Teaching Pearls in Noninvasive Mechanical Ventilation

Key Practical Insights

Antonio M. Esquinas
Editor

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To my family…, great motivation in my live

Preface

In the last decades, we have developed a broad knowledge base in noninvasive mechanical ventilation that supports the daily use of this technique in different settings and medical specialties. We have been able to establish solid knowledge and apply practical protocols as well as technological advances. From a critical perspective, one of these essential elements that have allowed us to ensure a correct application is supported by excellence in training and education plans in noninvasive mechanical ventilation carried out with the support of clinical teachers. In this original and first book, **Teaching Pearls in Noninvasive Mechanical Ventilation**, we offer the first original book whose bases is a teaching based on the critical analysis of selected clinical cases that represent the most common and real situations of use of noninvasive mechanical ventilation.

The structure of the book and chapters is based on the teaching that provides the critical analysis of the most common clinical cases present on a daily basis of clinical practice. This original book structure makes it ideal to be a reference book in training and education plans of pulmonary as well as critical care and sleep medicine fellowship programs, universities, and postgraduate courses in noninvasive mechanical ventilation. This book comes from the solid idea that teaching based on the "critical analysis" of the "clinical case" is the first and basic element to ensure the best transmission of knowledge and correct application. Besides, this book is conceived as a key tool for proper teaching for professors or teachers in the field of **Noninvasive Mechanical Ventilation**.

If you want to learn, teach (Marcus Tullius Ciceron)

Murcia, Spain
March 2021

Antonio M. Esquinas

Contents

Abbreviations

AASM	American Academy of Sleep Medicine
ABG	Arterial blood gas analysis
ACBT	Active cycle of breathing technique
AChR-Ab	Autoantibodies against the acetylcholine receptor
ACPE	Acute cardiac pulmonary edema
ADH	Anti-diuretic hormone
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AE-IPF	Acute exacerbation of IPF
AF	Atrial Fibrillation
AFC	Alveolar fluid clearance
AG	Anion gap
AHI	Apnea hypopnea index
AHRF	Acute hypoxemic respiratory failure
AI	Asynchrony index
AI%	Asynchrony index
AIH	Apnea hypopnea index
AKI	Acute kidney injury
ALI	Acute lung injury
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
APACHE II	Acute Physiology and Chronic Health Evaluation II
APCV	Assist pressure control ventilation
APE	Acute pulmonary edema
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
ASV	Adaptive servoventilation
ATS	American Thoracic Society
AUC	Area under the curve
AVAPS	Average volume-assured pressure support

Bf	Bronchofiberoscopy
BGA	Blood gas analysis
BiPAP	Bilevel positive airway pressure
BiPAP-S	BiPAP spontaneous mode
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
bpm	Beats per minute
C	Compliance
CAP	Community acquired pneumonia
CCHS	Congenital central alveolar hypoventilation syndrome
CF	Cystic fibrosis
CHRF	Chronic hypercapnic respiratory failure
CI	Confidence interval
CKD	Chronic kidney disease
CLD	Chronic liver disease
cm H_2O	Centimeter of water
CMO	Comfort measures only
CMT	Charcot–Marie–Tooth disease
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary edema
CPH	Chronic pulmonary hypertension
CPT	Chest physiotherapy
CRF	Chronic respiratory failure
CRP	C-reactive protein
CRX	Chest radiograph
CSA	Central sleep apnea
CT	Computed tomography
CTPA	Computed tomographic pulmonary angiography
CURB-65	Confusion, urea, respiratory rate, blood pressure – 65 years of age
CVP	Central venous pressure
CWP	Centimeters of water pressure
CXR	Chest X-Ray
DAD	Diffuse alveolar damage
DE	Diaphragmatic excursion
DEX	Dexmedetomidine
DLCO	Carbon monoxide diffusion capacity
DLT	Double lumen tube
DMD	Duchenne muscular dystrophy
DNI	Do-not-intubate
DNR	Do not resuscitate
DOT	Domiciliary oxygen therapy
DP	Driving pressure

DRG	Dorsal respiratory group
DT	Diaphragm thickness
e	Elastance
EAdi	Electrical activity of diaphragm
EADi/Edi	Electrical activity of the diaphragm
ECCO2R	Extracorporeal CO_2 removal
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ED	Emergency Department
EEN	Effective enteral nutrition
EF	Ejection fraction
EPAP	Expiratory positive airway pressure
ERS	European Respiratory Society
ES	Excessive sleepiness
OSAS	Obstructive Sleep Apnea Syndrome
IAH	Index of apnea-hypoapnea
PSG	Polysomnography
RSD	Respiratory sleep disorder
ESICM	European Society of Intensive Care Medicine
ESS	Epworth sleepiness scale
EVLW	Extra-vascular lung water
Flow	Gas flow
FBS	Fiberoptic bronchoscopy
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in the first second
FEV1/FVC ratio	Forced expiratory volume in the first second/forced vital capacity
FiO_2	Fraction of inspired oxygen
FM	Face-mask
FMV	Face-mask ventilation
FOB	Fiberoptic bronchoscopy
FRC	Functional residual capacity
FVC	Forced vital capacity
GCS	Glasgow Coma Scale
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GORD	Gastro-oesophageal reflux disease
GPB	Glossopharyngeal breathing
HACOR	Heart rate, Acidosis, Consciousness, Oxygenation, and Respiratory rate
HAP	Hospital-acquired pneumonia
Hb	Hemoglobin
HCO_3^-	Bicarbonate
HDU	High Dependency Unit
HES	Hypercapnic encephalopathy syndrome
HFNC	High flow nasal cannula

HINPPV	High-intensity noninvasive positive pressure ventilation
HR	Heart rate
HRCT	High-Resolution Computed Tomography
HRQoL	Health-Related Quality of Life
Htc	Hematocrit
IAP	Intra-abdominal pressure
IBP	Invasive blood pressure
IBW	Ideal body weight
IC	Inspiratory capacity
ICP	Intracranial pressure
ICS	Inhaled corticosteroid
ICSD-3	International Classification of Sleep Disorders, Third Edition
ICU	Intensive Care Unit
I:E Ratio	Ratio of inspiratory and expiratory time
IGHMBP2	Immunoglobulin helicase μ-binding protein 2
ILD	Interstitial lung disease
IMV	Invasive mechanical ventilation
IPAP	Inspiratory positive airway pressure
IPF	Idiopathic pulmonary fibrosis
IPPB	Intermittent positive pressure breathing
ISS	Injury Severity Score
IT	Inspiratory time
IV	Intravenous
IVS	Interventricular septum
KMS	Kelly-Matthay Scale
L/min	Liter per minute
LA	Left atrial
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
LMWH	Low molecular weight heparin
LoS	Length of stay
LRTI	Lower respiratory tract infection
LTMV	Long-term mechanical ventilation
LTOT	Long-term oxygen therapy
LUS	Lung ultrasound
LUS-ReS	Lung Ultrasound Reaeration Score
LV	Left ventricle
LVR	Lung volume recruitment
MAC	Manually assisted cough
MDT	Multidisciplinary team
MEP	Maximal expiratory pressure
mg/h	Milligram per hour
MI	Mechanical insufflations
MIC	Maximum insufflation capacity
MI-E	Mechanical Insufflation-Exsufflation

MIP	Maximal inspiratory pressure
mL/kg	Milliliters to kilograms
mm/Hg	*Millimeters* of mercury
mmol/L	Millimoles per liter
MODS	Multiple organ dysfunction syndrome
MOF	Multiple organ failure
MRF	Maugeri Respiratory Failure questionnaire
MV	Mechanical ventilation
NAVA	Neurally adjusted ventilatory assist
NC	Nasal cannula
NEX	Distance of nose tip earlobe and processus xyphoideus
NIMV	Noninvasive mechanical ventilation
NIOV	Noninvasive open ventilation
NIPSV	Noninvasive pressure support ventilation
NIV	Noninvasive ventilation
NIV-BF	Noninvasive positive pressure facilitated bronchofiberoscopy
NMBAs	Neuromuscular blocking
NMD	Neuromuscular disease
NPPV	Noninvasive positive pressure ventilation
NPV	Negative pressure ventilation
NREM	Non-rapid eye movement
NT-proBNP	N-terminal pro-brain natriuretic peptide
NVS	Noninvasive ventilatory support
O_2	Oxygen
O_2-LT	Oxygen long-term therapy
O_2T	Oxygen therapy
OCS	Oral corticosteroids
OD	Oxygen desaturation
ODI	Oxygen desaturation index
OHS	Obesity-hypoventilation syndrome
OR	Odds ratio
OSA	Obstructive sleep apnea
P/F-PaO_2/FiO_2	Ratio of PaO_2 to fraction of inspired oxygen
P/F ratio	Partial pressure of arterial oxygen/fraction of inspired oxygen ratio
P/I Index	Ratio of EADi peak value and EADi inspiratory AUC
$PaCO_2$	Partial pressure of arterial carbon dioxide
$PaCO_2$	Arterial carbon dioxide tension
Pal	Alveolar pressure
PaO_2	Arterial oxygen partial pressure
PAV	Proportional assist ventilation
Paw	Airway pressure
PAWP	Pulmonary arterial wedge pressure
PBW	Predicted body weight
PC-BIPAP	Control pressure – Bilevel positive airway pressure

PCA	Patient control analgesia
PC-BiPAP	Pressure control bilevel positive airway pressure
PCF	Peak cough flow
pCO_2	Carbon dioxide tension
PCV	Pressure control ventilation
PEEP	Positive end-expiratory pressure
PEEPi	Intrinsic positive end-expiratory pressure
PEF	Peak expiratory flow
PE	Pulmonary embolism
$PetCO_2$	End-tidal CO_2
PFTs	Pulmonary Function Tests
pH	Potential of hydrogen
PH	Pulmonary hypertension
pNIV	Portable noninvasive ventilation
pO_2	Peripheral oxygen saturation
PPC	Postoperative pulmonary complications
PPE	Personal protective equipment
Ppl	Pleural pressure
PPV	Positive pressure ventilation
PR	Pulmonary rehabilitation
PVR	Pulmonary vascular resistance
PS	Pressure support
PSG	Polysomnography
P-SILI	Patient self-induced lung injury
PSV	Pressure support ventilation
$PtcCO_2$	Transcutaneous carbon dioxide
pts	Patient/s
PVA	Patient–ventilator Asynchrony
PVD	Patient ventilator dyssynchrony
PY	Pack year
Raw	Airway resistance
RCT	Randomized clinical trial
REM	Rapid eye movement
RF	Respiratory failure
RHDCU	Respiratory high-dependency care unit
RICU	Respiratory Intensive Care Unit
ROM	Range of motion
RR	Respiratory rate
RRT	Renal replacement therapy
RV	Residual volume
RVent	Right ventricle
RVSP	Right ventricular systolic pressure
S/T Mode	Spontaneous/Timed Mode
SaO_2	Oxygen saturation
SAPS II	Simplified Acute Physiology Score II

SAPS	Simplified Acute Physiology Score
SAPS3-CNIV	Simplified Acute Physiology Score 3-Customized NIV
$SatO_2$	Arterial oxygen saturation
SB	Spontaneous breathing
SD	Swallowing disorders
SDB	Sleep disordered breathing
SGRQ	St George's Respiratory Questionnaire
SID	Strong ion difference
SMA	Spinal muscular atrophy
SMARD1	Spinal muscular atrophy with respiratory distress type 1
SOFA Score	Sequential Organ Failure Assessment Score
SPN-CPAP/PS	Spontaneous - Continuous positive airway pressure or Pressure support ventilation
SpO_2	Peripheral oxygen saturation
SRBDs	Sleep-related breathing disorders
SrH	Sleep-related hypoventilation
SrHDs	Sleep-related hypoventilation disorders
SRI	Severe Respiratory Insufficiency questionnaire
StO_2	O_2 saturation
SVA	Subject ventilator asynchrony
T90	Time spent SpO_2 <90%
TAPSE	Tricuspid annular plane systolic excursion
TB	Tuberculosis
TBI	Traumatic brain injury
$TcCO_2$	Transcutaneous carbon dioxide
TEE	Transesophageal echocardiography
Ti	Inspiratory time
TI	Thickening fraction
TLC	Total lung capacity
TRV	Tricuspid regurgitation velocity
TTE	Transthoracic echocardiography
TV	Tidal volume
Tv	Tricuspid valve
UIP	Usual interstitial pneumonia
Va/Q	Ratio of ventilation to perfusion
VAP	Ventilator-associated pneumonia
VAPS	Volume-assured pressure support
VATS	Video-assisted thoracoscopic surgery
VC	Vital capacity
VCI	Vena cava inferior
VCV	Volume-controlled ventilation
VDd	Dead space of the mask
VDdyn	Dynamic dead space
VDph	Physiologic dead space
VIDD	Ventilator-induced diaphragmatic dysfunction

VILI	Ventilator-induced lung injury
VPF	Ventilatory pump failure
VPW	Vascular pedicle width
VRG	Ventral respiratory groups
VS	Versus
Vt	Tidal volume
WBC	White blood cell count
WOB	Work of breathing
WSS	Woodhouse-Sakati syndrome
ΔP	Pressure change
ΔV	Volume change
μL	Microliter
% pred	Percent of predicted value

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Part I
Clinical Cases in Noninvasive Ventilation: Interfaces, Methodology

Chapter 1
Facemask and Total Face Mask

Edoardo Piervincenzi, Giorgio Zampini, and Daniela Perrotta

1.1 Introduction

Avoiding endotracheal intubation in adult and pediatric population has undiscussed advantage.

Nowadays there is a great development by the companies of new masks and physicians have a wide selection of interfaces available.

At the same time, there are few recommendation about which interface are better than other in each clinical situation, and data about tolerance and efficacy are lacking especially for paediatric patients.

Every ICU anyway, should have several types of mask/interface to provide a tailored therapy on each patient to provide the best possible comfort and efficacy during NIV therapy administration.

Facemask (oro-nasal mask) and full-face mask are both valid instruments to provide non-invasive positive pressure ventilation therapy.

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Also the helmet has shown over the years to be a valid alternative to supply NIV with some precautions in the setting of the mechanical ventilator.

In this chapter, the main aspects of the NIV delivered through masks will be analyzed, NIV will be intended as a ventilation with an inspiratory and an expiratory pressure level both generated by the mechanical ventilator. CPAP therapy or HFNC will not be treated as topics in this paper [1–6].

1.2 NIV-Mask

1.2.1 Caratheristics

A first differentiation must be considered between vented and non-vented mask, this will lead to the use of different circuits, different ventilators with intrinsic characteristics; all aspects that have repercussion on NIV supply (see Fig. 1.1).

In ICU/PICU usually are preferred non-vented mask with double tube circuits due to large diffusion of ICU-ventilators instead of Home Care Ventilator.

But in some patient especially in chronic ones, Home Care-Ventilators are more tolerated and offer a lot of interesting options with particular ventilation modalities.

It is superfluous to point out that unvented interfaces cannot absolutely be used on single-limb circuits because it would cause enormous damage due to an impossible expiration.

