and X-linked myotubular myopathy (XLMTM) which has a potential to impact the clinical course of these conditions. The respiratory care is crucial for the survival of these children, and its delivery is increasingly challenging not just for clinicians but also for the carers. In this chapter, the latest development in the principles of respiratory management of these patients with noninvasive ventilation is discussed.

55.2 Clinical Update and Clinical Trials' Results

A bibliographic search was made using Medline database and Cochrane library. The following keywords were selected and combined in multiple steps: "Noninvasive ventilation", "Continuous positive airway pressure", "Bi-level positive airway pressure", "Pulmonary function", "Neuromuscular disorder", "Congenital myopathy", "Duchenne muscular dystrophy", "Spinal muscular atrophy", "Congenital muscular dystrophy", "Myotubular myopathy", "Nocturnal hypoventilation", "Nusinersen", "Raxone", and "Idebenone". Articles in all languages were selected for this review. The time period of the review was January 2017 to 4 March 2019. We only selected paediatric studies. In this time period, standard of care has been revised for Duchenne muscular dystrophy [7] and spinal muscular atrophy [8]. There were only two randomised controlled studies. Evidence is mainly from observational studies, case reports, and expert opinion using the Delphi method. Table 55.1 summarises all the studies included in our analysis.

55.3 Recent Technological Advances

55.3.1 Airway Clearance and Secretion Management

A clear airway is dependent on healthy mucociliary function and an effective cough for clearance of secretions. Effective cough has three components, including inspiration, glottic closure requiring bulbar function, and effective contraction of expiratory abdominal and intercostal muscles. In NMD muscle weakness can cause ineffective coughing and the function of

Table 55.1 Clinical update and clinical trials' results

Author	Year of publication	Outcome
Trucco et al. [12]	2018	The aim of the study was to detect early nocturnal hypoventilation in neuromuscular disorders prior to onset of altered gas exchange. A total of 46 patients with dystrophinopathy, SMA, and congenital myopathy/dystrophy had transcutaneous CO_2 and SpO_2 monitoring. Thirteen patients had isolated nocturnal hypercapnia without NH suggesting that this measurement can be used in addition to the other respiratory sleep measurements to detect NH
Luo et al. [16]	2017	This Cochrane review looked into the role of invasive versus NIV for acute respiratory failure in neuromuscular diseases and chest wall disorders. There were no randomised trials for or against the use of NIV for acute respiratory failure. Observation studies support the trial of NIV for respiratory failure except those with bulbar dysfunction
Birnkrant et al. [7]	2018	This is a review article describing the latest care considerations for patients with DMD for respiratory, cardiac, bone health, and orthopaedic care. Guidance is prepared from expert consensus as there is lack of randomised controlled trials (RCTs). The outcome strongly endorses NIV for treating respiratory dysfunction for DMD. The criteria for NIV are defined. Indication of nocturnal NIV for asymptomatic hypoventilation of sleep disordered breathing or abnormal sleep study. For asymptomatic individuals if FVC is <50% predicted, MIP < 60 cm water or a weak base line $SpO_2 < 95\%$ or $pCO_2 > 45$ mmHg Daytime NIV for symptomatic dyspnoea or SpO_2 less than 95% or $pCO_2 > 45$ mmHg
DELOS study		Multicentre, randomised, double-blind, placebo-controlled efficacy and safety study for patients with DMD (ambulatory and non-ambulatory) aged 10–18 years not taking steroids studying the benefit of idebenone (Raxone®) on lung function. Patients were randomised in a 1:1 ratio to receiving either idebenone (900 mg/day) or placebo three times a day with meals for 52 weeks
	McDonald et al. [27] 2016	More patients in the placebo group compared to the idebenone group experienced bronchopulmonary adverse events (BAEs): placebo, 17 of 33 patients, 28 events; idebenone, 6 of 31 patients, 7 events; the overall duration of BAEs was 222 days (placebo) vs. 82 days (idebenone); antibiotic usage in the placebo group, 13 patients (39.4%) compared to 7 patients (22.6%) in the idebenone group. There was a protective effect of idebenone on respiratory function with a reduced risk of bronchopulmonary complications and a reduced need for systemic antibiotics
	Mayer et al. [28] 2017	The change over 1 year in FVC and FVC% predicted showed a consistent pattern in favour of idebenone treatment across multiple analysis methods, and fewer patients in the idebenone group declined by a margin of 10% or more in FVC and FVC% predicted compared to placebo supporting that idebenone can slow the respiratory deterioration
	Meier et al. [10] 2017	Upper limb function was monitored using Brooke score. There was a considerable drop in dynamic lung function associated with loss of upper limb function from Brooke score category 4 to category 5
	Buyse et al. [29] 2017	Highest flow generated during an inspiratory FVC manoeuver (maximum inspiratory flow; $V'I$,max(FVC)) and the ratio between the largest inspiratory flow during tidal breathing (tidal inspiratory flow; $V'I$,max(t)) and the $V'I$,max(FVC) were assessed in the study group. The fraction of the maximum flow that is not used during tidal breathing has been termed inspiratory flow reserve (IFR). Patients in both treatment groups of DELOS (idebenone, $n = 31$; placebo, $n = 33$) had comparable and abnormally low $V'I$,max(FVC) at baseline. During the study period, $V'I$,max(FVC) further declined by −0.29 L/s in patients on placebo (95% CI, −0.51, −0.08; $P = 0.008$ at week 52), whereas it remained stable in patients on idebenone (change from baseline to week 52, 0.01 L/s; 95% CI, −0.22, 0.24; $P = 0.950$). During the study period, IFR improved by 2.8% in patients receiving idebenone and worsened by −3.0% in placebo group. These findings suggest that idebenone preserved inspiratory muscle function as assessed by $V'I$,max(FVC) and IFR

(continued)

Table 55.1 (continued)

Author	Year of publication	Outcome
Finkel et al. [8]	2018	This is the standard of care recommendations for SMA. This article has recommendations for pulmonary and acute care, medications, supplements, and immunisation. The guidance for non-sitters suggests airway clearance with cough assist and mechanical ventilation, chest physiotherapy, and suction. NIV should be used for all symptomatic patients. For asymptomatic patients, initiation of NIV is judged on the basis of adequate gas exchange or sleep study For sitters regular spirometry at each visit and surveillance with sleep study are recommended. NIV should be initiated in symptomatic patients or any evidence of NH
Grychtol et al. [19]	2018	This is a review article about sleep diagnostics and NIV in children with SMA. Summary of existing knowledge about sleep disordered breathing and respiratory failure in patients with SMA1 is given. Practical consideration and ethical concerns in the new landscape of the advent of new therapies suggests Nusinersen is explained
Fitzgerald et al. [31]	2018	Review article concentrates on the strategies of respiratory management of children with SMA type 1 in the light of changing expectations since availability of treatment with Nusinersen
Deborah Boroughs [23]	2017	This study analyses the use of education programme for carers of ventilation-dependent SMA children. Eleven children were enrolled in this study aged between 6 months and 18 years. A training curriculum involving pre-test to check the baseline of emergency care scenarios was tested. This was followed by training in simulation lab teaching them correct techniques by nurse educator. Carers were tested after the training. One hundred percent participants reported increase in confidence in responding effectively to the emergencies. This small study showed that repeated caregiver education is essential to retain memory and training is needed to care for ventilated patients
Inoue et al. [20]	2017	Case study of an infant with SMA type I commenced on NIV that helped to improve ventilation, prevent atelectasis, and improve quality of life (QOL)
Inoue et al. [25]	2018	Case report of an infant with XLMTM and pectus excavatum responding positively from NIV after a year. The chest deformity improved

mucocilia being hampered by multiple chest infections. Approach is now very pro-active especially for patients with SMA type 1 with early initiation of chest physiotherapy and mechanical insufflation-exsufflation (MI-E, Cough Assist^{R}). The insufflation-exsufflation pressures are to be titrated to the level of maximal tolerance. Oral suctioning with mechanical suction pump is important for very weak patients with ineffective cough.

Several airway clearance techniques are available which should be individualised depending on patient co-operation and level of weakness. Cough augmentation for older children can be effective when the bulbar muscle function is adequate. The maximal insufflation capacity (MIC) is attained when patient able to take deep breath and hold breath and then air stacking is applied with glossopharyngeal breathing or bag-valve mask device. Glossopharyngeal breathing also called "frog breathing" consists of series of pumping strokes of lips, tongue, soft pallet, pharynx, and larynx. The high-frequency chest wall oscillation (VEST) therapy can be provided by intermittent compression of the chest wall by a snug inflatable jacket on thorax. Vibrations of chest wall produce oscillatory flow with mobilisation of secretions. This technique though useful for older children is not effective for SMA patients [8], although it can be used for younger patients along with positive pressure ventilation to maintain airway patency. Manual assisted

cough involving synchronous compression of abdomen when patient coughs increases the expiratory flow which in combination of air stacking can enhance expiratory airflow while coughing.

There is no clear evidence about routine use of antibiotics to prevent infections as a useful therapy for secretion management, and MI-E device is more suitable for this purpose. The use of glycopyrrolate or topical/oral hyoscine can be tried with caution as it can cause thickening of secretions which would be tackled with hypertonic saline nebulised treatment. The other pharmacological interventions would be nebulised ipratropium bromide or salbutamol or oral atropine. Botulinum toxin injection of salivary gland has been tried in children with neurodisability as a temporary measure [9] for 3–6 months. Figure 55.1 summarises the methods useful for secretion management.

Standard of care for SMA [8] recommends using palivizumab during RSV (respiratory syncytial virus) season for first 2 years of life along with annual influenza vaccination after 6 months of age. Pneumococcal vaccination is adopted for routine childhood vaccinations in the UK, and in most developed countries. Gastro-oesophageal reflux should be promptly treated, and insertion of nasojejunal tube should be considered if there is recurrent aspiration.

55.3.2 Detection of Early Nocturnal Hypoventilation

Children with NMD need regular assessment for respiratory symptoms and function. Regular monitoring with spirometry is recommended for all patients with NMD who are able to perform and co-operate. Height, arm span or ulna length, and age are used to predict expected lung function. Forced vital capacity (FVC) correlates with survival in patients with Duchenne muscular dystrophy (DMD), and there is considerable drop with loss of upper limb function [10]. Respiratory muscle strength can be assessed by maximum inspiratory pressure (MIP), sniff nasal inspiratory pressure (SNIP), and maximal expiratory pressure (MEP) [11]. Effectiveness of cough is measured by cough peak flow (CPF). Children with CPF <270 L/min at risk of chest infections and CPF <160 L/min are not able to clear the airway.

Sleep disordered breathing (SDB) may be an effect of NH or obstructive sleep apnoea (OSA) or a combined effect of both of them. NH occurs first in active sleep (AS or rapid eye movement, REM) when the function of intercostal, upper airway, and accessory muscles is compromised. Symptoms of hypoventilation are tiredness, early morning or continuous headaches, poor concentration, nausea, hypersomnolence, dyspnoea, and

Fig. 55.1 Summary (pathophysiology or diagnosis/treatment) (Obligatory)

- Positioning
- Suction
- Nebulisers: saline, ipratroprium
- Humidification: MyAirvo
- Anti-sialogogues:
  hyoscine, glycopyrronium, atropine
- Mucolytics:
  carbocysteine, *N*-acetyl cysteine, erdosteine, deoxyribonuclease
- Cough Assist
- Vest / RTX oscillator
- Ventilation
- Tracheal toilet / bronchial lavage

nocturnal awakening. OSA presents as snoring, increased breathing effort, and arousal. Progressive muscle weakness may affect all stages of sleep before proceeding to daytime hypoventilation. Daytime hypoventilation presents as headache, nausea, dyspnoea, tachycardia, sweating, vasodilation/vasoconstriction, fatigue, or anxiety. Overnight monitoring should include a measure of carbon dioxide and can be done by oxycapnography (using transcutaneous or end-tidal carbon dioxide), respiratory polygraphy (cardiorespiratory sleep study), and polysomnography (continuous electroencephalograph, electromyogram, and electro-oculogram in addition to cardiorespiratory function). Recent study by Trucco et al. [12] emphasised on monitoring for nocturnal hypoventilation in patients with NMD.

55.3.3 Assisted Noninvasive Ventilation

Assisted ventilation in children with NMD is used to treat symptomatic and asymptomatic nocturnal hypoventilation, daytime hypoventilation, and frequent chest infections.

In DMD treatment with mechanical ventilation is necessary in the advanced non-ambulatory stage of the condition. Progressive muscle weakness results in weak cough, increasing the risk of atelectasis, pneumonia, and ventilation-perfusion mismatch leading to respiratory failure. The risk of respiratory failure is exacerbated with respiratory tract infections. Assisted ventilation has shown to prolong the survival of the patients with DMD [13]. Standard of care 2018 [7] endorses NIV for assisted ventilation in preference to ventilation via tracheostomy. It recommends nocturnal assisted ventilation for symptomatic hypoventilation or SDB irrespective of pulmonary function. For asymptomatic patients, assisted ventilation should be commenced if there is evidence of significant hypoxaemia or hypoventilation. Ventilation devices should have a safe backup rate to avoid apnoea.

NIV for patients with NMD is not only recommended for hypoventilation but also can be used for acute procedures involving sedation or anaesthesia or a step down from extubation during respiratory infections [14]. With the disease progression, patients may increase the duration of NIV to 24 h/day. The indication of daytime assisted ventilation is low SpO_2 < 95% or pCO_2 > 45 mmHg or symptomatic dyspnoea. Continuous NIV can be delivered via mouthpiece (sip ventilation) with a portable pressure ventilation when awake and nasal ventilation with a bi-level pressure device when asleep. Alternatively nasal ventilation with a bi-level pressure device can be used for all day effectively and is well tolerated [15]. Consider tracheostomy and invasive ventilation if using >16 h/day of NIV.

The use of NIV during acute respiratory illness or failure can be challenging if there is swallowing difficulty. The Cochrane review [16] comparing invasive versus noninvasive ventilation for acute respiratory failure found no evidence in favour of either from randomised studies. Evidence from observation studies suggest that NIV should be trialled in all patients except for the ones with bulbar dysfunction [16]. The decision to progress to ventilation via tracheostomy is substantial and involves discussion with the family about relative risks and benefits [17].

In SMA, NIV tends to be used mostly to help treat LRTIs (lower respiratory tract infections) and manage secretions. Problem with gaseous exchange is seen at later stage of the disease. NIV should be used in all symptomatic infants with SMA [18] and in non-sitters before the onset of respiratory failure to prevent chest wall distortion and palliative dyspnoea. The ventilation mode of choice is bi-level positive airway pressure which can support inspiration by application of peak inspiratory pressure (PIP). Continuous positive airway pressure (CPAP) ventilation is not generally suitable for treating respiratory failure but may be used with caution in younger babies who are unable to synchronise with the ventilator and are not markedly hypercapnic. The aim is to improve the functional residual capacity (FRC). In CPAP as exhalation is against positive end-expiratory pressure (PEEP) increasing the duration of ventilation to prevent a bell-shaped chest deformity with high amplitudes, inspiratory positive airway pressure (IPAP) and expiratory positive

airway pressure (EPAP) can be used but in clinical experience are uncomfortable. The titration of NIV is done clinically with a focus on correcting gaseous exchange and reducing the work of breathing. The clinical profile will be complicated with additional complications of bulbar dysfunction, swallowing difficulties, scoliosis, and chest wall deformity. Children with SMA type 1 are very vulnerable and can decompensate with minor chest infections due to poor cough, aspiration, and mucus blocking making these children at risk of multiple hospital admissions [19]. Protocols for intensive secretion clearance with the use of MI-E devices along with increasing ventilation pressures and increasing the extension of NIV up to 24 h [8] can help to prevent hospitalisation and intubation. A case study of an infant treated with NIV reported prevention of atelectasis and good quality of life (QOL) [20].

The choice of ventilator should safely deliver low tidal volumes and sensitive flow trigger for good synchronisation. Very weak children will not be able to trigger, even with the maximum sensitive fitting, and hence a backup rate and an adequate (minimum) inspiratory time are recommended [21].

The latest review of NIV in SMA, especially type 1 children, elaborates the practical and ethical consideration in the back drop of new therapies like nusinersen [19]. Children with SMA1 with aggressive respiratory treatment on ventilation experience discomfort and are at risk of suffering [19]. Equally carers are at risk of psychological burden leading to physical exhaustion, social isolation, and financial difficulty [22]. Increased complexity of care highlights the need for training of adult carers in looking after such a vulnerable population [23].

Wallgren-Pettersson et al., at the 117th ENMC workshop have published guidance about ventilatory support for patients with congenital myopathies and muscular dystrophies [24]. Nocturnal mechanical ventilation showed improvement of arterial blood gas and survival advantage in this group of population. A recent case study showed that using NIV in severe XLMTM with high PIP and daily MI-E had improvement of pectus excavatum after a period of 12 months [25].

55.3.4 Set-Up of the Ventilator

The two main ventilators available for the patients with NMD are volume-targeted and pressure-targeted devices, and some can be a hybrid. Volume-targeted device has the advantage to assist with air stacking for assisted coughing but is limited as would not be able to overcome the leaks. Pressure-targeted device on the other hand is good for overcoming leaks but as a single- limb circuit being used, exhaled air is vented through the ports near the face or nasal mask. Different modes of ventilation are available to allow better synchronisation between the child and ventilator. Asynchrony between the ventilator and the child can be identified effectively by polysomnography or cardiorespiratory polygraphy [1, 26] or less precisely by clinical observation with oxycapnography [1].

The mask fit is important for the success of NIV. Different varieties of nasal and face mask are available for children. Nasal masks are preferred in non-sitters, due to the bulbar dysfunction and risk of aspiration. Nasal masks are well tolerated and usually are first choice but can have air leaks that can occur from open mouth which can be reduced by a chin strap. Skin breakdown on the bridge of the nose or forehead can be prevented using hydrocolloid wound care tape. Pressure from the mask can also cause midface hypoplasia by affecting maxillary growth, causing dental malocclusion giving a concave facial appearance.

55.3.5 New Pharmacological Treatments

DELOS study [10, 27–29] was a multicentre, randomised, double-blind, placebo-controlled efficacy and safety study for patients with DMD (ambulatory and non-ambulatory) aged 10–18 years studying the benefit of idebenone (Raxone®) on lung function. Patients were randomised to either idebenone (900 mg/day) or placebo three times a day with meals for 52 weeks. The primary end point was the difference between Raxone® and placebo in the change from baseline to week 52 in peak expiratory flow

(PEF as percent predicted, PEF%, a measure of respiratory muscle strength) as measured by hospital-based spirometry. PEF was also measured by the patient at home using the handheld device (secondary end point). Other respiratory end points included forced expiratory volume in 1 s (as percent predicted, FEV1%p, an additional measure of respiratory muscle strength) and forced vital capacity (as percent predicted, FVC%p, a measure of restrictive lung disease predictive of morbidity and mortality in DMD). The main outcomes of this study showed that there was a protective effect of idebenone on respiratory function with a reduced risk of bronchopulmonary complications a reduced need for systemic antibiotics [27] and reduced respiratory decline over a year as measured by FVC and FVC% predicted [28]; pulmonary function parameters considerably declined with loss of upper limb function from Brook score category 4 to category 5 [10]; idebenone preserved inspiratory muscle function as assessed by $V'I$,max (FVC) and IFR (inspiratory flow rate) [29]. The outcome of this study has limited significance; no patients in the study were treated with corticosteroid.

ENDEAR study [30] examined the clinical efficacy of nusinersen administered intrathecally to patients with infantile-onset SMA. Nusinersen is an antisense oligonucleotide drug that modifies pre-messenger ribonucleic acid (RNA) splicing of the SMN2 (survival motor neuron) gene and thus promotes increased production of full-length SMN protein. This was a double-blind, randomised sham-controlled study. The primary end points were a motor-milestone response (defined according to results on the Hammersmith Infant Neurological Examination) and event-free survival (time to death or the use of permanent assisted ventilation). In the interim analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (21 of 51 infants [41%] vs. 0 of 27 [0%], $P < 0.001$). In the final analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]), and the likelihood of event-free survival was higher in the nusinersen group than in the control group (hazard ratio for death or the use of permanent assisted ventilation, 0.53; $P = 0.005$). Authors concluded that patients who received nusinersen were more likely to be alive and have improvements in motor function. Nusinersen is approved in many developed countries, but its direct effect on respiratory function is not analysed. Fitzgerald et al. have described the changing respiratory expectations following treatment with nusinersen for patients with SMA type 1 [31]. The efficacy of this treatment in improving respiratory function is yet to be proven (Table 55.2).

Table 55.2 Expert opinion

Main conclusion	Future perspective
Respiratory health assessment should be part of regular medical assessment for children with NMD. This should involve identifying progressive muscle weakness, frequency of chest infections, aspiration, and evidence of SDB	Benefit of new novel therapies to be correlated with respiratory function and events
For very weak children, secretion management and maintaining patent airway are challenging	Development of effective treatments for secretion management
Measurement of FVC and PCF should be done for patients who are capable of performing spirometry at each visit	Development of 'apps' that can monitor respiratory function at home
Patients who have FVC <60%, never walked, or lost the ability to walk should have annual surveillance for SDB	Development of home monitoring devices and accuracy of measurement
Hypoventilation as defined by nocturnal hypercapnia should be considered for NIV	Systematic review of the reference ranges of blood gas parameters
Once established on NIV, children should be regularly assessed with sleep study to ensure effective treatment of hypoventilation	Cost-effectiveness assessed by reduced frequency of hospital admissions

55.4 Recommendations and Practical Guidelines

55.4.1 Learning Points

- Respiratory care is crucial to the management of children NMD.
- NMD can present with respiratory compromise at differing stages of illness.
- Very weak children with SMA type 1 or congenital myopathy/dystrophy have problems of copious secretions compromising airway.
- Recurrent chest infections and aspiration are the main reasons for multiple hospital admissions.
- Regular monitoring for respiratory and motor decline helps to identify the need for assisted ventilation.

55.4.2 Critical Points

- NMD is a varied population, and some very weak children pose a major challenge for respiratory care.
- The changing landscape with introduction of novel treatments and better supportive care is changing the natural history of condition.
- Longer survival of patients means extra need for provision of high dependency beds adding pressure to health costs for managing patients with NMD.
- The psychological burden on caregivers looking after these patients needs to be considered as a part of holistic management.

55.4.3 Key Summary

Respiratory care is crucial in the management of NMD, and clinical assessment requires monitoring of lung function and level of motor weakness. The progression of disease is variable, and assisted ventilation is commenced for managing NH or daytime hypercapnia. In some very weak children, maintenance of clear airway can be challenging due to excess secretion and ineffective cough. Antisense oligonucleotides and gene therapy trials in specific diseases are changing the landscape of this group of disorders. This will come with extra burden for health-care providers, and the psychological burden of carers should not be overlooked (Fig. 55.2).

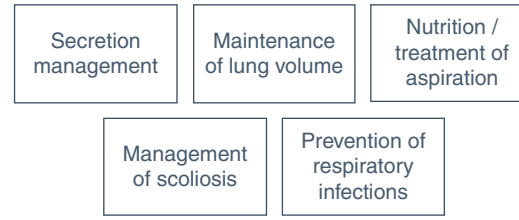

Fig. 55.2 Key areas for maintaining respiratory health in NMD

References

1. Hull J, Aniapravan R, Chan E, et al. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. Thorax. 2012;67(Suppl 1):i1–i40.
2. Panitch HB. The pathophysiology of respiratory impairment in pediatric neuromuscular diseases. Pediatrics. 2009;123(Suppl 4):S215–8.
3. Mellies U, Ragette R, Dohna Schwake C, et al. Long-term noninvasive ventilation in children and adolescents with neuromuscular disorders. Eur Respir J. 2003;22:631–6.
4. Young HK, Lowe A, Fitzgerald DA, et al. Outcome of noninvasive ventilation in children with neuromuscular disease. Neurology. 2007;68:198–201.
5. Simonds AK. Chronic hypoventilation and its management. Eur Respir Rev. 2013;22:325–32.
6. Ward S, Chatwin M, Heather S, et al. Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. Thorax. 2005;60:1019–24.
7. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, Part 2: Respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. 2018;17:347–6.
8. Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018;28(3):197–207.

9. Rodwell K, Edwards P, Ware RS, et al. Salivary gland botulinum toxin injections for drooling in children with cerebral palsy and neurodevelopmental disability: a systematic review. Dev Med Child Neurol. 2012;54(11):977–87.
10. Meier T, Rummey C, Leinonen M, et al. Characterization of pulmonary function in 10–18 year old patients with Duchenne muscular dystrophy. Neuromuscul Disord. 2017;27(4):307–14.
11. Verma R, Chiang J, Qian H, et al. Maximal static respiratory and sniff pressures in healthy children. A systematic review and meta-analysis. Ann Am Thorac Soc. 2019;16(4):478–87.
12. Trucco F, Pedemonte M, Fiorillo C, et al. Detection of early nocturnal hypoventilation in neuromuscular disorders. J Int Med Res. 2018;46(3):1153–61.
13. Phillips MF, Quinlivan RC, Edwards RH, et al. Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med. 2001;164:2191–4.
14. Bach JR, Goncalves MR, Hamdani I, Winck JC. Extubation of patients with neuromuscular weakness: a new management paradigm. Chest. 2010;137:1033–9.
15. Bach JR, Goncalves MR, Hon A, et al. Changing trends in the management of end-stage neuromuscular respiratory muscle failure: recommendations of an international consensus. Am J Phys Med Rehabil. 2013;92:267–77.
16. Luo F, Annane D, Orlikowski D, et al. Invasive versus non-invasive ventilation for acute respiratory failure in neuromuscular disease and chest wall disorders (Review). Cochrane Database Syst Rev. 2017;(12):CD008380.
17. Macauley R. To trach or not to trach, that is the question. Paediatr Respir Rev. 2019;29:9–13.
18. Petrone A, Pavone M, Testa MB, et al. Noninvasive ventilation in children with spinal muscular atrophy types 1 and 2. Am J Phys Med Rehabil. 2007;86(3):216–21.
19. Grychtol R, Abel F, Fitzgerald DA. The role of sleep diagnostics and non-invasive ventilation in children with spinal muscular atrophy. Paediatr Respir Rev. 2018;28:18–25.
20. Inoue K, Kimura N, Higuchi Y, et al. Non-invasive positive pressure ventilation during the management of severe spinal muscular atrophy type I. No To Hattatsu. 2017;49(2):141–4.
21. Finkel RS, Weiner DJ, Mayer OH, et al. Respiratory muscle function in infants with spinal muscular atrophy type I. Pediatr Pulmonol. 2014;49(12):1234–42.
22. Qian Y, McGraw S, Henne J, et al. Understanding the experiences and needs of individuals with spinal muscular atrophy and their parents: a qualitative study. BMC Neurol. 2015;15:217.
23. Boroughs DS. An evaluation of a continuing education program for family caregivers of ventilator-dependent children with spinal muscular atrophy (SMA). Children (Basel). 2017;4(5):33.
24. Wallgren-Pettersson C, Bushby K, Mellies U, et al. 117th ENMC workshop: ventilatory support in congenital neuromuscular disorders—congenital myopathies, congenital muscular dystrophies, congenital myotonic dystrophy and SMA (II). Neuromuscul Disord. 2004;14(1):56–69.
25. Inoue K, Kumada T, Hiejima I. Successful use of non-invasive positive pressure ventilation in a patient with the severe form of X-linked myotubular myopathy. Brain Dev. 2018;40(5):421–4.
26. Caldarelli V, Borel JC, Khirani S, et al. Polygraphic respiratory events during sleep with noninvasive ventilation in children: description, prevalence, and clinical consequences. Intensive Care Med. 2013;39:739–46.
27. McDonald CM, Meier T, Voit T, et al. Idebenone reduces respiratory complications in patients with Duchenne muscular dystrophy. Neuromuscul Disord. 2016;26(8):473–80.
28. Mayer OH, Leinonen M, Rummey C, et al. Efficacy of idebenone to preserve respiratory function above clinically meaningful thresholds for forced vital capacity (FVC) in patients with Duchenne muscular dystrophy. J Neuromuscul Dis. 2017;4:189–98.
29. Buyse GM, Voit T, Schara U. Treatment effect of idebenone on inspiratory function in patients with Duchenne muscular dystrophy. Pediatr Pulmonol. 2017;52(4):508–15.
30. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med. 2017;377(18):1723–32.
31. Fitzgerald DA, Doumit M, Abel F. Changing respiratory expectations with the new disease trajectory of nusinersen treated spinal muscular atrophy [SMA] type 1. Paediatr Respir Rev. 2018;28:11–7.

56 NIV in Pediatric Patients with Rare Diseases: Useful as a Primary or Adjunctive Therapy but Not the Absolute Final Destination

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56.1 Introduction

Definition of *rare disease* changes according to the area of the world it is defined. For example, in the United States, a condition that affects fewer than 200,000 people is considered a rare disease, while in the European Union, a disease is defined as rare when it affects fewer than 1 in 2000 people. There are many different etiologies of rare diseases. Most of these diseases are genetic which are either passed in the family or occur randomly.

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In this chapter we will discuss articles published within the last 2 years concerning noninvasive ventilation in pediatric patients with rare diseases. There may be as many as 5000–8000 rare diseases. So it is not feasible to screen for every disease according to whether there is documented use or clinical trial of NIV in these patients.