Likewise, the vented interfaces cannot be used on double-limbs circuits due to the enormous pressure losses that would result.

The non-vented Oro-nasal or full-face masks with ICU ventilator is more effective in dyspnoeic patients due to a lower amount of risk of rebreathing CO_2 (see Figs. 1.2 and 1.3).

Fig. 1.1 Different connector for vented single limb circuit (**a**) and for non-vented double limb circuit (**b**)

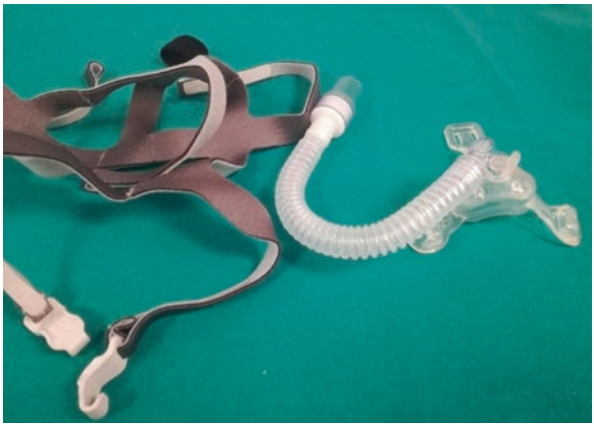

Fig. 1.2 Example of nasal mask

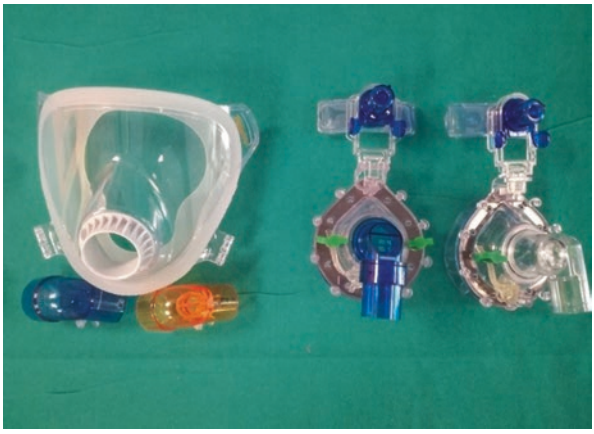

Fig. 1.3 Example of oronasal: fullface masks

The nasal masks or nasal pillows can be used only in cooperative non-dyspnoeic adult patient or in small infants that have still nasal breathing, the patient usually better accepts these masks than the other interfaces, but the power in gas exchange improvement is low.

In collaborating non-dyspnoeic adult patient however, any interface that is comfortable for the patient can be reasonably used only if, however, we know its characteristics and strategies to get better its effectiveness.

The success or not of NIV therapy depend on the capability to reduce amount of WOB and to increase alveolar minute ventilation.

Leaks and patient-ventilator asynchrony are the two main negative determinants responsible for the failure of the NIV.

An interesting data from literature is that seems to have more weight on the outcome the choice of a correct interface rather than the ventilation mode.

In addition, the poor tolerance, for claustrophobia, for an uncomfortable interface that develops too much pressure on the skin inevitably leads to an excessive discomfort and therefore to the interruption of the treatment.

Patient comfort play a key-role in ensuring continuous therapy without interruption thus allowing effective alveolar recruitment and adequate rest of the respiratory muscles.

Therefore, is crucial to choose masks that have adequate fixing systems capable of distributing the pressures and possessing well adherent but at the same time soft cushion (see Fig. 1.4).

From a physiological point of view, any type of mask increase the dead space but peep level correctly set could gain a better CO_2 washout and cut down the risk of rebreathing.

Saatci et al. have investigated the properties in terms of dead space of several facemask.

The different design of each mask could influence not only the absolute but also the dynamic dead space [7]. R. Fodil et al. tested several numbers of interfaces comparing them in term of dead space and his clinical impact.

The different interfaces available have shown to be all, each with its own small differences and peculiarities, a good way to delivering NIV therapy. The airway pressure, neuromuscular drive, inspiratory muscle effort, work of breathing (WOB), arterial blood gases does not shown great difference [8].

With the appropriate setting of the mechanical ventilator, also the differences in terms of WOB can be effectively overcome.

This paper, with an elegant fluid-dynamics study, show how the effective dead space called interface dead space it's not equivalent to real interface volume.

This means that, in this bench study, with a normal adult tidal volume the bigger interface does not entail a significant exhaled gas rebreathing.

The authors explain this phenomenon by demonstrating that when the interface has a large internal volume, as in the case of the helmet, each single breath influences the variation of internal gases by a small percentage and convective flux inside

Fig. 1.4 Different type of headgears

has a relative role. When the interface has smaller internal volume (much more near to Vt), a predominant role in the variation of gas composition is assumed by the convective flow that develops inside and the real death space is almost the same to internal volume (see Table 1.1).

If this is true in adult, with a tidal volume in the order of hundreds of milliliters, it may not be equally true in the child although there is no currently experimental strong data to verify it.

In this paper the authors suggest that, for extremely low VT, maybe the better interface to reduce CO_2 and to prevent gas rebreathing are Helmet. Unfortunately, the Helmet, with a low tidal volume ventilation has enormous problems in term of sensivity of inspiratory trigger and in synchronization.

Davide Signori et al. have shown, in another paper, how the use of non-vented double-tube interfaces significantly reduce CO_2 rebreathing during NIV and the presence of a flow-by amplified this effect [10].

In a bench-study by Conti el al. has been studied in details the synchronization and the interaction between patient and ventilator with different paediatric interfaces during PSV in a mixed obstructive restrictive model.

PSV ventilation present several problems of asynchrony/interaction especially for high respiratory frequencies.

From this study emerge that Helmet has the worst patient interaction, especially during high respiratory frequency (>30 rr) even in a normal lung model in PSV.

All the results available to date seem to indicate the use of a mask as a preferential delivery strategy in the NIV, in the pediatric population, albeit with the theoretical limits linked to rebreathing as explained above [9].

Finally, as emerged from the PEMVECC, to date, there are no strong date to recommend method or timing for NIV in paediatric population.

Despite the bench studies, there are not enough RCTs to define if an interface is better than another one.

As recommended in adult, it should be used the more fitting interface with less percentage of leaks monitoring patient-ventilator synchrony to improve efficacy and comfort [11, 12].

Table 1.1 Characteristics of principal interface to erogate NIV

	Nasal mask	Oro-nasal mask	Full face mask	Helmet
Statical dead space	−	−/+	+	+++
Claustrophobia	−	−/+	+	++
Secrection clearance	++	+	+	−/+
Aspiration risk	−	+	+	+
Flow resistance	++	−/+ (depends on prevalence of nasal breathing or not)	−/+ (depends on prevalence of nasal breathing or not)	−
Patient-ventilator interaction	−/+	++	++	−

In adult such as in paediatric population, success of NIV is even closely related to underlying disease.

In fact, is particularly effective in cardiogenic oedema or in acute exacerbation of chronic respiratory failure, it is much less effective in respiratory failure secondary to oncologic disease or to ARDS.

NIV is also used efficiently as a ventilatory therapy for respiratory distress occurring after extubation both in adults and in children.

The keystone of a successful treatment is a well adaptation of the patient with the NIV: few asynchronies, good comfort and small leaks associated to a good reduction in WOB and in an improvement in gas exchange.

If all this is not achieved in a rather short time the NIV is in the adult that in the child will have high failure rates that will inevitably lead to intubation.

1.3 Bronchopulmonary Displasia

Northway et al. descripted BPD in 1967 for the first time as a diffuse lung disease in a premature lung.

Low volumes and a progression to chronic disease heterogeneous with infiltrates and hyperinflation areas with sponge-like or cystic lesion inside characterized the disease.

BPD now is considered a chronic lung disease typically of premature child with an abnormal distribution of small pulmonary vessels with a hyper-reactive arteriolar tone. These anatomo-pathological modifications lead to pulmonary hypertension and right ventricular hypertrophy.

BPD is still the most frequent disease for premature infant born before the 30th gestational week and persist as chronic respiratory disease in childhood.

To date, there are lacking data from literature about consequences and late outcomes of this disease in childhood, however we know how these children are much more susceptible to respiratory infective events and how they often need MV to overcome these exacerbation.

Going on with age, the disease tends to develop fewer exacerbations episodes even if, from the latest data in the literature, it seems to be responsible for permanent pathological changes in the lungs like pulmonary hypertension, asthma-like symptoms and a permanent compromised lung function [13–15].

Clinical Case

BPD patient 2 years and 4 months old.

Chronic therapy since 4 months ago with Sildenafil, PEG on 2018.

No requirement of O_2 home therapy.

N1H1 pulmonary infection on January 2019.

At presentation on ED in March 2019, there was bilateral crackles, a SpO_2 of 90% and on chest x-ray hyper-insufflation, atelectasis zones and air bronchogram sign.

Viral PCR on tracheal aspirate positive for coinfection from Adenovirus and Metapneumovirus.

Was diagnosed a superior right lobar and left medium-basal pneumonia.

EGA on room air: pH 7,29, PaO_2 41, $PaCO_2$ 52, BE −4, Lac 1.2.

First line therapy was high flow nasal oxygen with FiO_2 40% at 2 L/kg/min, aerosol therapy with beta2 agonist and ipratropium. In addition, was started a broad-spectrum antibiotic therapy with Amoxicillin/clavulanate plus Claritromicin ev.

EGA after 2 h of oxygen therapy: pH 7,28, PaO_2 65, $PaCO_2$ 54, BE −4.2, Lac 1.0.

Despite therapy after 24 h, there was no improvement of EGA and respiratory mechanics; moreover, indexes of phlogosis and neutrophilia raised up so it was decided to admit the patient in PICU.

Was performed an Echocardiography that shown increased right side pressure so we started a full face NIV, diuretics therapy and Sildenafil ev. beyond the therapies already in progress.

NIV treatment was started with an oro-nasal face alternating it with a full-face mask every 8 h to prevent pressure sore in PRVC controlled ventilation with peep level of 7 cmH_2O, a FiO_2 of 40% and a target volume of 7 mL/kg with a Servo-u ventilator.

EGA after 6 h of NIV: pH 7.36, PaO_2 95, $PaCO_2$ 41, Be −1.3, Lac 0.9.

Two days after we received the result from microbiological tracheal colture positive for E. Coli and antibiotic therapy was changed with Meropem instead of Amoxicilline/clav.

After 4 days, in anticipation of a shift of the patient to a sub-intensive respiratory therapy unit, the ventilator strategy was modified in an S/T ventilation (ipap 16 epap 6 with a FiO_2 of 40% 35 rr) with an home care ventilator TRILOGY 200®.

The patient has been ventilated with a vented oronasal interface cycling NIV with HFNC allowed a progressive re-autonomization of spontaneous respiratory activity.

During the whole period in PICU, active respiratory physiotherapy was performed to increase airway secretions clearance prevent respiratory muscle atrophy and improve recovery.

Another 3 days of non-invasive mechanical ventilation in PICU allowed an improvement of the exchanges such as to be able to discharge the patient in the respiratory sub-intensive ward with a successful ventilation weaning after another 2 days of HFNC therapy and 2 on low flux oxygen nasal cannula.

Patient was successfully discharged from Hospital with a SpO_2 of 93% and a perfectly compensated pH without needing of oxygen.

Key Teaching Points
Strategy in NIMV with mask.

- The choice of right size interface for each patient is the first step to guarantee better tolerance and an optimal ventilator assistance.
  An incorrect mask size can lead to huge leaks hard to manage (compensate) even for ventilators with NIV algorithm.
  Moreover too big or too small mask, displacing easily, cause discomfort for the patient and less tolerability.
  Even the knows of ventilator available to provide NIV in ICU is fundamental to a successful treatment, each one has own strengths and weaknesses characteristic in NIV therapy.
- Do not try to make a mask fit by tightening the headgear, this will only lead to a lower tolerance of the mask
- Even the best mask after some hours creates discomfort due to the constant pressure applied on the facial tissues up to the formation of real pressure sore especially with high peep level.
  To ensure a long-term NIV tolerance it is important a constant daily rotation between at last two different interface available having different shape and then different pressure surface.
- In chronic pulmonary disease (in children as well as in adults), the assisted ventilation modalities are to prefer. These patient has already less respiratory muscle reserve because they are already chronically fatigued and even few days of controlled ventilation could compromise muscle function make weaning process much more difficult if not impossible.
- Physical rehabilitation and respiratory physiotherapy have a crucial role to help in airway secretion clearance and to maintain adequate physical conditioning to start respiratory weaning when clinical condition improve.
- A gradual passage from much more assisted to less assisted NIV and then from NIV to CPAP or HFNC is mandatory to successfully weaning process, especially in chronic disease. This variegate subset of illness has in common the difficulty of restoring the initial condition, tending to worsen after every single episode of exacerbation.

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Chapter 2
Helmet

Giorgio Zampini, Edoardo Piervincenzi, and Daniela Perrotta

2.1 Introduction

The management of respiratory distress in adults and in children is challenging for intensivists and pediatricians; proper treatment is crucial to avoid death and long-term disabilities. When respiratory distress is confirmed, its treatment requires correction and improvement of gas exchange, followed by the diagnosis of the underlying causes and complications [1].

Several studies have showed that Helmet CPAP has a high efficiency in resolving respiratory distress. This was mostly due to the effect of CPAP on alveolar extension, which causes an increase of the alveolar surface responsible for blood gas exchange.

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2.2 Helmet Interface

The helmets are made by a soft transparent plastic hood built on a hard plastic ring. The base of the plastic ring is connected whit a silicon/polyvinyl chloride soft collar that provides a pneumatic seal at the neck, while the hood contains the patient's entire head.

The collar provides a good seal without major compression at contact points. The lack of pressure points on the face avoids skin necrosis and pain, reduces discomfort, and improves patient tolerance.

The seal around the neck allows the use of the helmet also in patients with difficult anatomical situations that commonly do not allow the use of a facemask.

Different companies produce various types and sizes of helmets, each provided with various fixing and safety features. The choice of the right size generally depends on the circumference of the neck.

The helmet can be used as an alternative interface to the face mask during the NIV (Fig. 2.1) or it can be used to deliver an air flow with high oxygen concentration and a PEEP if simply connected to an air blender (Fig. 2.2).

When this is used instead of the face mask it is connected via an inspiratory branch and an expiratory branch to the mechanical ventilator. If you switch from a NIV therapy with a mask to a helmet it is good, as underlined by numerous works, to increase the inspiratory pressure by a 20%. this because the interface of the helmet has a greater volume and different structural characteristics.

There are little difference in intrinsic characteristics between helmet designed for CPAP (bigger inner volume and softer hood) and helmet designed for NIV (smaller inner volume and harder hood to transmit better the delta pressure).

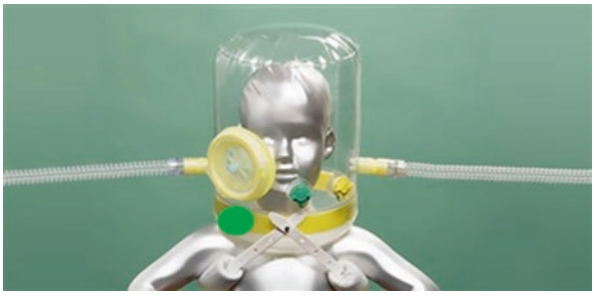

Fig. 2.1 Helmet for NIV therapy connected with two branch to the mechanical ventilator

Fig. 2.2 Helmet for CPAP therapy connected with one branch to the mechanical ventilator or gas blender

Table 2.1 How set gas flow to reach desired FiO_2 with a gas blender

Total Flow L/min	5	5	5	10	10	10	10	10	15	15	15	15	15
Air L/min	4	3	2,5	9	8	7	6	5	14	12	11	9	7,5
O2 L/min	1	2	2,5	1	2	3	4	5	1	3	4	6	7,5
FiO2%	37 %	53 %	61 %	29 %	37 %	45 %	53 %	60 %	30 %	37 %	42 %	53 %	60 %

Total Flow L/min	20	20	20	20	20	25	25	25	25	25	25	25	30	30	30	30	30	30	30
Air L/min	18	17	16	14	13	22	20,5	19	17,5	16	14	12,5	26,4	24,5	22,5	21	19	16,5	15
O2 L/min	2	3	4	6	7	3	4,5	6	7,5	9	11	12,5	3,6	5,5	7,5	9	11	13,5	15
FiO2%	29 %	33 %	37 %	45 %	49 %	30 %	35 %	40 %	45 %	49 %	56 %	60 %	30 %	35 %	41 %	45 %	50 %	57 %	60 %

Total Flow L/min	35	35	35	35	35	35	35	40	40	40	40	40	40	40	45	45	45	45	45	45	45
Air L/min	30,5	28,5	26,5	24,5	22	17,5	17,5	35	32,5	30,5	28	25	22	20	39,5	37,5	34,5	31,5	28,5	25	22,5
O2 L/min	4,5	6,5	8,5	10,5	13	15,5	17,5	5	7,5	10,5	12	15	18	20	5,5	8	11	13,5	16,5	20	22,5
FiO2%	31,5%	36 %	40 %	45 %	50 %	56 %	60 %	31 %	36 %	41 %	45 %	51 %	56 %	60 %	31 %	35 %	40 %	45 %	50 %	56 %	60 %

Total Flow L/min	50	50	50	50	50	50	50	55	55	55	55	55	55	55	60	60	60	60	60	60	60
Air L/min	44,5	41	38	35	32	28,5	25	49	45,5	41,5	38	34,5	31	27,5	53,5	49,5	45	41,5	38	34,5	30,5
O2 L/min	5,5	9	12	15	18	21,5	25	6	9,5	13,5	17	20,5	24	27,5	6,5	10,5	15	18,5	22	25,5	30
FiO2%	30 %	35 %	40 %	45 %	50 %	55 %	60 %	30 %	35 %	40 %	45 %	50 %	55 %	60 %	30 %	35 %	40 %	45 %	50 %	55 %	60 %

The volume delivered for each act, the respiratory frequency, the sensitivity of the cycling, the PEEP and the FiO_2 will be regulated by the mechanical ventilator options during bilevel ventilation.

During CPAP therapy we set only PEEP level, FiO_2 and liters per minute delivered into the helmet, the respiratory rate and the tidal volume is regulated by the patient.

Considering the significant increase in dead space and the very high compliance of the device may result in inconsistencies between the set volume and the volume actually delivered. This is shown even more clearly when the volumes set are very small [2].

For this reason the use of the helmet is currently reserved for NIV set in assisted ventilation with two pressure levels or CPAP therapy.

When for therapeutic purposes it is only necessary to set a higher FiO_2 together with a PEEP, it is possible to connect the helmet through its inlets port directly to the air blender.

The total air flow and the oxygen flow are regulated as indicated in the table to reach the total air flow and the desired oxygen concentration (Table 2.1).

Another port provide for expiratory exit; a threshold valve is mounted here to generate PEEP.

In addition, there is a pressure release valve which opens in case of sudden absence of air flow to prevent asphyxia in case of technical malfunction.

2.3 Bronchiolitis

Among etiological causes of respiratory distress in childhood, bronchiolitis is the most common etiology in infants <1 year of age admitted to the hospital [1, 3].

Several studies showed that bronchiolitis represents the greatest worldwide cause [4, 5] of infant hospitalization and the 17.1% of all non-elective pediatric ICU admissions [3].

Moreover, it is estimated that 1–3% of hospitalized infants will require treatment in an intensive care unit, especially when risk factors are present [5], and 7–9% of these infants require ventilatory support [6, 7].

The most common symptoms include coughing, wheezing, difficulty eating and sleeping, and apneas.

The principal underlying cause of Bronchiolitis is the respiratory syncytial virus (RSV) infection. It mostly affects children from 0 to 2 years [8] and 1–3% of the worldwide infant population is hospitalized for bronchiolitis during winter months [4, 5]. Management of bronchiolitis mostly involves supportive care that include rehydration and oxygen supplementation [9].

Inflammation of the infant's airways induces an increase in small airway resistance, causing increased ventilatory work [10].

In addition, the predominance of fast twitch muscle fibers in respiratory muscles accelerates fatigue and respiratory failure [11].

The most recent guidelines for management of infants with bronchiolitis and/or other causes of respiratory distress in hospitals emphasize the importance of oxygen therapy, respiratory support, and maintenance of hydration in hypoxia [12].

Respiratory support has traditionally been the cornerstone of intensive care settings and is usually provided by noninvasive techniques or intubation and mechanical ventilation [13–15].

The main common and effective noninvasive respiratory support methods in children with bronchiolitis and/or other etiologic causes, are the high- flow nasal cannula (HFNC) and CPAP, due to its ability to increase functional residual capacity with a reduction of apnoic episodes [16–18].

Both methods are efficient in improving the clinical conditions of patients with mild-to-moderate respiratory distress, although clinical response to helmet CPAP seems to be more efficient and rapid compared with that of HFNC [19].

During CPAP administration, the patient's airway is maintained throughout the respiratory cycle at a selected constant pressure (CPAP) higher than the atmospheric pressure. This method improve respiratory mechanics and gas exchange in patients without neuromuscular diseases, and represent a good supportive therapy in patients with various forms of respiratory distress.

CPAP acts through improving arterial oxygenation and respiratory mechanics and reducing the patient's respiratory drive and effort.

Because the inspiratory effort creates a negative pressure inside the thorax, the ventricle afterload decrease. Accordingly, a decrease in inspiratory effort implies a reduction in the left ventricle afterload. Therefore, venous return and ventricle sizes are reduced with a parallel drop in the wall tension and myocardial oxygen consumption.

In patients with non-hydrostatic pulmonary edema, CPAP could improve gas exchange and respiratory mechanics, thereby increasing the end-expiratory lung volume and preventing alveolar collapse.

The alveolar extension provides a greater gas exchange surface, which improves the respiratory mechanics of ventilation and results in a consequent decrease of $PaCO_2$ in blood gas analysis [20].

Case Report

A 10 months old- infant, 3.5 kg, with negative familiar and medical history, arrived in Emergency Department complaining fever and dry cough from 3 days. At the moment of arrival she presented SpO_2 88% and a blood gas analysis with pH 7.36, pCO_2 44, pO_2 60, Na+ 136; K+ 4.6, Cl- 106, glycaemia 124; Lac 0.8; Hb 11.1; EB -0.5; HCO3- 24.3.

The chest X-ray showed widespread thickening of the bronchial walls and of the peribronchovascular interstitium which is associated with the presence of two shaded areas of increased density localized respectively in the right para-cardiac site and left basal, of possible atelectasis significance.

The patient was admitted in the Intensive Observation Unit and HFNC 2 L/kg/min., hydration, aerosol and antibiotic therapy were promptly started.

During the night an impairment of respiratory mechanic occurred with an increase of respiratory and cardiac rate, fever (T 38.6 C), wheezing and respiratory distress with nasal flaring, chest retractions and increase of respiratory effort.

The physical exam highlighted bilateral and diffuse crackles and a persistent several hypoxemia, despite maximal HFNC therapy, was detected at blood gas analysis.

The chest X-ray was repeated and showed that the areas of hypodiafania with an atelectasis significance appear increased. The widespread thickening of the bronchial walls remains bilaterally. Pleural cavities free from effusion. Cardio-mediastinal image within the limits, in axis.

The infant was admitted in Pediatric Intensive Care Unit and Helmet CPAP 40 L/min FiO_2 50% and peep valve set on 10 cm/H_2O was started.

CPAP was connected to a blender and an active humidification system that deliver a mixture of medical gas at the temperature of 32 °C.

The significant improvement in gas exchange, vital signs and sedation protocol, was reported in the Table 2.2.

Table 2.2 Patient improvement after Helmet CPAP therapy

Timing	pH	PaO_2	P/F	$PaCO_2$	Therapy	BP	HR	RR	Sedation
Pre CPAP	7.34	63	157	51	HFNC 40%	80/55	145	55	Morfine 0.01 mg/kg/h
1 h CPAP	7.36	117	228	51	CPAP 50% PEEP 10 cmH_2O	120/60	95	35	Dexdor 0.7 mcg/kg/h
12 h CPAP	7.42	128	256	44	CPAP 50% PEEP 10 cmH_2O	115/70	98	35	Dexdor 0.7–1.4 mcg/kg/h
24 h CPAP	7.40	178	356	42	CPAP 50% PEEP 10 cmH_2O	109/60	83	30	Dexdor 1.4 mcg/kg/h

Key Teaching Points

- NIV/CPAP erogated with Helmet is safe, well tolerated and effective to improve gas exchange and respiratory system workload.
- Humidity and temperature is two fundamental point to evaluate during CPAP with high fresh gas flow, especially in children, and if it is possible it should be used always an humidification system.
- When Helmet is used instead a mask to deliver NIV remember to set a 15–20% higher pressure to avoid CO_2 rebreathing and optimize respiratory workload
- Helmet is not a good interface to provide NIV in children due to excessive patient ventilator asynchronies and difficult triggering.

Hydration support was maintained with 14 mL/kg/h.

Waiting for microbiological results, corticosteroid and antibiotic therapy with ceftriaxone and clarithromycin were started.

Microbiological tests for Chlamydia Pneumoniae, Mycoplasma Pneumoniae and Bordetella spp. resulted negative, while nasopharyngeal aspirates were positive for Rhinovirus.

Serial radiological controls were made during the hospitalization in the intensive care unit and they showed a progressive improvement of pulmonary ventilation with a persistent upper right lobar hypodiafania and diffuse accentuation of the peribronchus-vascular texture.

Helmet CPAP showed a good patient's tolerance that allowed to a prolonged therapeutic effect with a significant beneficial effect on respiratory mechanics and gas exchange.

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Chapter 3
Mouthpiece Ventilation

Jennifer Obi and Stephen M. Pastores

Case Report
A 34-year-old man with severe spinal injury following a motor vehicle accident and a 2-year history of nocturnal non-invasive ventilation (NIV) use via nasal mask was admitted to the hospital after being noted to be increasingly somnolent. In the emergency department he was found to be hypercapnic and hypoxemic. His mother reported excessive mouth leak. On examination, the patient was drowsy but easily arousable. A continuous face mask NIV was started with marked improvement. Once stabilized, he was discharged with a follow-up visit in the outpatient pulmonary clinic. He continued to use the nasal ventilation. At follow up review, respiratory acidosis reoccurred despite diurnal use of NIV.

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Question: What is the appropriate next step in the management for this patient?

Answer: Continue NIV with intermittent daytime mouthpiece ventilation (MPV) alongside overnight NIV via nasal or face mask.

Following institution of MPV, control of respiratory failure was achieved. Most importantly, independent living was maintained. Intermittent MPV is practical and effective where the limits of ventilator tolerance have otherwise been reached. MPV may reduce the need for tracheostomy ventilation and this case serves as a reminder of the increasing NIV interface options available to clinicians.

3.1 Introduction

The mouthpiece ventilation (MPV) was introduced in the 1950s as a ventilatory mode that can be used as daytime ventilatory support in combination with other ventilatory modalities and interfaces for nocturnal noninvasive respiratory support.

Alveolar hypoventilation is a major complication of many neuromuscular diseases (NMDs). It occurs initially during sleep and subsequently extends into the daytime [1]. Nocturnal noninvasive positive pressure ventilation is the standard mode of initial management of alveolar hypoventilation in NMDs [2]; however as respiratory muscles weakness progresses, the ventilator-free breathing time is reduced significantly. When the number of hours of ventilator use per day exceed an arbitrarily defined threshold (e.g. >16 or 20 h), many practitioners consider transitioning to invasive ventilatory support via tracheostomy.

MPV has been used as an alternative to tracheostomy ventilation for patients requiring continuous ventilatory support for over 60 years. However, there is still a poor understanding of this method's benefits compared with other modalities. This chapter aims to highlight the indications, benefits and drawbacks of MPV.

3.2 Types of Mouth Piece Interfaces

There are two types of oral NIV interfaces: standard narrow mouthpieces with various degrees of flexion, which are held by the patient's teeth and lips; and custom-molded bite-plates (Fig. 3.1). Oral interfaces are used, especially in North America, for long-term ventilation of patients with severe chronic respiratory failure due to severe neurological dysfunction.

The mouth piece is placed between the patient's lips and held in place by lip-seal oral NIV interfaces. Intermittent MPV is practical and effective where the limits of ventilator tolerance have otherwise been reached. MPV may reduce the need for

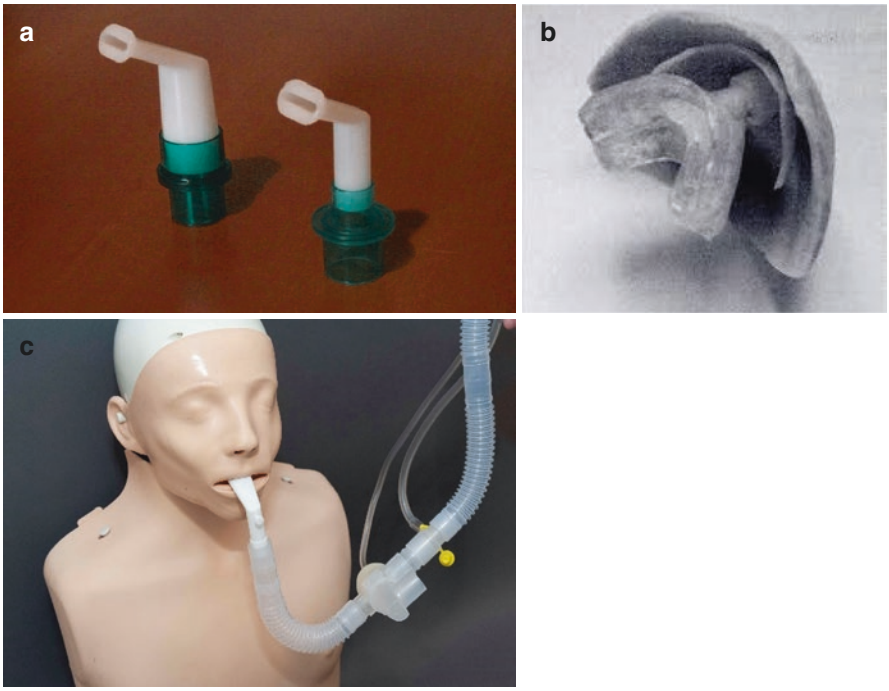

Fig. 3.1 Mouthpiece interfaces: (**a**) 22 and 15 mm angled mouthpieces with adaptors. (**b**) Custom-molded bite-plates. (Reprinted with permission from Copyright Clearance Center.) (**c**) Mouthpiece interface connected to ventilator circuit

tracheostomy ventilation and this case serves as a reminder of the increasing options routinely available to NIV clinicians.