Although we know from published literature and clinical experience that noninvasive ventilation is universally used in patients with (1) anatomic abnormalities of the face or the airway, (2) anomalies of the central nervous system disturbing the respiratory drive, (3) genetic disorders which cause metabolic diseases affecting either one or both of the central nervous system and/or airway (e.g., by storage of material or degeneration of tissue), and (4) neuromuscular diseases mainly, we can come across many rare diseases that do not fit into any of these four categories

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and in which any component of the respiratory system is primarily or secondarily affected [1]. Immune deficiencies, chronic lung diseases, autoimmune diseases, and vasculitic diseases can be listed as examples. For this reason, we followed a methodology which allows us to pick any clinical paper that includes data about the use of NIV in pediatric patients with rare diseases.

56.2 Methodology

Separate searches were carried out in PubMed with the group of words "noninvasive ventilation" "continuous positive airway pressure" "bilevel positive airway pressure," and "high-flow nasal cannula" since some of the published articles include the latter three concepts within the noninvasive ventilation and some don't. Data was filtered for 2017–2019 period as well as human studies, category of child (birth–18 years), and English language. A total of 517 (183 + 246 + 6 + 82) results were obtained. After elimination of surveys, guidelines, in vitro studies, and duplications, all of the titles and abstracts were screened.

Articles solely on irrelevant diagnostic tools, medical devices, or therapies or invasive ventilation with endotracheal intubation; articles on a single type of acute disease states which are not rare diseases (e.g., acute bronchiolitis, asthma exacerbation); and articles on groups of neonates or premature newborns (none of which were reported to have a rare disease) were excluded during screening. Neuromuscular diseases were not included in order to avoid repetition since they are discussed in another chapter of this book. Articles on obstructive sleep apnea (OSA) were included only if the patient group has a specific rare disease.

Seventeen articles were evaluated for eligibility. These included (1) five articles which were studies on characteristics or clinical course of a defined group of patients which included patients with rare diseases, (2) four case reports of patients with a rare disease in which NIV was used, (3) three series of patients in which a diagnostic or therapeutic procedure was carried out and some of the patients used NIV in any part of the clinical process, and (4) five articles on a rare disease managed with NIV.

Since there is no abundance of articles with data solely on NIV use in a specific rare disease, we aimed to extract the data of rare diseases from the first group of articles. One study was excluded because only two patients with genetically inherited interstitial lung disease were mentioned and it is without any comment about the effect of NIV treatment [2]. Another three was excluded because a number of patients with rare diseases were included but none of the study end points were studied specifically in these patients [3–5].

The three articles in the third group and one article in the fourth group mentioned NIV only as a therapeutic strategy and didn't give any specific data on NIV [6–9]. Eventually remaining nine articles will be discussed with a critical perspective in this chapter emphasizing clinical implications. The best five studies are summarized in Table 56.1.

56.3 Clinical Data

There are a number of anatomical abnormalities of the face or airway which are treated with NIV. The first clinical study we will discuss is a retrospective review of sleep studies and management of 43 children with achondroplasia [10]. In these patients, upper airway obstruction and OSA are caused by the combination of midface hypoplasia, micrognathia, and depressed nasal bridge causing narrow nasal passages, relative adenoid and tonsil hypertrophy, relative macroglossia, a high palate and decreased temporomandibular joint mobility, and airway muscle hypotonia. Twenty-four of the 43 children had OSA in polysomnography (PSG) and 4 of them were treated with NIV. NIV therapy was successful clinically from the aspect of nocturnal gas exchange and apnea-hypopnea index (AHI). In two patients it was combined with surgery. The authors argue that persistent OSA after surgery is not uncommon in this disease. Although studies earlier than 2017 are out of the scope of this book, the referred articles also confirm NIV is an effective treatment

Table 56.1 Summary of best clinical/bench trials

Study, year	Design	No of patients	Diagnosis	Main results	Discussed therapy	Therapy success/failure	Conclusions drawn
Tenconi et al., 2017 [10]	Retrospective review of sleep studies	43	Achondroplasia	24 had OSA on PSG	4 out of 24 had NIV (2 patients had surgery)	NIV successful in gas exchange and AHI	Persistent OSA after surgery is not uncommon in this disease. NIV is an effective treatment
Goudy et al., 2017 [11]	Retrospective analysis to define factors related to need for surgery	38 neonates	Pierre Robin sequence	Need for surgery was associated with neurological disease and use of CPAP/BiPAP	9 patients treated with positive airway pressure on admittance	8 patients required surgery	Neurological disease or early need for CPAP/BiPAP in PRS patients may be regarded as a predictor for surgery
Léotard et al., 2018 [12]	Retrospective file review	188	Osteogenesis imperfecta	12/15 patients with PSG had sleep-disordered breathing. OSA correlated only with walking autonomy	2 patients treated by NIV	Sleep disorder events disappeared in both patients	Systematic and repeated search for symptoms suggesting sleep-disordered breathing is advised in OI patients
Khayat et al., 2017 [24]	Retrospective chart review of patient PSGs with standard BiPAP S/T mode and a consecutive follow-up study with BiPAP iVAPS mode	8	Congenital central hypoventilation syndrome	Only different PSG variable: peak NREM transcutaneous CO_2 ($tcCO_2$)	Standard BiPAP S/T mode versus follow-up study with BiPAP intelligent volume assured pressure support (iVAPS) mode	Only peak NREM transcutaneous CO_2 was higher in standard BiPAP. No difference in sleep architecture or sleep quality. The peak pressures appeared higher with iVAPS	Longitudinal studies are needed to observe relative importance of peak $tcCO_2$ versus mean $tcCO_2$ with regard to neurocognitive outcomes
Mastouri et al., 2017 [25]	Retrospective cohort follow-up of children who were weaned from long-term NIV	213	Various underlying diagnoses	58 children weaned, longest duration in achondroplasia. 35 patients with malformations had a second sleep study	Weaning after: spontaneous improvement in 57%, surgery in 40%, transition to oxygen therapy in 3%	7 (20% of the patients with malformations 12% of the whole group) patients had a relapse of their OSA after a discontinuation of CPAP	Weaning is possible in long-term NIV but dependent on the underlying disorder. Long-term follow-up is necessary in children with associated disorders

OSA Obstructive sleep apnea, *PSG* polysomnography, *AHI* apnea-hypopnea index, *OI* Osteogenesis imperfecta, *PRS* Pierre Robin sequence, *NREM* Non-REM sleep

as well as surgery, and continuous positive airway pressure (CPAP) should be regarded as a therapeutic option in patients who do not benefit from surgery. The decision to adopt a strategy with or without surgery should be given by a multidisciplinary approach (pediatric ENT, maxillofacial specialists), but the literature agrees that NIV stands as a noninvasive primary or adjunctive therapy in these patients and OSA is not the only indication. One patient in this study among the patients without sleep apneas, who has an alveolar hypoventilation due to a restrictive syndrome, was successfully treated by CPAP.

Another condition frequently presenting with airway obstruction is Pierre Robin sequence (PRS). The combination of cleft palate, glossoptosis, and micrognathia causes tongue-based airway obstruction. Goudy et al. in a logistic regression analysis of PRS patients requiring surgical intervention [11] analyzed 38 neonates and aimed to find factors associated with the need for surgery. Six of these patients had neurological abnormalities in addition to PRS. Nine patients were treated with positive airway pressure (CPAP, BiPAP) after admittance. Eight patients required surgical intervention. Among the variables of interest, several characteristics were associated with the need for a surgical airway, and with a stepwise regression model, there were significant independent associations with neurologic disease ($P = 0.031$) and use of CPAP/BiPAP ($P = 0.017$). The odds ratio for progressing to surgical airway among patients requiring positive pressure support via CPAP/BiPAP compared to those who needed less advanced airway support was 10.43. As the authors underlined, predicting which patients will fail conservative treatment and require surgical airway is clinically relevant. Many of these patients require prolonged hospitalization before a decision is made for surgery. NIV has positive impact on patient management in various clinical situations, but clinicians should be aware that arising need for NIV or escalation of therapy settings can be the sign of more severe or worsening condition.

Demonstrating underestimated rate of sleep-disordered breathing in children with osteogenesis imperfecta (OI), Léotard et al. reviewed files of 188 patients, and among the 15 patients (8%) with polysomnographic recordings, 12 (6.4%) had sleep-disordered breathing [12]. Besides the skeletal complications of the disease including multiple fractures, kyphoscoliosis, and skull base abnormalities, OI is a generalized connective tissue disorder with multiple extraskeletal manifestations, and pulmonary complications come forward as frequent causes of death. In spite of the small number of patients which prevented them from doing multivariate analyses, the authors study clinical factors such as scoliosis, arthrodesis, facial abnormalities, and obesity to find out if respiratory impairments caused by these factors result in OSA. They don't report significant correlation with any of the factors other than walking autonomy. The authors discuss that kyphoscoliosis may result in trunk deformation with muscular weakness, mostly responsible for nocturnal hypoventilation instead of obstructive apnea. Two children received CPAP. In both cases, the treatment was effective, with disappearance of sleep respiratory events. They encourage the reader to systematically and repeatedly search for symptoms suggesting sleep-disordered breathing in OI patients. We recommend this approach for all of the genetic syndromes with anatomical or neurological abnormalities or obesity, in order not to miss the opportunity of successful treatment with either CPAP or BiPAP [9].

Cases of Fragile X syndrome and Goldenhar syndrome that had obstructive sleep apnea were reported to be treated by continuous positive airway pressure (CPAP) [13, 14]. Facial morphology, anatomical obstruction, connective tissue dysplasia, and hypotonia are the precipitating factors for OSA. In both patients, the treatment resulted in improvement in sleep study parameters, specifically apnea-hypopnea index (AHI). Obstructive sleep apnea and its results affect the quality of life in patients with multiple comorbidities or cognitive dysfunction. Any improvement is highly appreciated by both the patient and the caregiver.

Anomalies of the airway are not limited to the face. Severe tracheomalacia or bronchomalacia can present as a single phenomenon or accompany

stigmata of syndromes. High-flow nasal cannula (HFNC) treatment has found a wide range of clinical application areas. User comfort and avoiding invasive procedures like tracheostomy are main factors. Vezina et al. reported use of HFNC in an infant with severe tracheomalacia [15]. The authors discussed improvement of the delivered oxygen concentrations and providing low-level distending pressure to the upper airway just like CPAP; but they were criticized for using nasojejunal tube feeding decreasing the effectivity of the treatment. Commenters also draw attention to the high HFNC pressures and possible side effects as well as to the possibility of CO_2 retention in patients with tracheomalacia and bronchomalacia [16]. As with any ventilatory support strategy, institution of HFNC treatment should be decided and watched by clinicians experienced on the field, and both advantages and disadvantages should be considered.

In the report of anesthetic management of a child with hypoplastic lungs because of Jeune syndrome, Kotoda et al. [17] argue that preoperative management of the patient should have included recruitment of lung volume by adjustment of CPAP parameters. Actually, during any intervention in a child maintained in noninvasive ventilation, adjustment of therapy should be considered according to potential needs and risks, including possible transition to another mode of respiratory support. Any setting that is sufficient for basal needs can become insufficient in emerging circumstances. Recruitment of lung function and assistance in airway clearance by NIV have been documented in cystic fibrosis [18, 19]. Not only in chronic lung diseases but also in acute loss of function, noninvasive ventilation can be utilized for recruitment. Although we didn't come across any pediatric article on this issue eligible for inclusion in this chapter, we can refer our own clinical experience on NIV to be successful in primary or secondary immune deficiencies and vasculitis patients complicated by pulmonary hemorrhage. Other than patient comfort and adherence, these vulnerable patients with rare conditions benefit by decreased secondary infections and avoiding complications of intubation [20–23]. General schematic drawing of the potential uses of NIV in various types of underlying pathophysiology/diagnosis is given in Fig. 56.1.

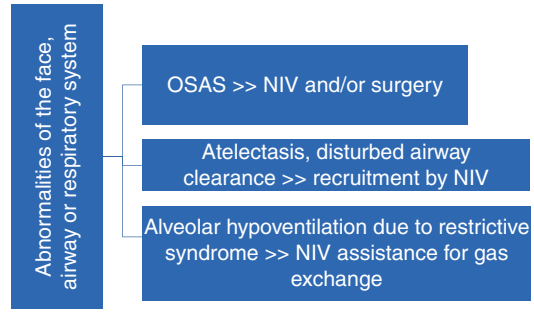

Fig. 56.1 Summary (diagnosis-treatment)

Diseases of the central nervous system also cause respiratory impairments which result in the need for treatment by NIV. Congenital central hypoventilation syndrome (CCHS) is characterized by ventilatory insensitivity to hypercapnia and hypoxemia during sleep and/or wakefulness. There is variability in control of breathing between NREM (non-rapid eye movements) and REM sleep in these children. Central and peripheral chemoreceptor sensitivity is impaired. In patients with CCHS, carbon dioxide levels are highest during NREM sleep when ventilatory responses are primarily regulated by the chemoreceptors. Because of the impaired response in CCHS, tidal volume and respiratory rate do not increase sufficiently and the result is alveolar hypoventilation. Khayat et al. carried out a retrospective chart review of CCHS patients who underwent both a titration polysomnogram (PSG) with standard BiPAP S/T mode and a consecutive follow-up study with BiPAP intelligent volume-assured pressure support (iVAPS) mode [24]. In this mode of BiPAP, the pressure support is automatically modulated to ensure a constant alveolar ventilation. Patients were included if they were positive for genetic mutation and previously established on nocturnal BiPAP therapy and if they were ≥30 kg. The only PSG variable that was significantly different between the two BiPAP modes was the peak NREM transcutaneous CO_2 ($tcCO_2$). The peak pressures appeared higher with iVAPS. Although the authors stress the importance of patient comfort in CCHS,

which is a disease for which patients use BiPAP mainly at nights, there were no difference in adherence to therapy. The peak $tcCO_2$ was below 50 mmHg in all patients except one during a BiPAP therapy S/T mode titration. There was no difference in sleep architecture or sleep quality between the two modes.

When choosing an equipment or mode of NIV and adjusting the settings, end points of therapy should be defined. The therapeutic option should have as many advantages as possible for the underlying condition but also shouldn't underestimate the importance of patient comfort. It should be kept in mind that although new technology has evolved the assisted ventilation broadly, usage of these devices is not without complications like sores on the face or air leaks. Optimal benefit should be sought from each device and mode, but the clinician shouldn't set incompatible targets at the expense of side effects. Also in many patients and disease types, discontinuation of NIV can be possible regardless of the long period of support. Although *rare diseases*—most of them being genetic—are not usually expected to be cured completely, the respiratory disturbance in many of them, as mentioned above, are caused by anatomical abnormalities and can be surgically ameliorated.

Follow-up of children requiring long-term NIV should include the evaluation of tolerance and efficacy but also the need to continue NIV [25]. Mastouri et al. in their retrospective cohort of patients with long-term NIV treatment who were eventually weaned defined the use of NIV for more than 2 months after hospital discharge as long term and aimed to line out the underlying disorders, weaning criteria, and clinical outcomes. They included patients who could be weaned for at least 3 months. Discontinuation of NIV was authorized when all four major criteria were fulfilled with at least two minor criteria. The major criteria were (1) disappearance of nocturnal and daytime symptoms of sleep-disordered breathing after several nights sleeping without CPAP/NIV, (2) percentage of recording time spent with a $SpO_2 \leq 90\%$ <2%, (3) percentage of recording time spent with a $PtcCO_2 \geq 50$ mmHg <2%, and (4) OAHI <10 events/h for patients who underwent a PSG/PG. The minor criteria were (1) minimal $SpO_2 > 90\%$, (2) maximal $tcCO_2 < 50$ mmHg, and (3) ODI ≤1.4 events/h. Forty percent of the patients could be weaned after surgery, 57% had spontaneous improvement, and another 3% were transitioned to oxygen therapy. Bronchopulmonary dysplasia, Pierre Robin syndrome, laryngomalacia, laryngeal paralysis, and Prader-Willi syndrome were the underlying diagnoses in patients who had spontaneous improvement. The median length of NIV therapy in weaned patients was 1.12 years (0.16–8.85). NIV was started at an older age in children with achondroplasia or Prader-Willi syndrome with the longest duration of CPAP being observed in patients with achondroplasia.

In long-term clinical follow-up, 35 patients with craniofacial or upper airway malformations had a second sleep study, and 7 (20%, 12% of the whole group) patients had a relapse of their OSA after a discontinuation of CPAP since 1–3 years. Among these, a patient had neurosurgical intervention and CPAP was resumed for the other 6 patients 2 of which had maxillofacial surgery afterwards. No patient died or required a tracheotomy. The authors conclude weaning in children treated with long-term NIV is possible but is highly dependent on the underlying disorder. They report no neuromuscular patients weaned from NIV with acknowledgment of prior reports of weaning these patients. The results of this study underline that long-term follow-up by specialists both during therapy and after discontinuation of NIV is necessary in children with associated disorders. Main conclusions of this review is summarised in Table 56.2.

56.4 Final Conclusions

56.4.1 Learning Points

- Obstructive sleep apnea in patients with anatomical abnormalities may persist after surgery, and NIV may be a good adjunctive therapy option.
- High-flow nasal cannula treatment may be used for upper airway anomalies providing low level of distending pressure, but patients should be monitored for carbon dioxide reten-

Table 56.2 Main conclusions/future perspective

– NIV stands as a noninvasive primary or adjunctive therapy for OSA and/or hypoventilation in patients with anatomical abnormalities of the upper and lower respiratory system
– Patients with anatomical abnormalities managed by NIV should be evaluated regularly for failure of conservative treatment and requirement of surgical airway
– Clinicians undertaking the care of patients who have genetic syndromes with anatomical or neurological abnormalities should regularly search for clinical signs and symptoms of obstructive sleep apnea
– Children with genetic diseases who have multiple comorbid conditions may require multiple surgery or procedures to be carried out. During—or in preparation of—any intervention in a child maintained in noninvasive ventilation, adjustment of therapy should be considered according to potential needs and risks, including possible transition to another mode of respiratory support
– When instituting NIV in any patient, end points of therapy should be defined. The clinician shouldn't set incompatible targets at the expense of side effects. Studies should focus on targets of therapy in patients with rare diseases who may have the involvement of more than one organ system by disease process
– In many patients and disease types, discontinuation of NIV can be possible even though the underlying disease is not curable. Follow-up of these children should include the evaluation of the need to continue NIV

tion as well as efficient oxygenation.

- Weaning from NIV is possible in many rare diseases even after long-term support; spontaneous improvement may occur, but most children with anatomical abnormalities require surgical intervention.

56.4.2 Critical Points

- In any patient with decreased lung capacity and chronic need for assistance, even temporary removal of support may result in collapse which should be foreseen and prevented.
- Long-term follow-up is necessary after weaning off NIV, since clinical conditions like OSA may relapse especially in patients with anatomical abnormalities and syndromes with comorbid factors.

56.4.3 Key Summary

Children with rare diseases usually have multiple abnormalities, comorbidities, or risk factors which multiply disease burden. NIV is an important alternative for other more invasive therapies (intubation, tracheostomy, or other surgery), or it can be used as temporary or adjunctive therapy. Follow-up of children requiring long-term NIV should include evaluation of tolerance, efficacy, and possibility of weaning NIV.

References

1. Fedor KL. Noninvasive respiratory support in infants and children. Respir Care. 2017;62(6):699–717.
2. Nattes E, Lejeune S, Carsin A, Borie R, Gibertini I, Balinotti J, Nathan N, Marchand-Adam S, Thumerelle C, Fauroux B, Bosdure E, Houdouin V, Delestrain C, Louha M, Couderc R, De Becdelievre A, Fanen P, Funalot B, Crestani B, Deschildre A, Dubus JC, Epaud R. Heterogeneity of lung disease associated with NK2 homeobox 1 mutations. Respir Med. 2017;129:16–23.
3. Castro-Codesal ML, Dehaan K, Bedi PK, Bendiak GN, Schmalz L, Katz SL, MacLean JE. Longitudinal changes in clinical characteristics and outcomes for children using long-term non-invasive ventilation. PLoS One. 2018;13(1):e0192111.
4. Nathan AM, Loo HY, de Bruyne JA, Eg KP, Kee SY, Thavagnanam S, Bouniu M, Wong JE, Gan CS, Lum LC. Thirteen years of invasive and noninvasive home ventilation for children in a developing country: a retrospective study. Pediatr Pulmonol. 2017;52(4):500–7.
5. Chau SK, Yung AW, Lee SL. Long-term management for ventilator-assisted children in Hong Kong: 2 decades' experience. Respir Care. 2017;62(1):54–64.
6. Müller-Hagedorn S, Buchenau W, Arand J, Bacher M, Poets CF. Treatment of infants with Syndromic Robin sequence with modified palatal plates: a minimally invasive treatment option. Head Face Med. 2017;13(1):4.
7. Kamata M, McKee C, Truxal KV, Flanigan KM, McBride KL, Aylward SC, Tobias JD, Corridore M. General anesthesia with a native airway for patients with mucopolysaccharidosis type III. Paediatr Anaesth. 2017;27(4):370–6.
8. Griffon L, Amaddeo A, Mortamet G, Barnerias C, Abadie V, Olmo Arroyo J, de Sanctis L, Renolleau S, Fauroux B. Sleep study as a diagnostic tool for unexplained respiratory failure in infants hospitalized in the PICU. J Crit Care. 2017;42:317–23.

9. Yeung JC, Katwa UA, Lee GS. Sleep disordered breathing in Bardet-Biedl Syndrome. Int J Pediatr Otorhinolaryngol. 2017;102:127–32.
10. Tenconi R, Khirani S, Amaddeo A, Michot C, Baujat G, Couloigner V, De Sanctis L, James S, Zerah M, Cormier-Daire V, Fauroux B. Sleep-disordered breathing and its management in children with achondroplasia. Am J Med Genet A. 2017;173(4):868–78.
11. Goudy S, Jiramongkolchai P, Chinnadurai S. Logistic regression analysis of Pierre Robin sequence patients requiring surgical intervention. Laryngoscope. 2017;127(4):945–9.
12. Léotard A, Taytard J, Aouate M, Boule M, Forin V, Lallemant-Dudek P. Diagnosis, follow-up and management of sleep-disordered breathing in children with osteogenesis imperfecta. Ann Phys Rehabil Med. 2018;61(3):135–9.
13. Curran C, Debbarma S, Sedky K. Fragile X and obstructive sleep apnea syndrome: case presentation and management challenges. J Clin Sleep Med. 2017;13(1):137–8.
14. Abraham C, Virbalas J, DelRosso LM. Severe obstructive sleep apnea in a child with Goldenhar syndrome and nasal obstruction. J Clin Sleep Med. 2017;13(6):825–7.
15. Vézina K, Laberge S, Nguyen TTD. Home high-flow nasal cannula as a treatment for severe tracheomalacia: a pediatric case report. Pediatr Pulmonol. 2017;52(8):E43–5.
16. Hatipoğlu Z, Esquinas AM, Ozcengiz D. Can high flow nasal cannula be used in a pediatric patient with tracheomalacia? Pediatr Pulmonol. 2018;53(1):9.
17. Kotoda M, Ishiyama T, Okuyama K, Matsukawa T. Anesthetic management of a child with Jeune syndrome for tracheotomy: a case report. A A Case Rep. 2017;8(5):119–21.
18. Lima CA, Andrade Ade F, Campos SL, Brandão DC, Fregonezi G, Mourato IP. Effects of noninvasive ventilation on treadmill 6-min walk distance and regional chest wall volumes in cystic fibrosis: randomized controlled trial. Respir Med. 2014;108(10):1460–8.
19. Rodriguez Hortal MC, Nygren-Bonnier M, Hjelte L. Non-invasive ventilation as airway clearance technique in cystic fibrosis. Physiother Res Int. 2017;22(3)
20. Wang KR, Zhou YF. Diffuse alveolar hemorrhage in a patient with ANCA-associated vasculitis after thyroidectomy: a case report. Medicine (Baltimore). 2019;98(8):e14630.
21. Taniguchi H, Kondoh Y. Acute and subacute idiopathic interstitial pneumonias. Respirology. 2016;21(5):810–20.
22. Moreno-González G, Corral-Ansa L, Sabater-Riera J, Solanich-Moreno X, Mañez-Mendiluce R. Pulmonary thromboembolism and diffuse alveolar hemorrhage in granulomatosis with polyangiitis vasculitis. Respir Care. 2014;59(12):e206–9.
23. Ikpeama LC, Bailes BK. Diffuse alveolar hemorrhage-induced respiratory failure. Crit Care Nurs Q. 2012;35(2):124–33.
24. Khayat A, Medin D, Syed F, Moraes TJ, Bin-Hasan S, Narang I, Al-Saleh S, Amin R. Intelligent volume-assured pressured support (iVAPS) for the treatment of congenital central hypoventilation syndrome. Sleep Breath. 2017;21(2):513–9.
25. Mastouri M, Amaddeo A, Griffon L, Frapin A, Touil S, Ramirez A, Khirani S, Fauroux B. Weaning from long term continuous positive airway pressure or non-invasive ventilation in children. Pediatr Pulmonol. 2017;52(10):1349–54.

57 Noninvasive Ventilation in Pediatric Obstructive Sleep Apnea: What's New?

Maria Cristina Mondardini, Maria Elena Latrofa, Leonardo Costa, and Fabio Caramelli

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Abbreviations

AHI	Apnea-hypopnea index
AT	Adenotonsillectomy
CPAP	Continuous positive airway pressure therapy
FRC	Functional residual capacity
HFNC	High-flow nasal cannula
NAFLD	Non-alcoholic fatty liver disease
NPPV	Noninvasive positive pressure ventilation
OSAS	Obstructive sleep apnea syndrome
PAP	Positive airway pressure therapy
PSG	Polysomnography
REM	Rapid eye movement
SDB	Sleep disordered breathing

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57.1 Introduction

Obstructive sleep apnea syndrome (OSAS) is a respiratory disorder that consists in episodic complete cessation of respiratory airflow (apnea) or partial prolonged airflow limitation (hypopnea) during sleep due to upper airway obstruction [1].

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OSAS is the most common form of obstructive sleep disordered breathing (SDB) in children and affects about 4% of the pediatric population with a peak prevalence between ages 3 and 6 years because of the pharyngeal lymphatic tissue hypertrophy compared to the limited size of the upper airway.

Craniofacial abnormalities as midfacial hypoplasia, high arch palate, macroglossia, micrognathia and retrognathia, Pierre Robin syndrome, Beckwith-Wiedemann syndrome, Crouzon syndrome, or other syndromal diagnoses are additional underlying etiological factors as well as neuromuscular disorders. Children with Down syndrome have increased vulnerability to OSAS due to confluence of smaller bony structure, larger soft tissues, and lower airway tone. OSAS peak incidence reaches up to 66% in children with Down syndrome [2].

Severe OSAS disrupts the normal sleep pattern and leads to impairments in ventilation; the respiratory pauses may induce hypercapnia and hypoxia. OSAS is associated with short- and long-term consequences including neuropsychological dysfunction and cardiovascular disease. The patients are at risk of ventricular hypertrophy, hypertension, tachycardia, pulmonary hypertension, and autonomic dysregulation. This pathology can lead to neurocognitive deficits, learning disability, behavior abnormalities, and metabolic derangements such as insulin resistance [3, 4]. The early recognition and treatment is essential to prevent deleterious sequelae.

The economic burden of OSA disease is high due to treatments, visits, hospitalizations, and high rates of upper respiratory tract infections [5].

57.2 Methods

A systematic search was made using PubMed/MEDLINE, EMBASE, and Cochrane Library databases. The following Medical Subject Headings (MeSH) were identified to build the search: "Sleep Apnea Syndromes," "Noninvasive Ventilation," and "Continuous Positive Airway Pressure." Custom date range from January 2017 to March 2019 and child age additional filter were applied. Inclusion criteria were prospective and retrospective studies conducted in pediatric ages and narrative reviews and systematic reviews focusing on obstructive sleep apnea syndrome epidemiology, pathophysiology, recent innovative investigations, and treatments. Articles written in languages other than English were excluded. The search resulted in 40 citations; after excluding studies that did not meet inclusion criteria based on abstracts review, 15 articles were selected and analyzed (Table 57.1).