3.3 Indications

MPV is mainly indicated for patients with NMD and chronic respiratory failure when they develop daytime hypercapnia despite optimized nocturnal ventilatory support or when they manifest deteriorating daytime respiratory status with increasing ventilator dependence. In individuals with adequate bulbar muscle function but chronic respiratory muscle insufficiency, intermittent MPV can be an effective alternative to tracheostomy.

Majority of patients considered for MPV have already been using mechanical ventilation for several years. However, the experience of MPV is quite different and some patients may feel uncomfortable and express reluctance to continue. Hence, the application of MPV requires active participation from the patient, increased nursing time and longer periods of training [1].

3.4 Mechanisms

A good candidate for MPV must be able to rotate his neck and grab the mouthpiece with his lips while maintaining good control of his upper airway muscles [3]. The patient activates the breath by putting the mouth on the mouthpiece and creating a small negative pressure in the circuit by sipping or inhaling from the mouthpiece. The negative pressure generated by a sip is much higher than that generated by a maximum static inspiratory pressure and can explain why a patient with advanced NMD can activate trigger without any inspiratory effort after a sip maneuver.

MPV is usually delivered via a home ventilator in the volume-assist-control mode with the tidal volume commonly set between 0.7 and 1.5 L (to correct for air leaks), zero positive end-expiratory pressure (PEEP) and a back-up respiratory rate ideally set to zero [1, 4]. Thus, the patient has the ability to define his pattern of breathing according to his own ventilatory needs by taking as many breaths as he requires and by modifying the quantity of leak [5]. This method is complemented by ancillary strategies of which the most important are the "air-stacking" maneuver and the glossopharyngeal breathing technique [1, 3, 4].

Air stacking requires an adequate glottic closure and is based on achieving maximum lung insufflation by delivering consecutive volumes of air [1, 6].

3.5 Advantages

The mouthpiece ventilator interface has the following significant advantages: less negative psychosocial impact on the patient, no risk of facial pressure sores, enhanced speech and swallowing, and improved self-imagery.

MPV allows the patient to be able to use glossopharyngeal breath in the case of sudden failure of the ventilator or accidental disconnection. It can significantly prolong survival while optimizing convenience, safety, and communication. The benefits of MPV are summarized in Table 3.1.

3.6 Disadvantages and Contraindications

The greatest disadvantage of mouthpiece ventilation is its limitation to being useful during waking hours except when retained by a lip covering interface like the Lipseal shown in Fig. 3.2.

MPV may elicit excessive salivation and long-term use can cause orthodontic deformities after use for 20–30 years. Air may also be swallowed leading to gastric distension and possibly vomit aspiration.

Table 3.1 Beneficial effects of mouthpiece ventilation for patients with neuromuscular disease

Site of action	Benefits
Airways	Improves patency of the upper airways Stabilizes gas exchange
Sleep	Improves quality of sleep and maintains gas exchange during the day
	Reduces symptoms related to chronic hypoventilation
Respiratory muscles and lungs	Favors the rest of respiratory muscles Resets the sensitivity of central chemoreceptors Improves lung compliance Slows thoracic deformity and decline in lung function
Infections	Reduces complications secondary to intercurrent infections
Overall effect on life	Improves quality of life Decreases morbidity and reduces mortality

Fig. 3.2 Lip seal interface

MPV is not successful when patients are uncooperative, cannot access the interface, or when a severe bulbar dysfunction causes aspiration of saliva such that the oxygen saturation at baseline remains below 95%. It can cause or exacerbate dry mouth. Such patients may benefit from heated humidification or switching to oronasal interfaces.

Despite remarkable results reported over the years, MPV is underutilized. Some of the reasons for its underutilization include clinicians being cautious about a technique which looks uncertain, lack of knowledge on how to set it up; advances in other mask technology (including nasal pillow systems); the high prevalence of NIV centers that use only pressure cycled ventilators, previous lack of commercially available equipment to secure the mouthpiece to the wheelchair or bed and financial disincentives for NIV management. Potential problems and solutions with the use of MPV are listed in Table 3.2.

Table 3.2 Mouthpiece ventilation problems and solutions

Problem	Incidence	Remedies
Discomfort	Common	Reassurance Diminishes with adaptation
Hypersalivation	Common	Reassurance Diminishes with adaptation
Aerophagia	Common	Simethicone
Pressure sores on lips, gums	Infrequent	Decrease strap tension Consider custom fitting orthodontic problems
Vomit aspiration	Infrequent	Optimize ventilatory support (i.e. reduce pressures slightly) Consider antiemetics
Air leak	Common	Encourage lip closure around the mouthpiece Nasal pledges or nose clips can be used to avoid air leak

3.7 Conclusions

Noninvasive ventilatory support is sometimes reported as suboptimal in patients with neuromuscular diseases. The reasons for this include inadequate ventilator settings and/or lack of interface tolerance. Mouthpiece ventilation can be used as a viable alternative to continuous ventilatory support via a tracheostomy tube in these patients. It requires a more active participation of the patient and an initial training period for the staff to teach the patient how to use it.

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Chapter 4
Discomfort and Adaptation in Non Invasive Mechanical Ventilation: Mask Interface Problems

Alejandro Úbeda Iglesias, Irene Fernández Burgos, and Rosario Ana Torcuato Barrera

Abbreviations

ARF	Acute respiratory failure
BIPAP	Bilevel positive airway pressure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
FiO_2	Fraction of inspired oxygen
GCS	Glasgow coma scale
IPAP	Inspiratory positive airway pressure
NIV	Non invasive ventilation
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PC-BIPAP	Control pressure—bilevel positive airway pressure
PEEP	Positive end- expiratory pressure
PS	Support pressure
PVD	Patient-ventilator dyssynchrony
$SatO_2$	Arterial oxygen saturation
VDd	Dead space of the mask
VDdyn	Dynamic dead space
VDph	Physiologic dead space

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Case Clinic
A 67-year-old man with COPD went to the emergency room due to exacerbation of his lung disease. On arrival at the emergency department, the patient was in a situation of hypercapnic encephalopathy, GCS 10 points, oxygen saturation (SpO_2) 60% with a Venturi oxygen mask at fraction of inspired oxygen (FiO_2) = 30%. The clinical exploration showed superficial breathing, tachypnea (25 breaths per minute), sweating and cyanosis. Arterial blood gases showed pH 7.01; PaO_2 45 mmHg; $PaCO_2$ 155 mmHg. The patient was transferred to the ICU for treatment of respiratory failure. The patient was connected to a NIV ventilator, with an oro-nasal mask, in BIPAP mode. The parameters initially programmed were: IPAP 12 cmH_2O, EPAP 5 cmH_2O, FiO_2 0.5, inspiratory ramp 100 ms. Initial adaptation to the ventilator was poor; leaks and discomfort prevented adequate ventilation so the interface was changed to a total face mask and optimized ventilator support. Few minutes later, a good adaptation was achieved, with almost all of the inspiratory efforts of the patient being assisted. The IPAP managed to ensure an appropriate tidal volume was 17 cmH_2O. One hour later, blood gas analysis showed pH 7.23; $PaCO_2$ 90 mmHg; PaO_2 70 mmHg. The level of consciousness improved. After 8 h of therapy, pH had normalized and the $PaCO_2$ was 56 mmHg. The patient remained with NIV for 3 days intermittently and finally discharged to hospitalization ward.

4.1 Choosing the Interface

Using a correct interface is crucial to success of the NIV. There are many different types of interfaces that can be used during NIV therapy in the acute setting (nasal, oronasal, total face mask and helmets) (Table 4.1). Choosing the appropriate interface involves consideration of patient preference and tolerance and selecting the correct size and fit is overrinding to successful ventilation (Fig. 4.1).

When choosing the most appropriate interface, great consideration should be given to minimize non-intentional leaks, which may impair the efficiency of NIV, in particular during the first few hours of ventilation when the patient needs to adapt to NIV[1]. Fortunately, ventilators for NIV are designed to compensate for a variable amount of air leaks.

Another challenge regarding interfaces is the amount of dead space. Dynamic dead space (VDdyn) derives from the physiologic dead space (VDph) plus the dead space of the device (VDd). The VDph is influenced by inspiratory flow rate, expiratory flow rate and tidal volume, while the VDd depends on the inner volume of the interface.

Although NIV is well tolerated by most patients, it is not entirely free from serious adverse side-effects and complications.

Table 4.1 Advantages and limits of different interfaces [1]

Interfaces	Advantages	Disadvantages
Nasal mask	Use of the mouth to drink, communicate, cough and expectorate	Decubitus Need for nasal patency Mouth leaks
Oro-nasal mask	No need for cooperation Breathing through mouth and nose	Vomiting, claustrophobia Decubitus Difficult communication and cough Edentulous
Nasal pillows	No decubitus	Reduces seal at high pressure (>15 cmH_2O) Nasal irritation Holes inside (no circuit with valve)
Total face mask	Few leaks Rapid to put on No need for cooperation Good for edentulous	Vomiting Claustrophobia Difficult cough and communication
Helmet	Few leaks Rapid to put on No facial decubitus No need for cooperation	Claustrophobia Vomiting Rebreathing Noise Asynchronies Axillary decubitus

4.2 Problems Related to the Interface [2, 3]

Air leaks. *There* are two kinds of air leaks: intentional and unintentional leaks.

- Intentional leaks are deliberately generated during NIV when a single-limb circuit without an expiratory valve is used. The aim is to avoid rebreathing by having holes in the mask or in the circuit to allow a leak proportional to their size and the set inspiratory pressure or mean inspiratory flow.
- An unintentional leak can occur between the mask and the skin, through the open mouth with nasal mask, or through the nose with mouthpiece ventilation.

Large air leaks have detrimental effects on the success of NIV, as leaks decrease the FiO_2 and arterial oxygen saturation ($SatO_2$) and increase ventilator autotriggering, increasing patient discomfort, which increase the risk of NIV failure. Moreover, air leaks may cause mouth and throat dryness, conjunctivitis or sleep disturbances.

Nasal/oral dryness and nasal congestion. Usually indicates air leakage through the mouth, which results in the loss of the nasal mucosal capacity to heat and to humidify inspired air. Increased nasal congestion and nasal resistance reduces tidal volume and patient discomfort [4].

Fig. 4.1 Different types of interfaces. (**a**) Total face mask. (**b**) Oro-nasal mask. (**c**) Nasal pillows. (**d**) Nasal mask. (**e**) Helmet

Patient-ventilator dyssynchrony (PVD). Of all interfaces, studies reported the helmet has more problems with patient-ventilator synchrony and ventilator cycling due to its soft compliant wall, upward displacement, and elevated internal compressible volume. This increases work of breathing [5].

Facial skin lesions. Nasal skin lesions such as erythema and ulcers may appear at the site of mask contact. It may occur in almost 100% of patients after 48 h of NIV with a mask. There are different types of skin lesions, ranging from slight redness over the nasal bridge to open ulcers or necrosis, which is an important factor that limits the tolerance and duration of NIV [3].

Arm oedema and deep venous thrombosis. The helmet is secured by two armpit braces; prolonged compression may produce venous and lymphatic stasis with consequent oedema, that may promote deep venous thrombosis in the axillary vein.

Carbon dioxide (CO_2) rebreathing. The interface represent an additional dead space which increases the chances of CO_2 rebreathing in proportion to dead space volume. The dead space of facial and nasal masks sin small compared with the tidal volume, and the amount of CO_2 rebreathed is also small. On the other hand,

helmets predispose to CO_2 rebreathing because its internal gas volume is larger than the tidal volume.

Claustrophobia. It may present as minor discomfort or as a frightening sense of restriction and suffocation. Nasal masks are less likely to cause claustrophobia than face mask. On the other hand, helmet use minimizes this event.

Discomfort. It is related to the device and the ventilation modality adopted for NIV. Among different of masks, tolerance is poorest for the mouthpiece followed by the nasal and oronasal masks. Helmets are better tolerated than masks, although a short NIV duration may explain lack of differences in comfort between the mask and helmet in the acute setting.

Noise. Device noise may increase patient discomfort, cause sleep disruption and affect ear function (tinnitus, hearing loss). Noise level is significantly greater during helmet NIV than during mask NIV [6].

Airways dryness. Cool and dry gases alter the tracheobronchial mucosa and may cause mucous plugging and atelectasis. This is less important during helmet NIV, because the high internal gas volume could serve as a mixing chamber between the heated humidified expired gas and the dry medical gas entering the helmet [7].

Gastric insufflation. Large tidal volumes, high airway resistance, low respiratory system compliance and short inspiratory time increase airway pressure and air entering the stomach. Gastric insufflation also facilitates vomiting and inspiration of gastric contents can cause severe complications.

Key Teaching Points

- The choice of the interface during NIV represents the main determinant of its success in an acute setting and one important factor contributing to the long-term tolerance and efficacy of NIV in a chronic setting.
- The availability of different types of masks could allow different approaches for each individual situation, optimizing patient tolerance and avoiding side effects.
- The main reasons for choosing a particular interface are patient comfort, the prevention of leaks or complications and the amount of dead space.

Questions and Answers

1. Which one is NOT a disadvantage of non invasive mechanical ventilation using a helmet?

   (a) Claustrophobia.
   (b) Noise.
   (c) Rebreathing.
   (d) Vomiting.
   (e) Nasal decubitus.

   Answer: (e) Nasal decubitus.

2. Arm oedema and deep venous thrombosis may appear more frequently in NIV with:

   (a) Nasal mask.
   (b) Oro-nasal mask.
   (c) Nasal pillows.
   (d) Helmet.
   (e) Total face mask.

   Answer: (d) Helmet.
3. Air leaks have different effects; choose the INCORRECT answer:

   (a) Decrease the FiO_2 received.
   (b) Decrease arterial oxygen saturation.
   (c) Increase patient discomfort.
   (d) Decrease ventilator autotriggering.
   (e) Increase the risk of NIV failure.

   Answer: (d) Decrease ventilator autotriggering.
4. Which of the following interfaces produces more carbon dioxide rebreathing?

   (a) Helmet.
   (b) Total face mask.
   (c) Oro-nasal mask.
   (d) Nasal mask.
   (e) Nasal pillows.

   Answer: (a) Helmet.
5. Airway dryness is an important problem related to the interface during NIV, but it less important when using…

   (a) Nasal mask.
   (b) Oro-nasal mask.
   (c) Nasal pillows.
   (d) Total face mask.
   (e) Helmet.

   Answer: (e) Helmet.
6. What is not a problem related to the interface during NIV?
   (a) Air leaks.
   (b) Facial skin lesions.
   (c) Gastric insufflation.
   (d) Discomfort.
   (e) All can be problems related to the interface during NIV.

   Answer: (e) All can be problems related to the interface during NIV.

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Chapter 5
Discomfort and Adaptation. Mask Interface Problems

Jennifer Obi and Stephen M. Pastores

Case Presentation

A 75-year-old woman presented to the emergency department with hypercapnic respiratory failure and severe pneumonia. The patient had several comorbidities including chronic obstructive pulmonary disease, uncontrolled hypertension, and ischemic heart disease. As her condition continued to deteriorate further, she was admitted to the intensive care unit (ICU). The patient was unable to maintain adequate arterial oxygen saturation via a face mask and nasal prongs. The attending physician ordered non-invasive ventilation (NIV) and a continuous positive airway pressure (CPAP) mask was applied. On day 3 of her ICU stay, one of the authors noticed a Grade II pressure ulcer on the bridge of her nose.

Examination of the patient showed a tight-fitting full facial mask. On further evaluation, the caregivers found that the CPAP mask had been kept in

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place for almost 24 h without any formal monitoring or inspection of pressure areas. The patient's family refused to consent to the physician's request for invasive mechanical ventilation. The patient is less hypercapnic and dyspneic but has a significant pressure ulcer on the bridge of her nose.

Question: What is the next appropriate step in the management of this patient?
Answer: Continue noninvasive ventilation with a different mask and establish goals of care

5.1 Principles of Management

5.1.1 Introduction

Noninvasive ventilation (NIV) refers to the delivery of ventilatory support through the patient's upper airway using a mask or similar device. This technique is distinguished from those which bypass the upper airway with a tracheal tube, laryngeal mask, or tracheostomy and are therefore considered invasive [1]. An increasing number of masks that are lighter and more comfortable are becoming available for use in patients with nasal obstruction. Currently available types of masks include nasal masks, nasal pillows, oronasal masks, and oral masks [2].

In the acutely ill patient, comfort may be less important than the efficacy of the treatment. However, even if the need for noninvasive positive pressure ventilation is short-term, mask fit, and care are required to prevent skin damage. The choice of interface is a major determinant of NIV success or failure, mainly because the interface strongly affects patient comfort [3, 4]. Furthermore, interface choice can strongly influence the development of NIV problems, such as air leak, claustrophobia, facial skin erythema, acneiform rash, skin damage, and eye irritation [5–13].

The most common sites of friction and skin damage are the bridge of the nose, the upper lip, the nasal mucosa, and (with the helmet) the axillae. Skin irritation is sometimes due to skin hypersensitivity to certain materials or excessive sweat. The most important approach to prevent skin damage is to avoid an excessively tight fit. Figure 5.1 shows a simple method to avoid this risk. It involves leaving enough space to allow two fingers to pass beneath the headgear [13]. A small amount of air leak is acceptable and should not significantly affect patient-ventilator interaction [14].

5.2 Interface Selection

Interface selection is mainly influenced by the patient's individual characteristics (such as facial anatomy, breathing pattern and individual level of comfort) and clinical effectiveness, but the experience of the staff, equipment availability and

Fig. 5.1 Two finger breath test

economic aspects are also relevant [14]. In the few studies comparing different types of interfaces in acute NIV, the improvements in respiratory parameters, i.e. dyspnea, respiratory rate and arterial blood gases, were usually similar. There is currently no strong scientific evidence that one type of mask is necessarily or consistently better than others in terms of clinical efficiency.

However, patients in acute respiratory failure (ARF) often mouth-breathe and, even if they can be started on a nasal mask, switching to an alternative interface covering the nose and mouth is necessary in many patients if mouth air leaks occur [15, 16]. In clinical practice, the most common initial interface to treat ARF with NIV is, therefore, an oronasal mask. In a large web-based survey conducted in Europe and North America, oronasal masks were the first choice of interface (70%) followed by total face masks, nasal masks and helmets [17].

In a retrospective analysis of all CPAP implementation polysomnograms, polysomnography results and patient data were compared according to mask type (n = 358). Compared to nasal mask types, oronasal masks were associated with higher CPAP pressures (particularly pressures ≥15 cmH_2O) and a higher residual apnea-hypopnea index (AHI) [18].

Discomfort and non-compliance with NIV interfaces are obstacles to NIV success. Ensuring compliance involves selection of a mask interface that is comfortable and easy to use. The characteristics of an ideal NIV Interface and Securing System are shown in Table 5.1.

5.3 Types of Interfaces

The classes of NIV interface shown in Fig. 5.2 include the Oral or Mouthpiece which is placed between the patients lips and held in place by lip-seal. The Nasal mask covers the nose but not the mouth while nasal pillows are plugs inserted into

Table 5.1 Characteristics of an ideal noninvasive ventilation interface and securing system

Ideal interface	Ideal securing system
Leak-free or minimal Good stability Non-traumatic, light-weight, long-lasting Non-allergenic material like silicone Low resistance to airflow Minimal dead space Low cost	Stable (to avoid interface movements or dislocation) Easy to put on or remove Nontraumatic light and soft breathable material Obtainable in various sizes Works with various interfaces Washable (if used at home) Disposable (for hospital use)

Fig. 5.2 Interfaces for noninvasive ventilation. Top (left to right): nasal mask, nasal pillows, oronasal mask. Bottom (left to right): total face mask, oral mask, hybrid mask

the nostrils. The Oronasal covers the nose and mouth while the Full-face mask covers the mouth, nose, and eyes. The Helmet interface covers the whole head and all or part of the neck with no contact with the face or head.

Each mask is built to meet the preferences of patients and their clinical needs while providing more comfortable, better-tolerated, easier-to-use, and safer interfaces. The advantages and disadvantages associated with each interface are shown in Table 5.2.

5.4 Mask Interface Problems and Solutions

5.4.1 Mask Claustrophobia

Claustrophobia is prevalent among adults treated with NIV mask interfaces that cover the mouth. It can influence both short-term and longer-term adherence. Claustrophobia is an anxiety disorder of specific phobia type in which individuals

Table 5.2 Advantages of and contraindications of interfaces for noninvasive ventilation

Types of mask	Indications	Landmarks for best fit	Advantages	Disadvantages
Full face	Critically ill patients Used for acute hypercapnic and hypoxemic respiratory failure	Below the lower lip with the mouth open. Corners of the mouth. Just below the junction of nasal bone and cartilage	Better ventilation Less leakage	Claustrophobia, Patients less able to communicate Risks of gastric insufflation with aspiration Increased dead space Difficulty in maintaining a seal Increased risk of pressure sores Increased aspiration risk Difficulty with speech Inability to eat with the mask on Difficulty with secretion clearance and possible asphyxiation
Nasal cushions or prongs	Suitable for patients with claustrophobia, skin sensitivities and need visibility	Plastic sizing gauge that is inserted in each nostril. Headgear tension should allow 1–2 fingers between the head straps and the face	Less risk of aspiration Greater secretion clearance Less claustrophobia Permits speech Less dead space	Increased leakage from mouth Less effectiveness with nasal obstruction Nasal irritation and rhinorrhea Mouth dryness
Nasal masks	Preferable for long-term ventilation but also used for acute hypercapnic and hypoxemic respiratory failure	Fitting over the nose	Less risk of aspiration Enhanced secretion clearance Less claustrophobia Easier speech Less dead space	Mouth leak Less effectiveness with nasal obstruction Nasal irritation and rhinorrhea Mouth dryness
Helmet mask	Acute hypoxemic respiratory failure Acute cardiogenic pulmonary edema	Not required	Allows prolonged continuous application of NIV due to less complications like skin necrosis, gastric distension, and eye irritation	Need for monitoring of volumes Difficult humidification Claustrophobia Tetraplegia

experience fear or avoid situations which involve enclosed places [19]. Claustrophobia includes components of fear of restriction and fear of suffocation. The incidence of claustrophobia ranges from 5 to 20% [20]. Potential causes include cumbersome face mask and underlying anxiety.

The solutions to claustrophobia includes choosing the correct interface and size. The use of manual mask application (i.e. placing the interface gently over face, holding it in place and starting ventilation to allow for acclimatization with the mask; subsequently the straps are tightened to avoid major air leaks). Starting with the lowest pressure support on initiation of NIV may help to improve patient comfort. Cognitive behavior therapy, change of interface (i.e. consider the helmet or nasal pillows instead of the face mask) and anxiety or mild sedative medication may also help reduce mask-associated claustrophobia.

5.4.2 Aerophagia

Aerophagia appears in up to half of the patients with NIV and may lead to discontinuing treatment. It refers to the abnormal accumulation of air in the gastrointestinal tract as a result of repetitive and frequent inflow of air through the mouth. During NIV, the ventilation volume distributes between lungs and stomach depending on respiratory system resistance and lower esophageal sphincter pressure (20–25 cmH_2O in adults) which, in turn, varies with head position, inflation flow rate, inspiratory time, and tidal volume [21]. Predisposing factors include large tidal volumes (800–1200 mL), high airway resistance, low respiratory system compliance, and short inspiratory time. These factors increase airway pressure and air entering the stomach. Symptoms present as bloating, abdominal distention, flatulence, or excessive belching [22].

When gastric insufflation occurs during NIV, gastric distension compresses the lungs, thereby decreasing lung compliance and requiring higher airway ventilation pressure [23, 24]. The latter is also associated with increased risk of gastric distension, thus generating a vicious cycle [23, 24]. The unusual respiratory pattern may be exacerbated by bronchoconstriction and bronchial hyperreactivity induced by gastric distention [24].Although rarely intolerable, gastric insufflation facilitates vomiting and inspiration of gastric contents and can cause serious complications (such as pulmonary aspiration, abdominal compartment and hypertension syndromes, stomach rupture, and, exceptionally, death).

Solutions for aerophagia include avoiding airway pressures higher than 20–25 cmH_2O. Drugs that accelerate gastrointestinal transit, changes in the respirator settings or changing the ventilatory modality may help to alleviate the problem. When the symptoms arising from abdominal distension due to NIV are intense and persistent, the coexistence of an underlying abdominal pathology must be ruled out [24].

5.4.3 Sore Nose, Skin Irritation and Ulcers

Skin rashes may develop due to hypersensitivity to the mask interface or infection. The incidence is about 10–20% [25]. Skin damage may result from the generic mask designs employing traditional polymer materials, which may not match the shape or compliance of an individual's facial features. In addition, there is little guidance for clinicians regarding the application of NIV masks, with straps often being applied with high tensile forces to achieve a seal with the face. The rashes typically respond to topical corticosteroids or antibiotics [25].

One of the most serious mask-related complications is ulcer on the nasal bridge. Progressive tightening of the harness, increasing the air volume in the mask cushions, and increasing inspiratory pressure are factors that promote nasal pressure ulcers [23].

It is vital to recognize patients at risk of developing pressure ulcers from the interface so that preventive strategies can be initiated early. An initial assessment of every patient receiving NIV should include examination of skin integrity on the face and around the head, in areas where the skin comes into contact with the headgear, and the common risk factors for healthcare and device-related pressure ulcers.

Worsely et al. investigated the effects of strap tension during non-invasive ventilation application mask and reported that strap tension had a significant effect on the pressure exerted on the nose. This can result in discomfort and an inflammatory response at the skin surface [25]. The two-finger breath test (Fig. 5.1) allows for a snug fit without excessive tension.

The most important strategy in the prevention of pressure ulcers is to keep the pressure applied to the skin as low as possible. It can be challenging to find the ideal strap tension and mask fit that allows for both a good seal and low pressure on the skin. Unfortunately, the pressure on the face cannot be measured quantitatively in everyday care or in every mask type and neither does it give information on single points of high pressure, for example the nasal bridge. Therefore, the clinicians who fit the mask must be guided by the patient's feedback and their experience. In addition, the skin should be reassessed at least once per nursing shift and ideally every time the mask is removed.

5.4.4 Air leaks

One of the main factors leading to NIV failure is air leak which can be major (10–20%) or minor (80–100%). Leaks include intentional leak through the passive exhalation port as well as unintentional leaks due to a loose-fitting interface. The incidence varies depending on the type of interface [22]. Leaks decrease arterial oxygenation by reducing tidal volumes and patient synchrony, and also causes mouth and throat dryness, conjunctivitis, and sleep disturbances [26]. Air leaks should be monitored closely and taken care of promptly. To reduce air leak, many

caregivers tighten the straps of the mask, unfortunately this may exacerbate patient discomfort by inducing nasal skin lesions, which potentially occurs in 50% of patients [26, 27].

Minimizing leaks can be achieved by adjusting the patient interface and pressure levels. A reduction in inspiratory pressure or tidal volume may help diminish air leaks. Specific algorithms for leak compensation have thus been incorporated into newer ventilators to reduce these adverse effects.

An important functional characteristic of bilevel ventilators is their ability to compensate for leaks. In the past, critical care ventilators did not adjust for leaks, however newer generation ventilators have in-built leak compensation with NIV modes. Lastly, masks that cover the nose and mouth help to minimize leaks and are the preferred initial choice in the acute care setting.

5.4.5 Carbon Dioxide Rebreathing

Carbon dioxide (CO_2) rebreathing is a complication of NIV. This may impair CO_2 removal and load the ventilatory muscles [28–33]. Rebreathing may be related to the interface used for NIV, ventilator circuit, and the mode and respiratory pattern of NIV delivery [34]. High respiratory rates and low external PEEP increase the risk of rebreathing because these are associated with shorter expiratory times and low CO_2 removal from the circuit. Systems that use true exhalation valves have shown significant variation in the resistance to exhalation through the valve. This increased resistance can increase the work of breathing associated with difficult exhalation [35].

The interface for NIV and ventilator circuit represent an additional dead space which increases the chances of CO_2 rebreathing in proportion to dead space volume [31–33]. The dead space of facial and nasal masks is small compared with the tidal volume, and the amount of CO_2 that is rebreathed is also small. Unlike masks, helmets predispose to CO_2 rebreathing because its internal gas volume is larger than the tidal volume [34].

Lowering the respiratory rate, ensuring an adequate inspiratory tidal volume, adding PEEP, and increasing the expiratory time have been advocated as general measures to reduce CO_2 rebreathing.

5.4.6 Nasal or Oral Dryness and Nasal Congestion

The nasal mucosa has a considerable ability to heat and humidify inspired air. Nevertheless, it can be overwhelmed by high flow rates and unidirectional flow occurring during NIV. Nasal/oral dryness affects 10–20% of patients and nasal congestion occurs in 20–50% of cases, particularly when a nasal mask or nasal CPAP

is used [35–38]. Nasal or oral dryness is usually indicative of air leaking through the mouth with consequent loss of the nasal mucosa's capacity to heat and to humidify inspired air.