Table 57.1 Summary of recent literature included

Author [ref], year of publication, state	Study design	Objective	Main results
Pullano et al. [14] 2017 Italy/USA	Review	To review sleep apnea monitoring and therapy devices employed in pediatric treatment and the emerging technologies proposed for domestic and clinical use	In recent years technology attempts to overcome monitoring and therapy devices limitations have been made, but further development still needs together with trials to prove their effectiveness
Khirani et al. [18] 2017 France	Observational	To compare the automatic scoring of residual respiratory events by the built-in software of continuous positive airway pressure (CPAP) devices with a manual scoring on the CPAP tracing, integrated SpO_2, and in-lab polysomnography (PSG)	The manual scoring of respiratory events by CPAP devices with the addition of an integrated SpO_2 signal may be helpful to assess CPAP efficacy

Table 57.1 (continued)

Author [ref], year of publication, state	Study design	Objective	Main results
Katz et al. [22] 2017 Canada	Prospective multicenter cohort study	To determine (1) the prevalence of cardiometabolic disease associated with obesity and sleep disordered breathing (SDB) and (2) whether PAP improves markers of cardiometabolic disease, in youth with obesity and newly diagnosed moderate-severe SDB	Metabolic dysfunction and hypertension are highly associated with obesity and SDB There are no statistically significant improvements in cardiometabolic markers 1 year after the prescription of PAP therapy, although clinically relevant improvements were seen in insulin resistance and systolic blood pressure load
Riley et al. [5] 2017 USA	Observational	To estimate costs and benefits of an intensive program that aimed to improve adherence in CPAP treatment relative to a standard approach	An intensive CPAP program leads to substantially higher adherence, follow-up, and CPAP titration rates; however costs are higher
Kaditis et al. [6] 2016 Europe	Review—European Respiratory Society (ERS) statement	To summarize the evidence and current practice on the diagnosis and management of obstructive SDB in childhood referring to children aged 2–18 years	Seven management steps regarding diagnosis (risk factors, coexisting morbidity, factors predicting long-term persistence, objective diagnosis and assessment of severity) and treatment (indications, stepwise treatment approach, recognition and management of persistent forms) are suggested
Kaditis et al. [15] 2017 Europe	Review—European Respiratory Society (ERS) statement	To summarize the evidence and current practice on the diagnosis and management of obstructive SDB in children aged 1–23 months	Similar to previous statement, six management steps are suggested. Obstructive SDB in children aged 1–23 months is a multifactorial disorder that requires assessment and treatment of all underlying abnormalities that cause upper airway obstruction during sleep
Sundaram et al. [23] 2018 USA	Pilot prospective	To determine the effects of treating obstructive sleep apnea/nocturnal hypoxia on pediatric nonalcoholic fatty liver disease (NAFLD) severity and oxidative stress	Treatment of obstructive sleep apnea/nocturnal hypoxia with CPAP in children with NAFLD may reverse parameters of liver injury and reduce oxidative stress
Fleck et al. [16] 2018 USA	Review	To address clinical indications for magnetic resonance imaging (MRI) protocol techniques and interpretation of the findings that help guide surgery. To suggest the ideal team members to involve in an effective multidisciplinary program and the basic anesthesia requirements	Dynamic cine MRI of the upper airway is a useful adjunct to evaluate children with persistent obstructive sleep apnea (OSA) and to identify anatomical and physiological causes of airway collapse that can be addressed surgically
Alsubie and BaHammam [10] 2017 Saudi Arabia	Review	To analyze the major differences between pediatric and adult OSA and demonstrate why children are not little adults	Differences in sleep and respiratory physiology as well as OSA symptoms and treatment options between pediatric and adults are illustrated

(continued)

Table 57.1 (continued)

Author [ref], year of publication, state	Study design	Objective	Main results
Xanthopoulos et al. [25] 2017 USA/China	Survey	To evaluate the relationship between caregiver- and patient-reported self-efficacy, risk perception, outcome expectancies, and adherence to CPAP and moreover how demographic factors influence these relationships	Strategies to improve self-efficacy when initiating CPAP with children, adolescents, and their families may promote adherence. There is a significant association between a greater caregiver-reported self-efficacy and adherence
Chen et al. [24] 2017 USA	Case-control	To determine if real-time MRI (RT-MRI) method during CPAP can be used to measure neuromuscular reflex and/or passive collapsibility of the upper airway in adolescent with OSA and obesity	Simultaneous multi-slice (SMS) RT-MRI during CPAP can reproducibly identify physiological traits and anatomical risk factors that are valuable in the assessment of OSA. Furthermore this technique can locate the most collapsible airway sites with higher treatment priority
Mihai et al. [27] 2017 Australia	Retrospective	To compare autotitrating PAP (autoPAP)-derived treatment pressure to CPAP treatment pressure following titration PSG	Manual CPAP treatment pressure following titration PSG is the gold standard for establishment of treatment adequacy and fixed CPAP pressure prescription, but the use of autoPAP while waiting for such a test optimizes CPAP therapy over that period Mean autoPAP pressure is usually below treatment pressure determined by titration PSG
Dudoignon et al. [2] 2017 France	Retrospective cohort	To describe characteristics, sleep respiratory parameters, and management of OSA in a large cohort of children with down syndrome	The prevalence of OSA is high in Down syndrome, and upper airway surgery is not always able to correct OSA. Noninvasive respiratory support represents an effective treatment, and good compliance may be achieved in a majority of these patients
Brockbank [1] 2017 USA	Review	To update the pathophysiology and treatment of pediatric OSAS	Mechanical airway obstruction, neuromotor abnormalities, and central ventilatory control instability are all involved in the pathophysiology of childhood OSAS. Several surgical and non-surgical treatment are discussed
Hawkins et al. [28] 2017 USA	Observational	To report the efficacy, titration protocol, and potential mechanisms of high-flow nasal cannula (HFNC) treatment in children with OSA and CPAP intolerance	HFNC reduces respiratory events, improves oxygenation, reduces heart rate, and may be effective for CPAP-intolerant children with moderate-to-severe OSA
DelRosso et al. [21] 2018 USA/Italy	Retrospective	To evaluate the effect of CPAP treatment on blood pressure (BP) in children with OSA	Treatment with CPAP for 6 months in children with OSA reduces systolic BP suggesting that early treatment is effective in reducing BP and, possibly, other cardiovascular complications

This chapter also included the relevant contents of the European Respiratory Society (ERS) statement on the diagnosis and management of obstructive sleep disordered breathing in children aged 2–18 years albeit this seminal paper was published in 2016 [6].

57.3 Results

57.3.1 Update on Pathophysiological Mechanisms

The pathophysiology of OSAS is multifactorial (Fig. 57.1). In childhood OSAS the obstruction of the upper airway by tonsils and adenoids is a major factor, but it is not the only one since not all children also with severe adenotonsillar hypertrophy develop OSAS. Neuromotor factors and abnormalities in ventilatory control systems must significantly contribute to the pathogenesis [7].

Hypercapnia, hypoxia, or subatmospheric pressure in the upper airway activate upper airway dilator muscles. The tone increase of these accessory muscles of respiration is centrally controlled and may compensate for a narrow airflow. Children with OSAS could be unable to maintain adequate neuromuscular tone during changes in upper airway pressure [8, 9].

OSAS is different between adult and child because of different features in sleep and respiratory physiology.

REM (rapid eye movement) sleep is characterized by an irregular breathing pattern with variable respiratory rate and tidal volume. Because children sleep more than adults and have a higher percentage of REM sleep, they can more easily develop REM-associated sleep disorders such as OSAS [10].

Infants and young children have a lower functional residual capacity (FRC) consequent to an increased chest wall compliance which predisposes to atelectasis. Furthermore, infants show a lower diaphragmatic fatigue threshold due to a very low muscle mass, so they are prone to decompensate [11].

Arousal is an important protective mechanism against sleep disordered. In healthy children, arousals are less frequent than in adults because they have a higher arousal threshold which responds more to increased upper airway

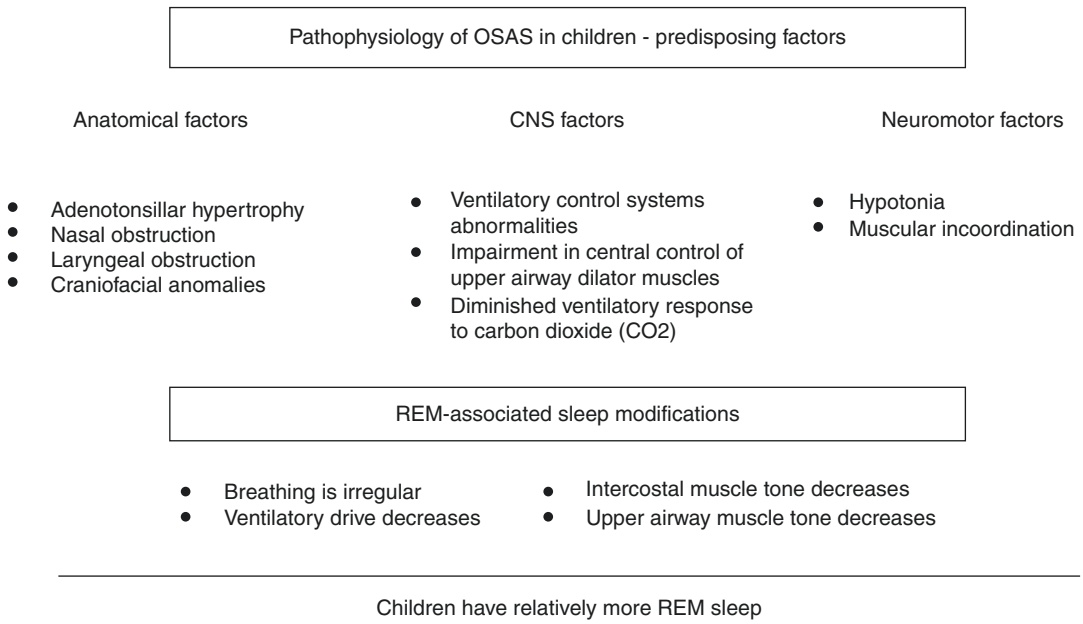

Fig. 57.1 Pathophysiology of OSAS

resistance and hypercapnia and less to mild hypoxia. Children with OSAS seem to have an even loftier threshold for arousal in response to inspiratory resistive loads [12, 13].

57.3.2 Update on Diagnosis

Obstructive sleep disordered breathing (SDB) includes a spectrum of clinical entities with variable severity. The prevalence of habitual snoring in children is about 7%, while OSAS prevalence ranges from 1% to 5%. The first step to diagnosticate SDB is to identify children at risk, recognizing pathologies frequently associated with this condition, and then to make a careful physical examination. History and clinical assessment should be deepened with instrumental evaluations and finally with polysomnography. In some situations where polysomnography is not readily available, other tests can be considered, such as nighttime pulse oximetry or other approaches for the automated detection of apneic events [14].

Children presenting with snoring and mouth breathing are considered at risk for SDB. Other significant medical conditions, as reported above, are obesity or failure to thrive, craniofacial abnormalities, and neuromuscular disorder. Complex abnormalities (achondroplasia, Chiari malformation, Down syndrome, Ehlers-Danlos syndrome, mucopolysaccharidoses, Prader-Willi syndrome) are independent factors associated with the development of OSAS.

Tonsillar size (Brodsky score) is informative together with oral cavity evaluation but a weak predictor of presence or severity of SDB [15].

Instrumental examinations such as lateral neck radiography, flexible nasopharyngoscopy, magnetic resonance imaging (MRI), dynamic cine MRI, and computed tomography (CT) are useful for the evaluation of the airway size in selected cases or to determine surgical indication [16].

Polysomnography (PSG) is the gold standard for the diagnosis and assessment of SDB severity; it involves monitoring and recording multiple physiological signals in parallel that together reflects sleep physiology. PSG is indicated when children show symptoms of SDB and prior to adenotonsillectomy.

Rules for the scoring of sleep, respiratory, and associated events in polysomnographic recordings are provided from the American Academy of Sleep Medicine (AASM) in the AASM manual. The AHI (the number of mixed, obstructive, and central apneas and hypopneas per hour of total sleep time) is the most commonly used polysomnography parameter for the description of SDB severity.

OSAS is defined as an AHI ≥2 episodes/h or an obstructive apnea index (obstructive apneas per total sleep time) ≥1 episode/h in the presence of SDB symptoms, adenotonsillar hypertrophy with or without obesity, and no other abnormalities. Mild OSAS is defined with an AHI of 2–5, moderate-to-severe OSAS is defined with an AHI >5, while severe OSAS is defined with an AHI >10.

Nighttime pulse oximetry is used for the diagnosis and assessment of SDB when PSG is not available, but the rate of inconclusive results for this test is high. Polysomnography is mandatory also to titrate continuous positive airway pressure (CPAP) or noninvasive positive pressure ventilation (NPPV) and is then repeated at least annually (or earlier if there is a clinical indication).

To complete the diagnostic pathway, in some cases the drug-induced sleep endoscopy is indicated as a second line, after PSG [6].

57.3.3 Update on Treatment

Treatment interventions should be applied stepwise until the goal of resolution of OSA is reached.

Adenotonsillectomy (AT) is the first-line treatment in most cases. Other more invasive surgical procedures may be indicated for complex craniofacial abnormalities, subglottic stenosis, or laryngomalacia.

In children with OSAS due to mild craniofacial anomalies that predispose to narrowed upper airway some effective treatment options should be encouraged. An oral appliance, oropharyngeal

exercises, and functional orthodontic devices, as rapid maxillary expansion, must be evaluated as a unique treatment or additionally to adenotonsillectomy [17].

Regarding the NIV treatment, the indications for positive airway pressure (PAP) are residual OSAS after adenotonsillectomy; OSAS related to obesity, craniofacial abnormalities, or neuromuscular disorders; and OSAS in children with surgical contraindication or in children awaiting surgery. Indication for NPPV is nocturnal hypoventilation (e.g., end-tidal carbon dioxide tension (PCO_2) >50 mmHg for >25% of total sleep time or peak end-tidal PCO_2 ≥55 mmHg) or failure of CPAP [6].

NIV treatment must be titrated and regularly reassessed by PSG [18]. In pediatrics, indeed, anatomic and neurofunctional growth of the pharynx, larynx, and maxillo-mandibular-frontal complex involves periodic changes in PAP level. PAP was successfully introduced by Guilleminault et al. for children with OSAS by severe underlying craniofacial disorders, as an alternative to the tracheotomy [19].

PAP is usually administered noninvasively using interfaces applied to the nose, mouth, and nose combined or full-face. The most common form of PAP ventilation is CPAP. CPAP acts as a pneumatic "splint" preventing upper airway collapse during sleep. Positive pressure increases the cross-sectional upper airway area and provides an increase in the lateral airway diameter; it also reduces both edema resulting from chronic vibration and occlusion and lateral pharyngeal wall thickness. Even a small increase in airway diameter can significantly decrease the airway resistance since this is inversely proportional to the fourth power of the airway radius [20].

Children with OSAS have higher systolic blood pressure; failure to treat OSA may result in an increased blood pressure, while treatment with CPAP decreases the systolic blood pressure. This finding suggests that early treatment is effective in reducing hypertension and probably other cardiovascular complications [21, 22].

Emerging evidence demonstrates that obesity-related obstructive sleep apnea is associated with nonalcoholic fatty liver disease (NAFLD) even in children. Pediatric patients with NAFLD and OSAS have more advanced liver disease and fibrosis than those without OSAS. A recent study showed that CPAP treatment in children with NAFLD may reverse liver injury and reduce the oxidative stress preventing progression of NAFLD [23].

The underlying mechanisms of airway tissue response to CPAP level change remain unclear. In a recent study, a simultaneous multi-slice real-time MRI (RT-MRI) technique is applied to image and quantify upper airway changes during rapid changes in CPAP pressure level. Four adolescents with OSA and obesity and three healthy volunteers were studied to determine if RT-MRI can be used to measure neuromuscular reflex and collapsibility of airway during CPAP. Authors measured upper airway loop gain (UALG) and fluctuation of airway area (FAA), the first parameter as an indicator of the stability of neuromuscular reflex system indicator and the second of the passive collapsibility of upper airway. The authors concluded that airway behavior in OSAS patients possesses large variations. Patients may deserve personalized examination before proceeding to a specific and personalized treatment. They also demonstrated that RT-MRI measurement can help to locate the most collapsible airway site. This experiment can be useful for a detailed CPAP titration or surgery planning [24].