In an experimental setting, Wiest and colleagues showed that dryness-related symptoms started to appear when absolute humidity was lower than 15 mgH_2O/L. [39] The flow of cold air through the nose dries the mucosa, resulting in the release of vasoactive and proinflammatory mediators. These boost superficial mucosal blood flow and cause inflammation of deeper capacitance vessels, leading to increased nasal resistance. This in turn promotes mouth breathing, setting up a vicious circle resulting in reduced tidal volume and patient comfort.

Strategies to decrease these complications include ensuring a proper fitting mask and humidifying the inspired air. Fortunately, most current NIV devices come with an integrated heated humidification system. These machines deliver more moisture than cold pass-over humidifiers and may be more effective in patients with mouth leak and nasal congestion.

5.4.7 Eye Irritation

Eye irritation or conjunctivitis can be caused by air leaks near the eyes if they are not noticed. Small air leaks can be assessed by placing the back of the hand over the area, and routinely asking the patient about eye irritation throughout the treatment and every time the mask is fitted. Artificial tears can also be used for dry eyes.

5.4.8 Noise

NIV delivery may be associated with noise which may exceed usual background noise and may theoretically increase patient discomfort, cause sleep disruption, and affect ear function. There is no problem with air leaks with the helmet interface, but the high-flow system creates a higher level of noise within the device than other interfaces and providing ear plugs for the patients can be helpful.

If air leaks create noise, the mask should be refitted, and a lining can be added to seal it. Choosing the correct interface and size, use of earplugs and sound traps may help decrease noise and improve patient comfort.

In conclusion, NIV is a valuable asset in clinical practice. However, in order to ensure favorable patient outcome, NIV should be applied by a trained and experienced team with knowledge of the indications for its use and proper interface selection. Mask fitting and prevention of mask-related problems are key components for NIV success. Patients should be assessed frequently for complications like ulcers, air leaks, and patient–ventilator interaction to ensure tolerance and comfort.

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Chapter 6
Unusual Facial Muscle Atrophy Associated with Noninvasive Ventilation

António Madeira Gerardo, Maria Inês da Luz Ferreira, Carla Filipa Alves Simão Valente, and Hedi Esteves Sequeira Liberato

Abbreviations

COPD	Chronic obstructive pulmonary disease
CRF	Chronic respiratory failure
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive lung disease
ICS	Inhaled corticosteroid
NIV	Noninvasive positive ventilation
OCS	Systemic corticosteroids
PEEP	Positive end-expiratory pressure
T90	Time Spent SpO_2 <90%

6.1 Introduction

Noninvasive positive ventilation (NIV) has undergone a remarkable evolution over the past decades and is assuming an important role in the management of both acute and chronic respiratory failure. Long-term ventilatory support should be considered

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a standard of care to treat patients with chronic ventilatory failure just like COPD patients. Several factors predispose severe COPD patients to chronic respiratory failure: severe airflow obstruction, hyperinflation, imbalances in the respiratory muscle length-tension relationship, malnutrition, chronic systemic steroid use and comorbid conditions [1].

A multicenter randomized controlled trial of 195 patients with stable COPD who were classified as having hypercapnic GOLD stage IV disease found, at 12-month follow-up, that the use of NIV was associated with lower mortality as compared with usual care (12% and 33%, respectively) [2].

NIV may have some adverse effects and complications, such as discomfort, facial edema, claustrophobia, nasal congestion, facial pain, eye irritation, aspiration pneumonia, hypotension, and pneumothorax. Problems such as aerophagia, rebreathing, abdominal distension, vomit, bronchoaspiration, morning headaches, face compression injuries, gas embolism and lack of adjustment of patients are inherent to the method and may restrict its use. However, these complications may be reduced with the use of adequate interface and with the experience of the physicians.

In patients who use NIV during multiple hours a day for many years, the side effects of NIV are more frequent [3].

6.2 Clinical Case

The authors discuss the case of a 73-year-old man, former smoker (84 pack/year). He has developed a dry, hacking, non-productive cough over the last 19 years. He has a number of other health problems, including pulmonary arterial hypertension, bronchiectasis on lung CT-scan (Fig. 6.1) with recurrent infections to *Pseudomonas aeruginosa*, depression and anxiety. His usual therapy consists of regular long-acting β2-agonist, inhaled corticosteroid (ICS) and a long-acting anti-muscarinic.

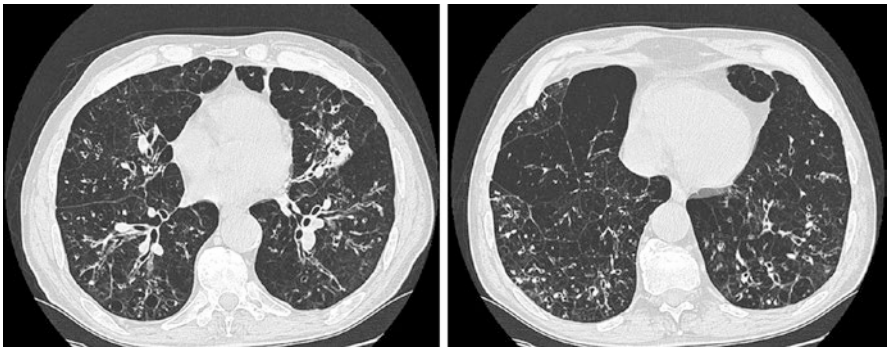

Fig. 6.1 Lung CT-scan showing bilateral findings of centrilobular emphysema, bronchial wall thickening and cylindrical bronchiectasis

His pulmonary function tests post-bronchodilator indicates a forced expiratory volume in 1 second (FEV1) of 920 mL (33% of predicted) and a forced vital capacity (FVC) of 3000 mL (70% of predicted), with mild elevated total lung capacity and residual volume suggesting hyperinflation and air trapping. The diffusion capacity of carbon monoxide (DLCO) is markedly reduced (30% of predicted). In the 6-Minute Walk Test he walked 150 m. Nocturnal oximetry showed T90 was 87%. He scored a BODE index of 8.

He has had a few years period without COPD exacerbations requiring hospitalization. However, in the past 4 years, he began to have gradually worsening exercise tolerance for which his inhalers seem to be largely ineffective. He developed chronic respiratory failure (CRF) that progressed to hypercapnic respiratory failure and started domiciliary NIV with BIPAP ST (BiPAP; Respironics Inc.; Murrysville, PA).

He had 6 hospitalizations for acute exacerbations (that were treated with nebulized bronchodilators, systemic corticosteroids (OCS), and antibiotics), two of them with mechanical ventilation that conduced to diminishing lung function and CRF requiring a progressive increase in the number of hours of NIV (22 h/day) and in the pressure values (IPAP 26 cmH_2O).

Due to the progressive worsening of lung function, this patient uses the NIV almost 24 h/day, which can lead to NIV-related complications. Simultaneously, this patient started to reveal bilateral facial muscle atrophy (Fig. 6.2), loss of limb muscle mass, body fat free mass and lastly a progress to cachexia.

Fig. 6.2 Bilateral facial muscle atrophy in a patient using high-pressures NIV almost 24 h/day for many years

6.3 Discussion

COPD is defined as a syndrome characterized by usually progressive chronic airflow limitation which is associated with a bronchial hyperresponsiveness and is partially reversible.

Progression of COPD is frequently associated with increasing dyspnea, indeed, patients with severe COPD constitute the largest group of patients with CRF. The dyspnea in these patients is mostly related to increased work of breathing, a consequence of an increased resistive load, of hyperinflation, and of the deleterious effect of intrinsic positive end-expiratory pressure (PEEP). Patients with end-stage COPD have limited treatment options, however, since the application of NIV improvements have been reported [4].

NIV provides a larger tidal volume with the same inspiratory effort, thus improving alveolar ventilation and decreasing the work of breathing (Fig. 6.3). This treatment can also decrease the work of breathing by partially overcoming auto-positive end-expiratory pressure (auto-PEEP), i.e., pressure remaining in the alveoli at the end of exhalation that is greater than the atmospheric pressure [5].

Because of the progressive worsening of lung function, the patient uses the NIV more and more hours a day until total dependence. This point is particularly important due to a higher probability of complications associated with NIV.

When NIV is applied, patients must be monitored and attention must be given to their comfort, level of dyspnea, respiratory rate, and oxyhemoglobin saturation. Patients must be watched for signs of ventilator–patient asynchrony, nasal-mask intolerance, serious air leaks, gastric distention, drying of the eyes, and facial-skin breakdown, especially at the bridge of the nose. Gastric distention is very unlikely with pressure-support levels lower than 25 cmH_2O [7]. The side-effects of NPV are reported in Table 6.1.

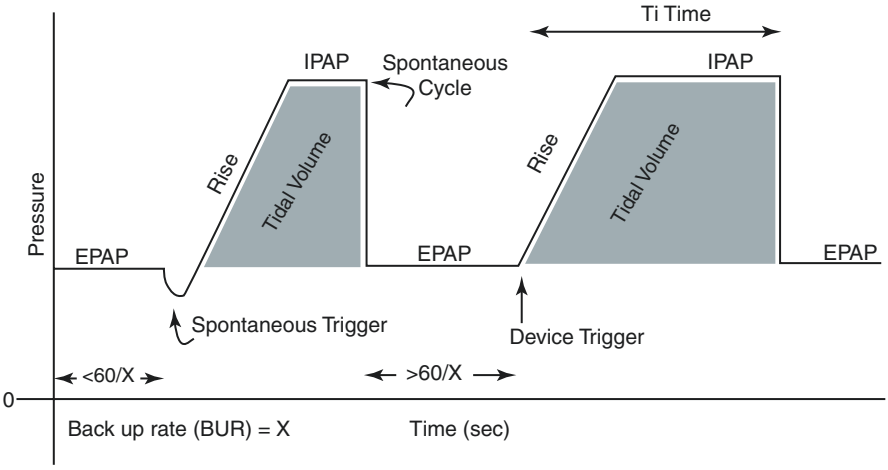

Fig. 6.3 Pressure waveform ST mode (spontaneous/timed) [6]

Table 6.1 Adverse events and complications of NIV with different interfaces and patient conditions [3]

	Frequency(%)	IF/Patient condition	Remedy
Interface related			
Carbon dioxide rebreathing	50–100	H > FM > NM	Reduce respiratory rate and IF size
Claustrophobia	5–10	FM > NM > H	Reduce inspiratory pressure, sedation
Discomfort	30–50	FM > NM > H	Change IF, sedation
Facial skin erythema	20–34	FM > NM > H	Check IF fit
Nasal bridge ulceration	7–100	FM > NM > H	Change IF
Arm edema and arm vein thrombosis	<5	H/ malnutrition	Check H armpits
Mechanical malfunction	<1	FM = NM = H	Check equipment
Noise	50–100	H > FM = NM	Change IF, use heat and moisture, earplugs, sound traps
Patient ventilator dyddynchrony	50–100	H > FM = NM	Add/increase PEEP
Air Pressure and Flow Related			
Air leaks	18–68	NM > FM > H	Check IF fit, reduce pressure
Nasal or oral dryness and congestion	20–50	FM = NM > H	Add humidificers and emollients, reduce inspiratory pressure
Gastric Distension	5–50	FM > NM > H	Reduce inspiratory pressure
Patient Related			
Aspiration pneumonia	<5	All IF/ileum	Follow NPSV contraindications
Barotrauma	<5	All IF/COPD, neuromuscolar disease, cystic fibrosis	Follow NPSV contraindications
Hemodynamic effects	<5	All IF/high blood pressure	Follow NPSV contraindications

COPD chronic obstructive pulmonary disease; *H* Helmet; *FM* face mask; *IF* interface; *NM* nose mark; *NPSV* noninvasive pressure support ventilation; *PEEP* positive end-expiratory pressure

There are limited data about the side effects of long use of NIV, including the effects on facial and cervical muscles. In patients with 24 h/dependency of NIV, facial deformity can occur due to the pressure applied by the mask on facial structures, the mask can cause erythema and skin necrosis. Skin injury was related to the use of the same mask every day, without an interface rotation. Bilateral facial muscle atrophy represents a rare collateral effect of NIV during multiple hours a day for many years. This effect has not been described before and we believe that its association with NIV is justified.

There is growing scientific evidence of COPD's multi-systemic impact. Limb muscle dysfunction is a major systemic consequence of COPD and may be associated with increased mortality, poor quality of life and increased healthcare use.

Key Teaching Points

- COPD is a chronic disease with high mortality and morbidity worldwide.
- Patients with end-stage COPD frequently develop chronic hypercapnic respiratory failure associated with end-of-life.
- The utility of NIV in acute hypercapnic respiratory failure in COPD is well-established. NIV improves outcomes in this patients.
- NIV can be associated with adverse effects. There is limited data about the side effects of long use of NIV, including the effects on facial and cervical muscles

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Chapter 7
Noninvasive Ventilation: Continuous Positive Air Pressure Ventilation (CPAP) and Pressure Support Ventilation (PSV)

Edoardo Piervincenzi, Giorgio Zampini, and Daniela Perrotta

Abbreviations

% pred	Percent of predicted value
AE-IPF	Acute exacerbation of IPF
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
CPAP	Continuous positive airway pressure
DAD	Diffuse alveolar damage
DNR	Do not resuscitate
DP	Driving pressure
$ECCO_2R$	Extracorporeal CO_2 removal
ETI	Endotracheal intubation
FEV1	Forced expiratory volume in the 1st second
FEV1/FVC ratio	Forced expiratory volume in the 1st second/Forced Vital capacity

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FiO_2	Inspired oxygen fraction
FMV	Face-mask ventilation
FVC	Forced Vital capacity
GCS	Glasgow Coma Scale score
HFOT	High flow oxygen therapy
HRCT	High resolution computed tomography
ICU	Intensive care unit
ILD	Interstitial lung disease
IMV	Invasive mechanical ventilation
IPF	Idiopathic pulmonary fibrosis
MOF	Multiple organ failure
MV	Mechanical ventilation
NIV	Noninvasive mechanical ventilation
NMBAs	Neuromuscular blocking
P/F	PaO_2/FiO_2: ratio of PaO_2 to fraction of inspired oxygen
$PaCO_2$	Carbon dioxide arterial pressure
PaO_2	Oxygen arterial pressure
PBW	Predicted body weight
PEEP	Positive end expiratory pressure
P-SILI	Patient self-inflicted lung injury percentage (%)
PSV	Pressure support ventilation
pts	Patient/s
RICU	Respiratory intensive care unit
RR	Respiratory rate
SaO_2	Arterial oxygen saturation
SAPS	Simplified acute physiology score
SB	Spontaneous breathing
TLC	Total lung capacity
TV	Tidal volume
UIP	Usual interstitial pneumonia
VAP	Ventilator-associated pneumonia
VILI	Ventilator-induced lung injury
WOB	Work of breathing

7.1 Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a chronic progressive-fibrosing interstitial pneumonia of unknown cause, with high morbidity and mortality in older adults [1]. Although most IPF patients (pts) show a gradually progressive course, some subjects follow a relatively rapid decline, whether this represents a distinct phenotype is still not known [2]. IPF acute exacerbation (AE-IPF) is characterized by a diffuse alveolar damage (DAD), with evidence of new bilateral ground-glass opacity and/or consolidation on an Usual Interstitial Pneumonia (UIP) pattern. It

results in the development or severe worsening of dyspnoea, typically <1 month in duration, without an identifiable cause, and is characterized by evidence of low PaO_2/FiO_2 ratio (P/F) that may lead to severe hypoxemia [1]. In this subset of subjects (5–10%) mechanical ventilation (MV) may be required in order to improve oxygenation when high flow oxygen-therapy is not sufficient, and can represent a palliative therapeutic option, which reduces patient's discomfort and helps avoiding more invasive approaches [3]. AE-IPF has a poor outcome with a median survival after diagnosis ranging from 3 to 5 years and Invasive Mechanical Ventilation (IMV) seems to be useless to ameliorate prognosis [4].

7.2 Mechanical Ventilation in IPF: Basic Topics

Current IPF guidelines recommend that the majority of patients with respiratory failure should not receive IMV [4]. The rationale is that both the structural lung disease and the precipitating condition causing ARF are irreversible and progressive [4]. Poor prognosis data about IMV in IPF are based on previous studies conducted before the lung protective strategies were performed [5]. An agreement was based on the consideration that a more severe baseline hypoxemia, higher mechanical ventilation pressures, and the presence of diffuse ILD are associated with a poorer outcome [6–8]. Despite numerous aetiologies, Interstitial Lung Disease (ILD) shows a progressive impairment in respiratory mechanics and in physiological lung function. The IPF alterations are of the restrictive kind, with a decreased lung capacity and an increased FEV1/FVC ratio. Reductions in lung compliance occur early, and may be tightly correlated with the degree of lung fibrosis [9]. This leads to a poor recruitment of the lungs, in spite of the use of high mechanical ventilation pressures needed to obtain adequate tidal volume (TV). AE-IPF presents several patho-physiological features linked to Acute Respiratory Disease Syndrome (ARDS) [10]. As reported in Marchioni et al. 2018, in the presence of DAD there is a partial overlap between AE-IPF pts and a fair percentage of ARDS pts [11]. Both ARDS and AE-IPF show an over-expression of pro-inflammatory cytokines produced by alveolar macrophages with chemotaxis of neutrophils [12]. The use of higher Positive End Expiratory Pressure (PEEP) value in AE-IPF pts may be harmful, just as in ARDS pts who have a low percentage of recruitable lung, since it simply overinflates lung regions that are already open [13]. Performing IMV in IPF pts is not useful, both because of a low percentage of recruitable lung areas and because their lungs are not edematous. As result in this kind of patients an "open lung strategy" with high levels of PEEP (>10 cmH_2O) may determine Ventilator-Induced Lung Injury (VILI) by provoking over-distension injury and bio-trauma. Moreover "the use of high PEEP to keep alveolar units opened during expiration exposes the lung at risk of injury by forming 'squishy ball' lung areas that aggravate the end-inspiratory transpulmonary pressure effects" [14]. Thus Marchioni et al. (2020) suggest using a "lung resting strategy", as opposed to "open lung approach" in IPF pts (with UIP pattern) under MV, "regardless of the underlying etiology"

[14]. When IMV has to be used in IPF pts, low TV and low PEEP should be employed (not that this topic is still under discussion in ARDS!) regardless of the mode of ventilation ("volume controlled or pressure controlled") [5]. The use of IMV in AE-IPF pts is associated with a high in-hospital mortality rate (86–100%) when it is performed at high TV [(>8 mL/kg of Predicted Body Weight (PBW)] [7]. On the other hand, mortality is reduced when low TV values (<8 mL/kg PBW) at 64% [15] and 67% [16] are used. This also occurred in a large cohort study, where the in-hospital mortality of IPF pts mechanically ventilated (IMV = 51.6% vs. NIV = 30.8%) was approximately 50% [17], due to a more frequent use of lung protective strategies that may have improved the outcomes. In conclusion, "these are encouraging results that may help physicians when it comes to making a decision on invasive mechanical ventilation and safer alternatives for patients with IPF" [18]. However poor prognosis associated with a higher risk of infections occurring during IMV may suggest the use of non-invasive ventilation (NIV).

7.3 Non-invasive Ventilation (NIV)

Indication to start NIV in IPF pts is generally based on the occurrence of moderate-to-severe dyspnoea, respiratory rate above 30 breaths/min, signs of increased work of breathing (WOB), and/or P/F < 200 not responding to the oxygen and pharmacological therapy. In pts with hypoxaemic respiratory failure[1] NIV is used with the aim of improving oxygenation, facilitating ventilation, decreasing WOB and dyspnoea, avoiding intubation, and reducing the complications associated with IMV [19]. A recent guideline statement from the American Thoracic Society (ATS)/European Respiratory Society (ERS) points to NIV as a treatment to consider a life-sustaining measure in some IPF pts who have survived an episode of acute pulmonary fibrosis, also as a bridge to transplant [4].

Furthermore, in end-stage pts when palliation is more appropriate for IPF pts, NIV can be taken into account as a major palliative option. Together with best supportive care, it may help reducing patient's discomfort by decreasing breathing work and permits management in a Respiratory Intensive Care Unit (RICU) [11]. In a nationwide analysis performed in the USA, IPF patients who received MV were younger with fewer chronic medical conditions; the number of IPF pts treated by NIV was increasing [7.9% (583) in 2009, 8.3% (550) in 2010, and 10.3% (862) in 2011 ($p = 0.112$)] [20]. Retrospective studies show a moderate success of NIV compared to IMV with a lower mortality in responder pts; a percentage from 85 to 100% died within 3 months, regardless of Endo-Tracheal Intubation (ETI) being imposed [21, 22]. Use of NIV instead of IMV for management of life-threatening AE-IPF

[1] Hypoxaemic respiratory failure is usually defined as significant hypoxaemia (P/F ≤ 200), tachypnoea (respiratory rate > 30–35 breaths·min^{-1}) or use of accessory respiratory muscles or paradoxical abdominal motion, and a non-COPD diagnosis (e.g. pneumonia and/or acute respiratory distress syndrome (ARDS) [19].

showed a better 60-day survival rate, a shorter high-care unit stay, and preserved oral communication with better quality of life and usage of medical resources [23]. Moreover, NIV may be applied in selected pts, such as those with less severe ARF, to identify early NIV-responder pts and to treat the causes of ARF, minimizing complications and the poor outcome linked to ETI and IMV [24]. Early NIV application in pts with less severe respiratory failure may improve patients' management and short-term outcomes (better 30-day survival) and can help avoiding complications related to intubation, such as Ventilator-Associated Pneumonias (VAPs) [21, 24]. Stratifying the results on the basis of the causes of ARF and the radiological pattern of ILD, Aliberti et al. 2014 evaluated NIV responsiveness in pts with ILD and ARF [6]. NIV improved oxygenation in pts with pneumonia, but not in those with AE-IPF, without differences in terms of radiological pattern [6].

Nevertheless in mechanically ventilated pts with ILD with autoimmune features, the prognosis was related to the extension of the lung fibrosis and the presence of a UIP pattern on CT scan rather than to the ILD etiology [25].

However, NIV responsiveness did not have a relevant impact on the poor prognosis related to the disease: one-year mortality rate in NIV-responders was ≥70% in all the evaluated studies [21].

7.3.1 NIV Mode: PSV vs. CPAP

NIV is generally performed in PSV ("Pressure Support Ventilation") mode (range: 5–15 cmH_2O), or in CPAP ("Continuous Positive Air Pressure") mode (range: 8–10 cmH_2O). In the absence of respiratory acidosis, the early NIV mode is often a CPAP. CPAP level is gradually increased with a range 8–10 cmH_2O. Inspired Oxygen Fraction (FiO_2) is set at the lowest value to keep PaO_2 at more than 60 mmHg [6]. During CPAP, which involves exclusively the application of a PEEP in a tight-fitting pressurized system (helmet or mask), all the respiratory work is performed by the patient and the only positive result consists in balancing the effects of the auto-PEEP and the recruitment of hypo-ventilated lung areas. Therefore CPAP is effective for treating hypoxemia with tachypnea, but does not improve hypercapnia (and acidosis), because it does not correct hypoventilation. Conversely, alveolar hypoventilation and hypercapnia do not occur frequently in the early stage of AE-IPF. This is probably due to respiratory muscle adaptation to the increased respiratory workload associated with lung stiffness [9]. In the end stages of the disease, this causes ARF in about 40% of pts. The onset of respiratory fatigue may lead to CO_2 retention and respiratory acidosis (pH < 7.35, $PaCO_2 \geq 45$ mmHg) that forces to perform CPAP mode (mean 10.1+/−2.5 cmH_2O) up to 12 cmH_2O to keep the lung open, and Spontaneous/Timed mode (mean inspiratory positive airway pressure/expiratory positive airway pressure; 15.0+/−3.3/10.2+/−2.9 cmH_2O) [21]. Treating a hypoxemic/hypercapnic patient with AE-IPF in NIV support can be extremely challenging for the clinician. PSV in NIV, the most frequent mode used in intensive care unit (ICU), exploits a flow trigger, a pressure supply with a pre-set

PEEP level and a loop cycling with a percentage (%) drop in flow. The developed TV depends on the patient's thoraco-pulmonary system compliance. L'Her et al. 2005 showed that in ARDS pts. NIV support pressure of 10–15 cmH_2O above a PEEP of 5–10 cmH_2O was the best combination in order to reduce inspiratory effort, dyspnea, and improve oxygenation [26]. In ILDs, the need for a support pressure level to assure fitted tidal volumes, unfortunately, limits the safety margins of the method. In a retrospective study on ILD pts treated with PSV through full face mask with homecare ventilators, Vianello et al. 2014 reported P-support and PEEP level respectively imposed equal to 15.4 ± 2.7 and 6.4 ± 2.5 cmH_2O, titrated to moderate TV (6–8 mL/kg PBW) [22]. The days under NIV therapy were 6.8 ± 7.0. The 45% of patients had a successful NIV treatment and did not require IMV, while they all survived during NIV therapy. All the pts in the 55% of NIV failure group died in few days (average 20 days) from Multiple Organ Failure (MOF)/sepsis or cardiac failure [22]. The authors underline that protecting the lung in fragile patients could play a key role in terms of survival rate, especially when an immunosuppressive/corticosteroid therapy is used [21, 22].

According to Marchioni et al. (2020) a "lung resting strategy" should establish a PEEP setting = 4 cmH_2O, TV = 6 mL/kg of PBW, Transpulmonary pressure at end-inspiration below 10–12 cmH_2O in inhomogeneous lung parenchyma, "tolerating hypercapnia" if the arterial pH remains above 7.25, with a PaO_2 above 50–60 mmHg or a SpO_2 above 88–90%. In patients in whom a DAD or ground-glass opacities at the CT predominate over the UIP pattern, higher PEEP levels might be considered, similarly to ARDS [14]. Criteria to interrupt the NIV therapy were defined by P/F > 200, respiratory rate (RR) <20 and clinical improvement of radiological findings [19]. In the presence of acute alteration of consciousness [Glasgow coma scale (GCS <8)], cardiac arrest, poor mask compliance, inability to clear secretions, or haemodynamic instability, IMV must be performed, unless the patient must previously declared a do not resuscitate (DNR) will [19].

7.3.2 NIV Interface: Helmet vs. Face—Mask

A brief trial with face-mask ventilation (FMV) is usually performed during the first 4 h (range: 2–6) in pts with higher $PaCO_2$ values, due to the higher performance of face-mask (vs helmet) to determine an improving in CO_2 elimination [27]. In hypoxemic patients, who required prolonged MV, face-mask treatment is not well tolerated and helmet is usually used as an interface. The helmet is a transparent hood that covers the entire head of the patient with a collar that adheres to the neck and ensures a sealed connection once the helmet is inflated. The ventilator delivers pressure to the patient through the helmet inlet; the patient exhales into the helmet, which is connected to the ventilator expiratory line. Advantages versus face mask: no skin lesions due to the helmet's lack of contact with the face; effective application of higher PEEP (i.e. 8–12 cmH_2O) with minimal air leaks during prolonged treatments without interruptions [28, 29]. Disadvantages: standard helmet's large inner volume

(12–15 L) results in a compressible volume, which interferes with circuit pressurization, trigger sensitivity, and WOB [30], thus facilitating rebreathing [31]. Additionally, the helmet can cause pain and discomfort as result of the pressure exerted on the skin of the axillary area due to armpit brace, and an upward displacement of helmet during ventilator insufflation, owing to the highly compliant soft collar [32]. Helmet requires high PS values in the early phase of inspiration to pressurize his inner volume. This actually cause a longer time to reach the required level of PS, and can result in patients' less assistance and in a higher risk of asynchrony for a significantly longer inspiratory trigger delay [33]. Chiumello et al. 2003 evaluated the breathing pattern and WOB with helmet and face-masks during CPAP and PSV. During CPAP, there was no difference in breathing pattern and WOB; on the contrary, the face-mask significantly reduced the WOB compared to the helmet during PSV [34]. Racca et al. 2005 also compared the helmet and face-mask during PSV with normal and high respiratory muscle load to simulate dyspnoeic pts. Both breathing pattern and respiratory effort were the same in presence of normal muscle load, but if respiratory muscle load was higher, the inspiratory effort was significantly higher when applying helmet than with face-mask [31]. These evidences suggest to use helmet in CPAP mode and face-mask in PSV [31]. An increasing in $PaCO_2$ is described while using single-limb-circuit bi-level ventilators which do not have efficient exhalation systems [27]. A new helmet recently introduced into clinical practice is characterized by an annular openable ring, placed underneath an inflatable cushion, that secures the helmet without the need of armpit braces, as opposed to the standard helmet. This improved comfort, rate of pressurization, and triggering performance. This procedure can be used in the clinical practice in order to determine an improvement in clinical outcome, especially in the most severe pts requiring NIV for prolonged periods of time [32].

1. **Other Side Effects of NIV**

   There is a significant hyper-activation of the respiratory drive that causes an increase in respiratory rate (RR) and significantly higher effort in patients with AE-IPF (as in ARDS pts) when applying the helmet than with the face-mask, due to the presence of air leaks [31]. This may be reduced by increasing the PS values [35]. Moreover, if the use of NIV-Helmet is prolonged over time in ARDS pts, the need for high PS values leads to an increase in trans-pulmonary pressures, reaching −30 to −40 cmH_2O, that may exacerbate the danger of developing patient self-inflicted lung injury (P-SILI) [35]. Only ARDS pts with a P/F ratio below 200 mmHg after 1 h of PSV-NIV and expired TV exceeding 9–9.5 mL/kg of PBW are exposed to the development of P-SILI [36]. In these pts the use of neuromuscular blocking agents (NMBAs) may counterbalance the potentially injurious effects of assisted breathing, thus resulting in improved survival [37]. We cannot rule out a P-SILI developing even in AE-IPF, because lung protective ventilator strategies (such as maintaining a low TV of 6 mL/kg of PBW) are more difficult to apply with NIV than with IMV, as the maneuvers (end—inspiratory/expiratory pauses) required for the measurements of transpulmonary pressure are difficult to perform in spontaneously breathing pts. This

raises a note of caution when using NIV that combines spontaneous effort with ventilator support [36]. Recently the ventilator-related causes of lung injury have been unified in a single variable, i.e. the mechanical power, that is the mathematical description of the mechanical energy (in joule/min) produced by MV and delivered to the respiratory system over time. The mechanical power is assessed by measuring the pressure-volume loops that can be computed from its components: TV/driving pressure (DP), flow, PEEP and respiratory rate (RR) [38]. It may help to estimate the contribution of the different ventilator-related causes of lung injury and of their variations, although it is still under discussion, because "...lung heterogeneity is not readily quantified, and clinicians at the bedside are left with what we can measure about the elements of the equation of motion" [39]. Furthermore, we cannot exclude that even in IPF (as in ARDS) a significant correlation between mechanical power and serum fibrosis biomarkers (TGF-β1 and CTGF) could be found [40].