CPAP is effective, but adherence is poor, mostly in the early stages. During pressure titration at the initiation of CPAP treatment, in fact, the drop-out rate may be high because children and parents do not quickly find the expected benefits [25].

Newer CPAP technologies and different varieties of interface have improved in recent years, to enhance acceptance and adherence of treatment [14]. Establishing a comfortable but effective interface is key to the treatment success, but comparative studies between different varieties are limited in children. In younger children and in those with craniofacial anomalies may be difficult to find a correctly fitting mask [26]. A poorly fitting mask leads to air leak and ineffective pressure, and tightening it around the face

can develop injuries or long-lasting deformations.

Autotitrating CPAP (autoPAP) or self-adjusting PAP provides variable pressure by constantly monitoring the patient's airflow at the interface level using different algorithms, depending on the device manufacturer. Therefore, autoPAP delivers different pressures in the different phases of sleep (REM or NREM) and based on sleeping positions (supine or non-supine), in response to the degree of upper airway obstruction. Although autoPAP may improve the compliance and the rapid achievement of therapeutic pressure in adult OSAS, it is not well studied in children. A retrospective review analyzed a group of children who initiated on auto-PAP showing that autoPAP was a safe and effective method to quickly reach the therapeutic CPAP pressure during time of CPAP initiation. The same authors had previously shown that establishing the correct treatment pressure early in therapy avoids long periods of uncomfortable subtherapeutic treatment and enhances adherence. Thus, autoPAP use during the initiation process may contribute to improved adherence. Authors concluded that manual CPAP titration PSG is still the gold standard to determine optimal CPAP pressure prescription, but the use of autoPAP while waiting for such a test optimizes CPAP therapy over that period [27].

A recent economic analysis estimated the effectiveness of an intensive CPAP program in improving adherence to treatment, proving that an intensive care model may lead to substantially higher follow-up and CPAP titration rates though costs are higher. A multidisciplinary healthcare team of nursing, physician, psychologist, and respiratory therapist from the patient's home hospital was involved. The team took care of patients and their families allowing earlier initiation of CPAP therapy and providing educational support [5].

Drug therapy with an intranasal corticosteroid and oral montelukast was used as CPAP alternatives for mild OSAS and may show, after several weeks of treatment, reduction in AHI. Postural and behavioral therapies may be adjuvant effective at reducing the severity of OSA.

High-flow humidified air via open nasal cannula (HFNC) has been proposed for CPAP-intolerant children with moderate-to-severe OSA. In the Hawkins et al. pilot study, authors evaluated the efficacy of HFNC in the treatment of ten OSAS pediatric patients (eight prospective evaluated) CPAP-intolerant. They concluded that HFNC is effective in treating moderate-to-severe OSAS. This treatment reduces respiratory events, improves oxygenation, reduces heart rate, and does not alter sleep quality. Potential HFNC mechanisms of action may be the activation of the protective airway reflex via stimulation of mechanoreceptors and thermoreceptors that increase airway tone and improve its patency. Moreover, HFNC reduces the dead space improving gas exchange [28].

57.3.4 Infant Features

In this chapter the term "infant" includes children aged between 1 and 23 months. Infants represent a unique subgroup with a predisposition to OSAS and thus require a specific diagnostic pathway and treatment (Table 57.2). Spontaneous neck flexion, high nasal resistance, reduced airway stiffness, and the abovementioned reduction in FRC predispose to obstructive events and desaturation during sleep. Furthermore daily sleep lasts longer ranging from 17 h in newborns to 12 h at 2 years. Nasal occlusion results in a switch to oral breathing only in a minority of infants [29].

Craniofacial syndromes, choanal stenosis, laryngomalacia, and subglottic stenosis may be associated with sleep-related airway obstruction. In infants the most common symptoms related to OSAS are movements during sleep, repeated awakenings, and failure to thrive. During the first 3 months of life, physical examination may reveal adenoidal hypertrophy, whereas tonsillar hypertrophy appears after the 6 months of age. The PSG is the gold standard both for diagnosis and staging even in infant OSAS, with the same AHI limits of adults for the severity degree. In some complex syndromes, nocturnal pulse oximetry can be preferred. Drug-induced sleep endoscopy may be used to select therapeutic strategy and the

Table 57.2 Differences in obstructive sleep apnea between infants and children

Characteristics	Children 2–18 years	Infants <24 month
Comorbid conditions	Adenotonsillar hypertrophy, obesity	Nasal obstruction, laryngeal obstruction (laryngomalacia), craniofacial abnormalities, complex syndrome, neuromuscular disorders
Signs/symptoms	Snoring, apnea, mouth breathing during sleep	Restless sleep, repeated awakenings, mouth breathing, symptoms reflecting obstruction frequently present also during wakefulness
Morbidity	Systemic hypertension, increased sympathetic nervous system activity, metabolic dysfunction, attention-deficit/hyperactivity disorder (ADHD), cognitive deficiencies, nocturnal enuresis	Pulmonary hypertension, failure to thrive
Diagnosis	Polysomnography, lateral neck radiography, flexible nasopharyngoscopy, magnetic resonance imaging (MRI), dynamic cine MRI, and computed tomography (CT)	Polysomnography (at least 4 h), nocturnal pulse oximetry, endoscopy
Assessment of severity: AHI cutoff values	No differences	
Surgical treatment	Adenotonsillectomy, supraglottoplasty, glossectomy, mandibular distraction, midface advancement, tracheostomy	Supraglottoplasty (laryngomalacia) Craniofacial surgery Adenoidectomy from age 3 months, adenotonsillectomy from age 6 months
Tonsillectomy risk	Normal	Highest for <2 years (double compared with 3–5 years)
NIV indications	Continuous positive airway pressure (CPAP): moderate-to-severe OSAS who are not candidate or do not improve after surgical intervention. OSAS related to obesity Noninvasive positive pressure ventilation (NPPV): Neuromuscular disorders High-flow nasal cannula (HFNC)	CPAP: moderate-to-severe OSAS who are not candidate or do not improve after surgical intervention A temporary intervention while waiting craniofacial surgery NPPV: Neuromuscular disorders
Medical treatment	Maxillary expansion Oral and functional orthodontic appliances Nasal steroids therapy Oral montelukast	Oral and functional orthodontic appliances

sequence of treatment interventions. In this age group, risk associated with adenotonsillectomy is increased. CPAP is indicated for moderate-to-severe OSAS in children <24 months of age who are not candidates for or do not improve after surgical intervention. Noninvasive positive pressure ventilation (NPPV) is indicated in case of OSAS coexisting with hypoventilation. In children <23 months of age, following initiation of CPAP, PSG is mandatory every 2–4 months in the first year of life and then every 6 months to confirm the continued need for treatment and to titrate positive airway pressure (PAP) [15].

57.4 Final Conclusions

57.4.1 Learning Points

- Surgical intervention is the first-line treatment in most cases of OSAS. Noninvasive ventilation treatment by continuous positive airway pressure (CPAP) is prescribed for patients who have residual syndrome after surgical treatment or who are not candidates for surgery.
- Positive pressure level must be titrated and regularly reassessed by PSG.

- Some patients, before proceeding to a specific and personalized treatment, may deserve emerging imaging, like dynamic MRI, in order to quantify upper airway changes and detailed CPAP pressure titration.
- Autotitrating CPAP may improve the compliance and the rapid achievement of therapeutic pressure during time of CPAP initiation.
- CPAP is effective also in reducing serious sequelae associated with OSAS such as systolic hypertension, metabolic dysfunction, and oxidative stress.
- For CPAP-intolerant children with moderate-to-severe OSAS, high-flow humidified air via nasal cannula (HFNC) has been recently used with promising results, but which still need more evidence.

57.4.2 Critical Points

- The economic burden of OSA disease is high due to treatments, visits, hospitalizations, and high rates of upper respiratory tract infections.
- Adherence to CPAP is an increasingly critical clinical concern.
- It is difficult to compare different technologies and methodologies for monitoring and treatment of pediatric OSA, due to the poor definition of standard parameters that take into account the different physiological and maturational changes of children breathing.
- Moreover, Randomized Controlled Trials comparing ventilation modalities as well as treatment strategies are currently lacking and most of the evidence comes from retrospective studies, case series or expert opinions.

57.4.3 Future Directions

- Develop adherence-promoting interventions to treatment strategies.
- Organize effective treatment management programs involving multidisciplinary team: pediatric pneumologist, intensivist, surgeon, respiratory physiologist, and orthodontist.
- Develop new medical devices and technologies for monitoring and therapy to ameliorate patient comfort.
- Investigate on the efficacy and safety of HFNC improving evidence on its indication and appropriate flow rate.

References

1. Brockbank JC. Update on pathophysiology and treatment of childhood obstructive sleep apnea syndrome. Paediatr Respir Rev. 2017;24:21–3.
2. Dudoignon B, Amaddeo A, Frapin A, et al. Obstructive sleep apnea in Down syndrome: benefits of surgery and noninvasive respiratory support. Am J Med Genet A. 2017;173(8):2074–80.
3. Marcus CL. Sleep-disordered breathing in children. Am J Respir Crit Care Med. 2001;164(1):16–30.
4. Blunden S, Lushington K, Kennedy D, et al. Behavior and neurocognitive performance in children aged 5–10 years who snore compared to controls. J Clin Exp Neuropsychol. 2000;22(5):554–68.
5. Riley EB, Fieldston ES, Xanthopoulos MS, et al. Financial analysis of an intensive pediatric continuous positive airway pressure program. Sleep. 2017;40(2)
6. Kaditis AG, Alonso Alvarez ML, Boudewyns A, et al. Obstructive sleep disordered breathing in 2 to 18-year-old children: diagnosis and management. Eur Respir J. 2016;47(1):69–94.
7. Marcus CL. Pathophysiology of childhood obstructive sleep apnea: current concepts. Respir Physiol. 2000;119(2–3):143–54.
8. Marcus CL, Lutz J, Hamer A, et al. Developmental changes in response to subatmospheric pressure loading of the upper airway. J Appl Physiol. 1999;87(2):626–33.
9. Marcus CL, Katz ES, Lutz J, et al. Upper airway dynamic responses in children with the obstructive sleep apnea syndrome. Pediatr Res. 2005;57(1):99–107.
10. Alsubie HS, BaHammam AS. Obstructive sleep apnoea: children are not little adults. Paediatr Respir Rev. 2017;21:72–9.
11. Muller N, Volgyesi G, Bryan MH, et al. The consequences of diaphragmatic muscle fatigue in the newborn infant. J Pediatr. 1979;95:793–7.
12. Arens R, Marcus CL. Pathophysiology of upper airway obstruction: a developmental perspective. Sleep. 2004;27(5):997–1019.
13. Marcus CL, Moreira GA, Bamford O, et al. Response to inspiratory resistive loading during sleep in normal children and children with obstructive apnea. J Appl Physiol. 1999;87(4):1448–54.
14. Pullano SA, Mahbub I, Bianco MG, et al. Medical devices for pediatric apnea monitoring and ther-

apy: past and new trends. IEEE Rev Biomed Eng. 2017;10:199–212.
15. Kaditis AG, Alonso Alvarez ML, Boudewyns A, et al. ERS statement on obstructive sleep disordered breathing in 1- to 23-month-old children. Eur Respir J. 2017;50(6)
16. Fleck RJ, Shott SR, Mahmoud M, et al. Magnetic resonance imaging of obstructive sleep apnea in children. Pediatr Radiol. 2018;48(9):1223–33.
17. Carvalho FR, Lentini-Oliveira DA, Prado LB, et al. Oral appliances and functional orthopaedic appliances for obstructive sleep apnoea in children. Cochrane Database Syst Rev. 2016;10:CD005520.
18. Khirani S, Delord V, Olmo Arroyo J, et al. Can the analysis of built-in software of CPAP devices replace polygraphy in children? Sleep Med. 2017;37:46–53.
19. Guilleminault C, Nino-Murcia G, Heldt G, et al. Alternative treatment to tracheostomy in obstructive sleep apnea syndrome: nasal continuous positive airway pressure in young children. Pediatrics. 1986;78(5):797–802.
20. Schwab RJ, Pack AI, Gupta KB, et al. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. Am J Respir Crit Care Med. 1996;154:1106–16.
21. DelRosso LM, King J, Ferri R. Systolic blood pressure elevation in children with obstructive sleep apnea is improved with positive airway pressure use. J Pediatr. 2018;195:102–7.
22. Katz SL, MacLean JE, Hoey L, et al. Insulin resistance and hypertension in obese youth with sleep-disordered breathing treated with positive airway pressure: a prospective multicenter study. J Clin Sleep Med. 2017;13(9):1039–47.
23. Sundaram SS, Halbower AC, Klawitter J, et al. Treating obstructive sleep apnea and chronic intermittent hypoxia improves the severity of nonalcoholic fatty liver disease in children. J Pediatr. 2018;198:67–75.
24. Chen W, Gillett E, Khoo MCK, et al. Real-time multislice MRI during continuous positive airway pressure reveals upper airway response to pressure change. J Magn Reson Imaging. 2017;46(5):1400–8.
25. Xanthopoulos MS, Kim JY, Blechner M, et al. Self-efficacy and short-term adherence to continuous positive airway pressure treatment in children. Sleep. 2017;40(7)
26. Ramirez A, Delord V, Khirani S, et al. Interfaces for long-term noninvasive positive pressure ventilation in children. Intensive Care Med. 2012;38(4):655–62.
27. Mihai R, Vandeleur M, Pecoraro S, et al. Autotitrating CPAP as a tool for CPAP initiation for children. J Clin Sleep Med. 2017;13(5):713–9.
28. Hawkins S, Huston S, Campbell K, et al. High-flow, heated, humidified air via nasal cannula treats CPAP-intolerant children with obstructive sleep apnea. J Clin Sleep Med. 2017;13(8):981–9.
29. Katz ES, Mitchell RB, D'Ambrosio CM. Obstructive sleep apnea in infants. Am J Respir Crit Care Med. 2012;185(8):805–16.

58 Noninvasive Ventilation and High-Flow Nasal Cannula Alternate Use in Pediatric Patients

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Abbreviations

ARF	Acute respiratory failure
BPAP	Bilevel positive airway support
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
HFNC	High-flow nasal cannula therapy
HR	Heart rate
IPAP	Inspiratory positive airway pressure
LOS	Length of stay
NIV	Noninvasive ventilation treatment
OAHI	Obstructive apnea-hypopnea index
OSA	Obstructive sleep apnea
PICU	Pediatric intensive care unit
RCTs	Randomized controlled trials
RF	Respiratory failure
RR	Respiratory rate
SA	Severe asthma
SpO_2	Oxyhemoglobin saturation

In this chapter, we described high-flow nasal cannula therapy (HFNC) and noninvasive ventilation treatment (NIV) modalities and told about their usage in pediatric intensive care unit (PICU). We discussed articles published within the last 2 years comparing NIV, especially continuous positive airway pressure (CPAP) and HFNC therapies in pediatric patients of different health situations as hypoxemic respiratory failure (RF), severe asthma exacerbations, acute bronchiolitis, pneumonia, and acute respiratory failure (ARF) after cardiac surgery. We paid special attention to choose the systematic reviews and meta-analysis and original articles with the largest study population issued in years between 2017 and 2019. However, our search for some of these topics resulted in only one or a few studies in childhood,

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and the issue dates were earlier than 2017. To ensure the integrity of the subject, we included some of the earlier studies and some of the adult studies where pediatric studies were not found.

58.1 High-Flow Nasal Cannula in Pediatric Intensive Care

Over the last decade, HFNC therapy has emerged as a new method to provide respiratory support for bronchiolitis. Nasal cannulae, which were first used to administer supplemental oxygen (low-flow therapy) on a large scale, also showed the capability for the administration of nasal CPAP through HFNC as it developed. Needless to say, apart from meeting specific physical criteria, a relative humidity of 100% and a temperature of 37 °C are the basic requirements of this intervention. The application of HFNC in the neonatal intensive care unit and PICU has developed significantly during the last decade due to the fact that not only is this system capable of providing a specific percentage of the respiratory oxygen, but it can also administer noninvasive respiratory support of constant-flow CPAP without the need for any further equipment [1].

HFNC is a well-tolerated noninvasive method of ventilatory support that permits high inspired gas flows at rates up to 8 L/min in infants and up to 60 L/min in children and adults with or without increased oxygen concentration [2, 3]. The increased flows are tolerated because the air is humidified; provision of HFNC requires a special circuit—it cannot be provided by simply turning up the flow from the wall unit. Flow rates ≥6 L/min can generate positive expiratory pressures in the range of 2–5 cm H_2O. The size of the nasal cannula, which is determined by fit, affects the size of the circuit and maximum amount of flow. In observational studies, HFNC has been associated with decreased respiratory rate, decreased work of breathing, and better oxygenation in patients of all ages and with a variety of conditions, including premature infants with respiratory distress syndrome, infants with bronchiolitis, and adults with hypoxemic respiratory failure. For the treatment of bronchiolitis in infants and children younger than 2 years, 8 L/min is generally the maximum flow rate, but higher rates may be used if cannula size permits [4, 5].

HFNC oxygen therapy is a simple system initially consisting in an air-oxygen blender directly connected to a flow meter (set up to 70 L/min) or in a turbine connected to an oxygen flow meter. The gas mixture containing up to 100% of oxygen is routed to a heated humidifier delivering gas conditioned at 37 °C and completely saturated with water (relative humidity, 100%). Gases are delivered to the patient via a simple interface, nasal prongs or cannulae, which are configured to provide high flow and limit water condensation.

Contraindications to HFNC include abnormalities of the face or airway that preclude an appropriate-fitting nasal cannula [6]. Relative contraindications include confusion or agitation, vomiting, excessive secretions, and bowel obstruction. In an observational study, nonresponse to HFNC has been associated with lower pretherapy pH and higher pretherapy PCO_2, highlighting the importance of early initiation [7].

Complications of HFNC include abdominal distension, aspiration, barotrauma, and pneumothorax (rare) [6]. However, the risk of pneumothorax is lower with HFNC than with mechanical ventilation following endotracheal intubation.

Infants receiving HFNC who are clinically deteriorating may develop significant respiratory acidosis (hypercapnia) despite high oxygen saturations (if they are receiving supplemental O_2). Oxygen saturation is a poor indicator of impending respiratory failure, which is better indicated by marked retractions, decreased or absent breath sounds, fatigue, and poor responsiveness to stimulation (e.g., weak or no cry). Blood gas analysis to assess ventilation (i.e., PCO_2 levels) may be warranted in infants receiving HFNC who become more dyspneic and/or tachycardic.

58.2 Noninvasive Ventilation Use in Pediatric Intensive Care

Noninvasive ventilation describes the delivery of mechanical respiratory support without the need for endotracheal intubation through an interface

(e.g., nasal prongs or mask, face mask, or helmet) that delivers CPAP or bilevel positive airway support (BPAP) [8]. CPAP refers to the administration of continuous positive airway pressure during all phases of the respiratory cycle of a spontaneously breathing patient, whereas BPAP, as the name implies, delivers two set levels of positive airway pressure, one during inspiration (IPAP) and one during expiration (EPAP). When the ventilator detects inspiratory flow, it delivers a higher inspiratory pressure until sensing a reduction in flow or when reaching a set inspiratory time limit. When inspiration terminates (based on flow or time), the device cycles to a lower expiratory pressure.

Both CPAP and BPAP are referred to as NIV and have a goal that is consistent with improving or adequately restoring the functional residual capacity in the lung while minimizing the inspiratory work of breathing. The primary goal for the use of CPAP is to improve oxygenation by improving functional residual capacity and lung inflation in patients with an adequate respiratory drive. NIV improves the effective minute ventilation enhancing CO_2 elimination by augmenting inspiration in patients with respiratory failure or expected respiratory failure without the use of an artificial airway. NIV also offers avoiding the risks and complications related to the placement of an endotracheal tube, administration of sedation and neuromuscular blockade, and delivery of invasive mechanical ventilation. NIV can be initiated during critical care transport, in the emergency department, in an intensive care unit, and in some "step-down" (e.g., intermediate or progressive care) units [9]. The first contraindication of NIV is the need for emergent intubation in some circumstances such as cardiac or respiratory arrest. Other contraindications of NIV are inability to cooperate, protect the airway, or clear secretions; impaired consciousness; nonrespiratory organ failure that is acutely life threatening; facial surgery, trauma, or deformity; high aspiration risk; prolonged duration of mechanical ventilation anticipated; and recent esophageal anastomosis. The major complications of NIV are barotrauma, aspiration risk, and hemodynamic instability. Minor complications can be regarded as skin breakdown, gastric distension, nasal mucosal trauma, and ocular injury.

58.3 Can High-Flow Nasal Cannula Be an Alternative for Noninvasive Ventilation in Pediatric Patients?

The use of HFNC is firstly begun in neonatal intensive care unit for its ease of use and increased patient tolerance. Then its use widened to children and adults. In recent years its use is more frequent, and we are now discussing whether it is an alternative of NIV in children. In literature search, studies describing the comparison of HFNC use versus NIV are more frequent in children with bronchiolitis, asthma, and all-cause ARF. However, there are few studies describing the postextubation and postoperative use in children.

Sarkar et al. [10] compared CPAP and HFNC in children with bronchiolitis in PICU of a tertiary care hospital in India. Sixteen infants received CPAP through a nasal mask (SERVO-i®, Maquet; Getinge Group, Sweden). CPAP was usually started at 4 cm H_2O and increased as necessary up to a maximum of 8 cm H_2O. Nasal prong or nasal mask (SERVO-i®, Maquet; Getinge Group, Sweden) of appropriate size which was snugly fitted and produces minimum leak and maximum comfort was used as interface. Fifteen infants received oxygen through HFNC (AIRVO™ 2, Fisher and Paykel Healthcare Limited, New Zealand), applied continuously through large-bore binasal prongs, with a gas flow rate of 2 L/kg/min for the children less than or equal to 10 kg and for children >10 kg 2 L/kg/min for the first 10 kg + 0.5 L/kg/min for each kg above that and FiO_2 of 0.4 at initiation. The fraction of oxygen in the gas flowing in the system was subsequently adjusted to maintain an oxyhemoglobin saturation (SpO_2) of 94% or more. One patient in each group had NIV failure and had to be intubated; hence, intubation rates were similar in both groups ($p = 0.29$). Functional and subjective respiratory parameters such as SpO_2, respiratory rate (RR), PaO_2, PCO_2,

and respiratory distress assessment index scores were compared between the two groups. All the parameters were improved steadily in both groups. Improvements in all end-points tested were comparable for both groups. Compared to CPAP, HFNC was better tolerated as indicated by better normalization of heart rate (HR) ($p < 0.001$) and better comfort score ($p < 0.003$). When secondary outcomes were evaluated, incidence of nasal injury was higher ($p = 0.021$) in CPAP ($n = 12$, 75%) as compared to HFNC ($n = 4$, 26.66%). Mean duration of NIV on CPAP (3.8 ± 0.80 days) and HFNC (3.6 ± 0.63 days) were comparable ($p = 0.33$). Average PICU lengths of stay (LOS) on CPAP (5 ± 1.788 days) and HFNC (5 ± 1.6 days) were also comparable ($p = 0.105$).

In the review by Oakley et al. [11], of 204 (5.7%) infants with bronchiolitis admitted to ICU, 133 (82.1%) received noninvasive ventilation (HFNC or CPAP), 7 (4.3%) received invasive ventilation alone, and 21 (13.6%) received a combination of ventilation modes. Infants with comorbidities such as chronic lung disease, congenital heart disease, neurological disease, or prematurity and infants 2–6 months of age were more likely to be admitted to ICU. HFNC use changed from 13/53 (24.5% [95% CI 13.7–38.3]) patient episodes in 2009 to 39/91 (42.9% [95% CI 32.5–53.7]) patient episodes in 2011. The authors pointed out that although being admitted to PICU is an uncommon occurrence in infants admitted with bronchiolitis, it is becoming common in infants with comorbidities and prematurity. They reported that majority of children with bronchiolitis are managed with noninvasive ventilation, with increasing use of HFNC.

In the study by Dohna-Schwake et al. [1], 146 infants with bronchiolitis requiring respiratory support in winter season 2015/2016 treated in either one of two regions in Central Europe, South of greater Paris region in France (group 1) and Ruhr area in Germany (group 2), were compared. Ninety percent of infants in group 1 were treated by nasal CPAP, while 80% of infants in group 2 were treated by HFNC. Duration of respiratory support was significantly shorter in group 1. Infants in group 2 received more frequently infusion therapy, more antibiotics, and more inhalation therapy. They concluded there was better outcome in children treated in France for bronchiolitis where CPAP was a more preferred treatment modality.

Pedersen et al. [12] in a retrospective study compared the use of a nasal CPAP to HFNC in infants with acute bronchiolitis. There were 27 children in nasal CPAP group and 22 children in HFNC group. Respiratory rate decreased faster in the CPAP group ($p < 0.05$). FiO_2 decreased in the CPAP group and increased in the HFNC group during the first 12 h, whereafter it decreased in both groups ($p < 0.01$). Heart rate development was similar in both groups. Twelve children (55%) changed systems from HFNC to CPAP due to disease progression. There was no difference in length of treatment, hospital stay, or transmission to intensive care unit between the groups. CPAP was more effective than HFNC in decreasing respiratory rate and FiO_2. The authors concluded CPAP was superior to HFNC in lowering RR and FiO_2 in infants with bronchiolitis.

In a meta-analysis by Mikalsen et al. [13], there were two studies comparing HFNC and CPAP in children, one with bronchiolitis and the other with ARF. Metge et al. [14] in a retrospective study compared the use of a nasal continuous positive airway pressure to an HFNC in infants with acute bronchiolitis. Parameters such as LOS in PICU and oxygenation were similar in the two groups. Oxygen weaning occurred during the same time for the two groups. There were no differences between the two groups for RR, HR, FiO_2, and CO_2 evolution. HFNC therapy failed in three patients, two of whom required invasive mechanical ventilation, versus one in the nasal CPAP group. Ten Brink et al. [15] in a prospective observational study compared HFNC and CPAP use in 109 children with mild to moderate ARF. There was no significant difference in the number of children requiring a higher level of respiratory support in the two groups. One-fourth of all children on HFNC required higher level of respiratory support, these had failure of normalization of heart rate and respiratory rate and not fall in FiO_2 after 2 h on HFNC.

In a systematic review and meta-analysis by Lin et al. [16], 2121 children with bronchiolitis in nine randomized controlled trials (RCTs) were compared. There was no significant difference in length of stay in hospital, length of oxygen supplementation, transfer to intensive care unit, incidence of intubation, respiratory rate, SpO_2, and adverse events in HFNC group compared with nasal continuous positive airway pressure group. There was a significant increase of the incidence of treatment failure (RR 1.61, 95% CI 1.06–2.42, $p = 0.02$) in HFNC group compared with nasal CPAP group. The authors concluded HFNC is safe as an initial respiratory management, but the evidence is still lacking to show benefits for children with bronchiolitis compared to nasal CPAP.

Vitaliti et al. [17] conducted a prospective interventional study in 40 children with respiratory distress between 1 and 24 months of age, with hemodynamically stable hypoxemia. All included subjects were randomly treated with helmet CPAP or HFNC in a 1:1 fashion until their clinical condition, oxygen saturation, and arterial blood gas parameters improved. They reported a more rapid clinical response to helmet CPAP than HFNC with fewer days of hospitalization in the first group of subjects. Furthermore, one of the HFNC-treated subjects was admitted to the PICU due to HFNC failure, with subsequent requirement of endotracheal intubation and invasive ventilation. No case of failure was reported in subjects treated with helmet CPAP. The authors concluded that being the first RCT in children with mild to moderate respiratory distress, clinical response to helmet CPAP was more efficient and rapid when compared to HFNC.

Shioji et al. [18] compared 35 children who received HFNC therapy for ARF after cardiac surgery in 2014–2015 (the HFNC group) with 35 children who had received NIV therapy for ARF after cardiac surgery in 2009–2012 as a control group. The reintubation rate within 48 h in the HFNC group tended to be lower than that in the NIV group (3% vs. 17%, $p = 0.06$). The reintubation rate within 28 days was significantly lower in the HFNC group compared to the NIV group (3% vs. 26%, $p = 0.04$). The HFNC group's ICU stays were significantly shorter than those of the NIV group: 10 (IQR, 7–17) days vs. 17 (11–32) days, $p = 0.009$. The authors concluded HFNC therapy might be associated with a reduced reintubation rate in children with ARF after cardiac surgery. In a previous observational study, Shioji et al. [19] reported that HFNC therapy started immediately after postextubation ARF after cardiac surgery in 20 children less than 48 months of age improved the RR of patients without any adverse events.

The role of HFNC in weaning patients with chronic obstructive pulmonary disease (COPD) with hypercapnia from invasive ventilation is unclear. In an adult study by Jing et al. [20], HFNC was compared to NIV on postextubation vital signs and arterial blood gases among patients with COPD. The study also evaluated the outcomes including comfort scores, need for bronchoscopy, use of pulmonary medications, and chest physiotherapy. At 3 h after extubation, pH in the NIV group was lower than HFNC group (7.42 ± 0.06 vs. 7.45 ± 0.05, $p = 0.01$). At 24 h after extubation, patients' mean arterial pressure (82.97 ± 9.04 vs. 92.06 ± 11.11 mmHg, $p = 0.05$) and pH (7.42 ± 0.05 vs. 7.46 ± 0.03, $p = 0.05$) in the NIV group was lower than in the HFNC group. No significant differences were found at 48 h after extubation. In the HFNC group, comfort scores were better (3.55 ± 2.01 vs. 5.15 ± 2.28, $p = 0.02$), and fewer patients needed bronchoscopy for secretion management within 48 h after extubation (2/22 vs. 9/20, $p = 0.03$). Summarizing all these studies, the authors concluded that HFNC may be considered as an intermediate level of oxygen therapy between conventional oxygen therapy and NIV.

Hawkins et al. [21] reported ten school-age subjects with varied medical conditions, moderate to severe obstructive sleep apnea (OSA), and CPAP intolerance who wore HFNC from 10 to 50 L/min of room air with oxygen supplementation if needed (room air alone for 6 of 10). HFNC reduced median obstructive apnea-hypopnea index (OAHI) greater than 1 event/h from 11.1 events/h (interquartile range 8.7–18.8 events/h) to 2.1 events/h (1.7–2.2 events/h; $p = 0.002$); increased SpO_2 mean from 91.3% (89.6–93.5%) to 94.9% (92.4–96.0%;

$p < 0.002$); increased SpO_2 from 76.0% (67.3–82.3%) to 79.5% (77.2–86.0%; $p = 0.032$); decreased SpO_2 desaturation index from 19.2 events/h (12.7–25.8 events/h) to 6.4 events/h (4.7–10.7 events/h; $p = 0.013$); and reduced heart rate from 88 bpm (86–91 bpm) to 74 bpm (67–81 bpm; $p = 0.004$). Stratified analysis of the six subjects with only room air via HFNC, the OAHI, obstructive hypopnea index, and mean SpO_2 still demonstrated improvements ($p = 0.031$). They concluded HFNC reduces respiratory events, improves oxygenation, reduces heart rate, and may be effective for CPAP-intolerant children with moderate to severe OSA.

In an observational study, Pilar et al. [22] compared 20 children who received HFNC therapy for severe asthma exacerbation (SA) with 22 children who received NIV for SA as initial respiratory support. The primary outcome measure was failure of initial respiratory support (need to escalate from HFNC to NIV or from NIV to invasive ventilation). Secondary outcome measures were the duration of respiratory support and PICU length of stay. There were no treatment failures in the NIV group, though 8 children (40%) in the HFNC group required escalation to NIV. The PICU LOS was similar in both the NIV and HFNC groups. However, on considering the HFNC failure subgroup, the median length of respiratory support was threefold longer (63 h) and the PICU LOS was also longer compared with the rest of subjects exhibiting treatment success. In the multivariate logistic regression analysis, when HR is >146 bpm and RR is >55 bpm, it is a possibility that HFNC might fail in children with SA. The authors concluded that the use of HFNC in children with status asthmaticus admitted to the PICU may delay initiation of NIV and therefore prolong the duration of respiratory support and the LOS in the PICU.

In an observational previous study by Kelly et al. [23], 38 children with SA were evaluated for HFNC, and they reported that triage RR greater than 90th percentile for age (OR, 2.11; 95% CI, 1.01–4.43), initial venous PCO_2 greater than 50 mmHg (OR, 2.51; 95% CI, 1.06–5.98), and initial venous pH less than 7.30 (OR, 2.53; 95% CI, 1.12–5.74) are associated with increased risk of HFNC therapy escalation to intubation. The authors concluded that HFNC is more likely to fail in hypercapnic subjects than in hypoxemic subjects. Similar to this study, Pilar et al. [22] identified heart rate and respiratory rate prior to respiratory support as factors related to failure of HFNC.

In the only randomized controlled trial comparing CPAP and HFNC in children with severe pneumonia in Bangladesh, 79 (35%) children got bubble CPAP, 67 (30%) children got low-flow oxygen therapy, and 79 (35%) children got high-flow oxygen therapy. Treatment failed for 31 (14%) children, of whom 5 (6%) had received bubble CPAP, 16 (24%) had received low-flow oxygen therapy, and 10 (13%) had received high-flow oxygen therapy. Significantly fewer children in the bubble CPAP group had treatment failure than in the low-flow oxygen therapy group (relative risk 0.27, 99.7% CI 0.07–0.99; $p = 0.0026$). No difference in treatment failure was noted between patients in the bubble CPAP and those in the high-flow oxygen therapy group (relative risk 0.50, 99.7% CI 0.11–2.29; $p = 0.175$). The authors concluded there was no difference in outcome of intubation, death, and clinical failure between children supported by HFNC or CPAP [24].

When we searched about the postextubation usage of HFNC versus CPAP, we could find only a few studies. In the study by Manley et al. [25], HFNC and CPAP were compared for the treatment failure in infants within 7 days of extubation. In the study, 34.2% of the HFNC infants experienced treatment failure, whereas 25.8% of the CPAP group demonstrated failure. Of the failures, 50% were successfully treated with CPAP without reintubation. Based on their predetermined criteria, this led to a conclusion that the use and efficacy of HFNC was not inferior and was therefore similar to that of CPAP as a form of respiratory support for very preterm infants following extubation. In the study by Coletti et al. [26], a total of 620 children were managed with HFNC for different purposes in a PICU. HFNC was used for postextubation period in 98 (16%) of all the children. Ninety-two percent of 63 subjects with congenital heart disease were treated successfully with HFNC in the postextubation period in the study.

In literature search for the alternative use of HFNC for NIV in immunocompromised patients, we could not find any pediatric age study. However, in the systematic review and meta-analysis conducted by Sclar et al. [27], random-

ized controlled trials or observational studies reporting the use of HFNC in immunocompromised subjects were evaluated to show its impact on mortality and invasive mechanical ventilation. The predominant cause of immunocompromised status was cancer. Bacterial pneumonia was the most common cause of acute hypoxemic respiratory failure with a median PaO_2/FIO_2 of 145 mmHg (interquartile range 115–175). HFNC was used as the first oxygen strategy in 474 subjects compared to NIV (242 subjects) and conventional O_2 therapy (703 subjects). There was a 46% rate of invasive mechanical ventilation and 36% mortality. Mortality at the longest available follow-up was lower with HFNC compared to the oxygen therapy controls (NIV or conventional O_2 therapy) in seven studies (1429 subjects; relative risk 0.72, 95% CI 0.56–0.93, $p = 0.01$). There was a lower rate of invasive mechanical ventilation with HFNC compared to the oxygen therapy controls across eight studies (1529 subjects, relative risk 0.81, 95% CI 0.67–0.96, $p = 0.02$). These results were robust across a series of sensitivity analyses. The authors specified that HFNC was found to decrease mortality and use of invasive mechanical ventilation compared to alternative noninvasive oxygen controls. They concluded that there was a need to develop a greater evidence base evaluating the utility of HFNC in immunocompromised subjects and called for higher-quality studies evaluating a more homogeneous population to further elucidate its benefit.

Summarizing all these studies, the authors concluded that HFNC may be considered as an intermediate level of oxygen therapy between conventional oxygen therapy and NIV. Large multiple center RCT is required to obtain robust data to compare effectiveness of these two methods of respiratory support for pediatric patients (Table 58.1).

Table 58.1 Summary of best clinical/bench trials

Author Year Citation	Type of study	Study population	Results	PICU LOS	Tolerability	Treatment failure
Sarkar 2018 [10]	Child bronchiolitis	16 CPAP, 15 HFNC	SpO_2, RR, PaO_2, PCO_2: similar Nasal injury: CPAP > HFNC	Similar	HFNC > CPAP	Similar
Pedersen 2017 [12]	Child bronchiolitis	27 CPAP; 22 HFNC	RR: CPAP > HFNC FiO_2: CPAP > HFNC HR: similar	Similar	No comment	No comment
Metge 2014 [14]	Child bronchiolitis	19 CPAP, 15 HFNC	RR, HR, FiO_2, and CO_2: similar	Similar	No comment	HFNC > CPAP
Ten Brink 2013 [15]	Child acute respiratory failure	72 HFNC, 37 CPAP	Escalation to a higher level of respiratory support: similar Prediction of escalation is due to: RR and HR	HFNC < CPAP	Good but not compared	Similar
Lin 2019 [16]	Child bronchiolitis	9 RCTs Total 2121 HFNC/CPAP	LOO: similar HR RR, SpO_2: similar	Similar	No comment	HFNC > CPAP
Vitality 2017 [17]	Child acute respiratory failure	20 CPAP; 20 HFNC; 20 COT	Clinical response to helmet CPAP was more efficient and rapid compared with HFNC	HFNC > CPAP	No comment	HFNC > CPAP

COT conventional oxygen therapy, *COPD* chronic obstructive pulmonary disease, *CPAP* continuous positive air pressure, *HFNC* high-flow nasal cannula, *HR* heart rate, *NIV* noninvasive ventilation, *RR* respiratory rate

References

1. Dohna-Schwake C, Mücher K, Stehling F, Rothoeft T, Roll C, et al. Differences of medical care for acute severe viral bronchiolitis in two urban areas in Europe. Klin Padiatr. 2018;230(5):245–50.
2. De Klerk A. Humidified high-flow nasal cannula: is it the new and improved CPAP? Adv Neonatal Care. 2008;8:98.
3. Lee JH, Rehder KJ, Williford L, et al. Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. Intensive Care Med. 2013;39:247.
4. Hutchings FA, Hilliard TN, Davis PJ. Heated humidified high-flow nasal cannula therapy in children. Arch Dis Child. 2015;100:571.
5. Hilliard TN, Archer N, Laura H, et al. Pilot study of vapotherm oxygen delivery in moderately severe bronchiolitis. Arch Dis Child. 2012;97:182.
6. Wing R, Armsby CC. Noninvasive ventilation in pediatric acute respiratory illness. Clin Pediatr Emerg Med. 2015; https://doi.org/10.1016/j.cpem.2015.07.004.
7. Abboud PA, Roth PJ, Skiles CL, et al. Predictors of failure in infants with viral bronchiolitis treated with high-flow, high-humidity nasal cannula therapy∗. Pediatr Crit Care Med. 2012;13:e343.
8. Najaf-Zadeh A, Leclerc F. Noninvasive positive pressure ventilation for acute respiratory failure in children: a concise review. Ann Intensive Care. 2011;1:15.
9. Nagler J, Cheifetz IM. Noninvasive ventilation for acute and impending respiratory failure in children. In: UpToDate. Topic last updated 2 May 2018. Accessed 17 Apr 2019.
10. Sarkar M, Sinha R, Roychowdhoury S, Mukhopadhyay S, Ghosh P, Dutta K, Ghosh S. Comparative study between noninvasive continuous positive airway pressure and hot humidified high-flow nasal cannulae as a mode of respiratory support in infants with acute bronchiolitis in pediatric intensive care unit of a tertiary care hospital. Indian J Crit Care Med. 2018;22(2):85–90.
11. Oakley E, Chong V, Borland M, Neutze J, Phillips N, Krieser D. Intensive care unit admissions and ventilation support in infants with bronchiolitis. Emerg Med Australas. 2017;29(4):421–8.
12. Pedersen MB, Vahlkvist S. Comparison of CPAP and HFNC in management of bronchiolitis in infants and young children. Children (Basel). 2017;4(4)
13. Mikalsen IB, Davis P, Oymar K. High flow nasal cannula in children: a literature review. Scand J Trauma Resusc Emerg Med. 2016;24:93.
14. Metge P, Grimaldi C, Hassid S, Thomachot L, Loundou A, Martin C, et al. Comparison of a high-flow humidified nasal cannula to nasal continuous positive airway pressure in children with acute bronchiolitis: experience in a Pediatric Intensive Care Unit. Eur J Pediatr. 2014;173:953–8.
15. ten Brink F, Duke T, Evans J. High-flow nasal prong oxygen therapy or nasopharyngeal continuous positive airway pressure for children with moderate-to-severe respiratory distress?∗. Pediatr Crit Care Med. 2013;14:e326–31.
16. Lin J, Zhang Y, Xiong L, Liu S, Gong C, Dai J. High-flow nasal cannula therapy for children with bronchiolitis: a systematic review and meta-analysis. Arch Dis Child. 2019. pii: archdischild-2018-315846. https://doi.org/10.1136/archdischild-2018-315846. [Epub ahead of print].
17. Vitaliti G, Vitaliti MC, Finocchiaro MC, et al. Randomized comparison of helmet CPAP versus high-flow nasal cannula oxygen in pediatric respiratory distress. Respir Care. 2017;62(8):1036–42.
18. Shioji N, Kanazawa T, Iwasaki T, et al. High-flow nasal cannula versus noninvasive ventilation for postextubation acute respiratory failure after pediatric cardiac surgery. Acta Med Okayama. 2019;73(1):15–20.
19. Shioji N, Iwasaki T, Kanazawa T, et al. Physiological impact of high-flow nasal cannula therapy on postextubation acute respiratory failure after pediatric cardiac surgery: a prospective observational study. J Intensive Care. 2017;5:35.
20. Jing G, Li J, Hao D, Wang T, Sun Y, Tian H, et al. Comparison of high flow nasal cannula with noninvasive ventilation in chronic obstructive pulmonary disease patients with hypercapnia in preventing postextubation respiratory failure: a pilot randomized controlled trial. Res Nurs Health. 2019;42(3):217–25.
21. Hawkins S, Huston S, Campbell K, Halbower A. High-flow, heated, humidified air via nasal cannula treats CPAP-intolerant children with obstructive sleep apnea. J Clin Sleep Med. 2017;13(8):981–9.
22. Pilar J, Modesto I, Alapont V, Lopez-Fernandez YM, et al. High-flow nasal cannula therapy versus noninvasive ventilation in children with severe acute asthma exacerbation: an observational cohort study. Med Intensiva. 2017;41(7):418–24.
23. Kelly GS, Simon HK, Sturm JJ. High-flow nasal cannula use in children with respiratory distress in the emergency department: predicting the need for subsequent intubation. Pediatr Emerg Care. 2013;29(8):888–92.
24. Chisti MJ, Salam MA, Smith JH, Ahmed T, Pietroni MA, Shahunja KM, et al. Bubble continuous positive airway pressure for children with severe pneumonia and hypoxaemia in Bangladesh: an open, randomised controlled trial. Lancet. 2015;386:1057–65.
25. Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, et al. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2013;369:1425–33.
26. Coletti KD, Bagdure DN, Walker LK, Remy KE, Custer JW. High-flow nasal cannula utilization in pediatric critical care. Respir Care. 2017;62(8):1023–9.
27. Sklar MC, Mohammed A, Orchanian-Cheff A, Del Sorbo L, Mehta S, Munshi L. The impact of high-flow nasal oxygen in the immunocompromised critically ill: a systematic review and meta-analysis. Respir Care. 2018;63(12):1555–66.

Correction to: Skin Injuries Associated with Noninvasive Mechanical Ventilation: Evidence-Based Synthesis

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The original version of chapter 14 was published with incorrect list of authors. This chapter has been now corrected.

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