2. **Predictors of MV failure in IPF**

   In subjects who receive NIV, APACHE II scores <20 and non-continuous demand for NIV show a higher survival compared to older subjects receiving IMV [16]. The presence of diffuse ILD ("widespread opacification") [8], Simplified Acute Physiology Score (SAPS II) >34 [7, 41], and the inability to improve P/F after 1 h of NIV, later requiring to switch to IMV, have shown to correlate with a higher mortality [21, 22]. An early start of NIV during AE-IPF is associated as well with a better 30-day survival, improving patients management and short-term outcomes [24]. With regards to the MV setting in ILDs pts, since high PEEP has effect neither on fibrotic, nor on recruitable areas, thus promoting VILI, a high in-hospital mortality rate is referred when high levels of PEEP (>10 cmH_2O) and high VT (>8 mL/kg) values are applied [10]. Recently, a comprehensive scale including heart rate, acidosis, consciousness, oxygenation and respiratory rate (the HACOR Scale) predicts NIV failure after 1 h-treatment in a large prospective cohort study with high specificity (90%) and good sensitivity (72%) [42].

7.4 Summary

All strategies used to prevent a worsening in the AE-IPF clinical outcome, not only in terms of mortality but also in terms of quality of life after the acute event, seem to be ineffective. All the routine ventilatory modes fitting to safeguard the residual healthy lung parenchyma are difficult to implement in most serious IPF onset, in which plateau and driving pressures, "higher than the considered threshold accepted for safety", are often to be applied. If NIV fails, and unless patients had previously declared a DNR will, a protective ventilation strategy in IMV with low TV and low driving pressure could be recommended similarly to ARDS. However the least harmful mechanical ventilation strategy is not yet fully elucidated in AE-IPF patients [14]. Furthermore, in IPF pts the greater susceptibility of the lung to develop

VILI, the impaired ability to repair the acute alveolar damage, and the patients older age may play a role to explain the worse mortality rate. Nevertheless early use of NIV in selected pts might avoid IMV and improve clinical conditions at ICU admission. In this way we can meet the new technologies of extracorporeal CO_2 removal ($ECCO_2R$) and high flow oxygen therapy (HFOT) that are beyond the aim of this chapter [43].

Key Teaching Points

- The abnormalities of the respiratory mechanics are common in patients with idiopathic pulmonary fibrosis. Most of the alterations are likely to be a result of the progressive inflammatory process that leads to interstitial fibrosis and re-organization of the lung architecture.
- Several non-invasive ventilation (NIV) modes can be used in IPF patients during the different stages of the diseases with various purposes: treating respiratory fatigue and tachypnea, hypoxemia with or without hypercapnia, palliation. CPAP is generally indicated for treating hypo-normocapnic hypoxemia with tachypnea, while PSV can be considered in late stages in the presence of respiratory fatigue, CO_2 retention, respiratory acidosis, and DNR will.
- Invasive Mechanical ventilation (IMV) was more frequent in IPF patients. Its use was associated with an increase in mortality. Overall mortality was approximately 50% for IMV and 30% for NIV.
- NIV may be useful for compassionate use, providing relief from dyspnoea and avoiding aggressive approaches. Further advances in IPF treatment and development of IPF-specific decision aids are needed to improve the outcomes and use of MV in IPF.

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Chapter 8
Continuous Positive Airway Pressure

Uğur Özdemir

Case

A 40-year-old male patient was presented to the Emergency Department with sudden onset cough, sputum, and respiratory distress. At admission, his blood pressure was 210/110 mmHg, pulse rate 154/min, respiratory rate 44/min and oxygen saturation with pulse oximetry was 70%. Bibasilar course crackles were heard at auscultation. There was no pretibial edema, ascites, cardiac murmur or gallop rhythm in physical examination. The patient had no known cardiac disease and was not using any antihypertensive treatment before. At admission to the emergency department, the arterial blood gas analysis taken in room air was as follows; pH: 7.31, partial arterial CO_2 pressure (PaCO2): 50 mmHg, partial oxygen pressure (PaO2): 48 mmHg, oxygen saturation (SaO2): 77%, bicarbonate level (HCO3-): 24.9 mmol/L and lactate level 3.4 mmol/L (Table 8.1). In laboratory tests; blood glucose was 153 mg/dL, hemoglobin level: 15.7 g/dL, white blood cell count: 12130/mm^3, platelet count: 315000/mm^3, blood urea nitrogen: 24 mg/dL, serum creatinine: 1.54 mg/dL, plasma sodium: 136 mmol/L, potassium: 3.1 mmol/L, aspartate transaminase: 29 U/L, alanine transaminase: 17 U/L, creatinine kinase-MB: 17.1 U/L, troponin-I: 12 ng/L, d-dimer: 2.04 ng/mL, Pro-B natriuretic peptide (Pro-BNP): 7020 pg/mL. Patient's electrocardiography (ECG) does not show any pathology other than sinus tachycardia. Anteroposterior chest x-ray showed a patchy infiltrative appearance in bilateral lower zones (Fig. 8.1a) Thoraco-abdominal Computerized

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Table 8.1 Arterial blood gas analysis

	At the ICU admission (No CPAP, under room air)	Under CPAP first day, FiO2:1	Before discharge (Without CPAP, under room air)
pH	7.31	7.34	7.42
$PaCO_2$	50 mmHg	46 mmHg	39 mmHg
PaO_2	48 mmHg	68 mmHg	82 mmHg
SaO_2	77%	90%	%98
HCO_3	24.9 mmol/L	28 mmol/L	26 mmol/L
Lactat	3.4 mmol/L	1.9 mmol/L	1.4 mmol/L

ICU intensive care unit, *CPAP* continuous positive airway pressure, $PaCO_2$ partial arterial CO_2 pressure, PaO_2 partial arterial O_2 pressure, SaO_2 oxygen saturation, HCO_3 bicarbonate level

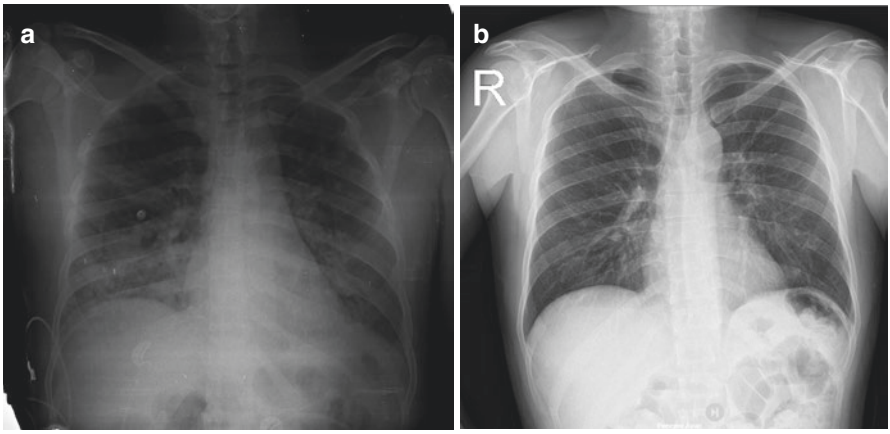

Fig. 8.1 (**a**) Anteroposterior chest x-ray shows a patchy infiltrative appearance in bilateral lower zones in emergency service. (**b**) Normal anteroposterior chest x-ray after treatment

Tomography (CT) was performed with suspected pulmonary and abdominal aortic thromboembolism, and it was revealed widespread ground glass appearance in both lungs (Fig. 8.2). There was no thromboembolism in the pulmonary artery, and abdominal aorta. Patient was admitted to intensive care unit (ICU) with the prediagnosis acute hypertensive pulmonary edema. Continuous positive airway pressure (CPAP) via face mask, oxygen supplementation with high fractional oxygen ratio as 100%, furosemide and nitroglycerin IV infusion treatments were started at admission to ICU. Additional inspiratory pressure support was not given because the patient was conscious and could create sufficient tidal volume. Initial CPAP value adjusted 5 cmH_2O. We were able to manage the tachypnea of the patient under this CPAP value. The patient's urine output was achieved after furosemide treatment, tachypnea and oxygen requirement decreased; however, CPAP was continued for about 3 days. The oxygen requirement of the patient gradually decreased. After these 3 days, the patient had no oxygen requirement, the respiratory distress had been improved and the posterior-anterior chest X-ray was considered to be normal

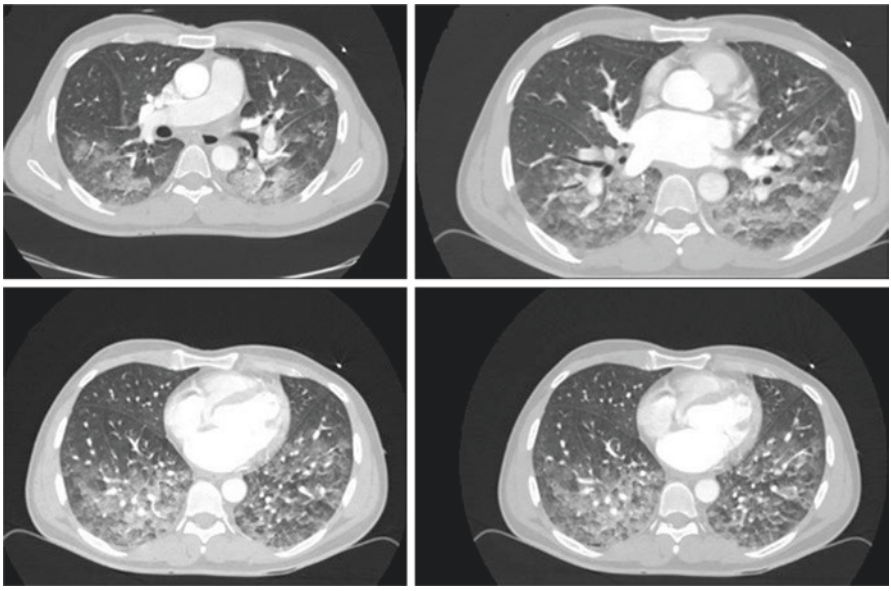

Fig. 8.2 Thoracic Computerized Tomography shows that widespread ground glass appearance in both lungs

(Fig. 8.1b). Blood gas analysis of the patient under CPAP treatment and before discharge from ICU are presented in Table 8.1. Then, patient was discharged from ICU with recommendations.

8.1 Introduction

Continuous positive airway pressure is one of the positive pressure ventilation types. CPAP that provided by non-invasive face mask ensures to keep airways of the patient continuously open through constant pressure applied to the airways including the upper airways. CPAP differs from bilevel positive airway pressure (BIPAP) because two different pressure levels are applied in BIPAP, depending on whether the patient is in inspiration or in expiration. However, CPAP applies the same pressure to the airways during both inspiration and expiration. The pressure provided by CPAP in the alveoli during expiration is the same as the positive end-expiratory pressure (PEEP). Therefore, the PEEP effect is prolonged and continued during inspiration through CPAP. CPAP has some positive effects on lung dynamics. Firstly, it improves the functional residual capacity of the lung by alveolar recruitment. As a result, right to left intrapulmonary shunt decreases, oxygenation improves and lung mechanics restores [1]. Secondly, it can reduce left ventricular afterload without cardiac index reduction. This effect is achieved by decreasing the intrathoracic negative pressure during the increased respiratory cycle through CPAP. At the

same time, a decrease in preload and in left ventricular end diastolic (LVED) volume can be expected due to decrease in the venous return to the heart during CPAP. Other one, the effect of dynamic hyperinflation and auto-PEEP due to increased respiratory work and obstruction in the bronchial tree can be relieved by CPAP administration. Lastly, If there is a condition that causes mechanical obstruction in the airway due to mucus plugs, tonsillar hypertrophy, presence of low muscle tone in upper airway, presence of excessive soft tissue in major airway, CPAP application will be useful in maintaining the patency of the airway [2]. Despite these favorable effects of CPAP, it is not suitable for all patients. In order to perform CPAP, the patient have to be conscious, patient should be produce respiratory cycle and inspiratory tidal volume in normal range. Therefore, BIPAP should be used if the patient does not have sufficient inspiratory effort and needs to be supported with a higher pressure than CPAP during inspiration. Conversely, the application of additional inspiratory pressure to CPAP in patients with adequate inspiratory effort may result to greater tidal volumes and it will generate distress in the lung parenchyma. CPAP treatment is an easy and not elaborate treatment method, therefore it is important to be applicable in such indications. At the same time, CPAP can be applied with some devices other than the ventilator. For example low gas flow generators with reservoir, high-flow jet venturi systems and high flow nasal oxygen devices.

8.2 Indications

The most important indications for CPAP can be listed as pulmonary edema due to congestive heart failure (CHF) [1], obstructive sleep apnea syndrome (OSAS) [3], obesity-hypoventilation syndrome (OHS) [4] and infants, whose lung development has not yet been completed [5]. CPAP can also be used to reduce weaning failure after operation of patients with a diagnosis of OSAS, OHS, CHF or other diseases [6]. Other less well-known applications for CPAP include community-acquired pneumonia, chronic obstructive pulmonary disease, muscular dystrophy, and carbon monoxide poisoning. More detailed informations on the use of CPAP were given at below for specific indications.

8.3 Use of CPAP in the pulmonary Edema due to Congestive Heart Failure

Heart failure is one of the most important causes of hospitalization. Acute cardiogenic pulmonary edema (ACPE) may occur in some cases during the course of heart failure and the mortality rate exceeds 30%, especially in severe cases. In parallel with the technological advances in last decade, non-invasive ventilation and CPAP methods have become more preferred in acute respiratory failure and in ACPE patients. It shown that the use of CPAP in the patients with ACPE has been reduce

the risk of endotracheal intubation, invasive mechanical ventilation and mortality rate. This positive effect was found to be similar with BIPAP or pressure support ventilation. Moreover, it has been emphasized in the reviews that CPAP is now the first-line treatment without increasing the risk of myocardial infarction in ACPE patients [7]. Currently, the opinion that the use of CPAP is unsuccessful in hypercapnic patients, is continuing among most clinicians. However, it has been shown that the use of CPAP has a strong beneficial effect on partial arterial CO_2 ($PaCO_2$) values in patients with hypercapnic ACPE. However, if the patient is also diagnosed with COPD, BIPAP can be expected to be more beneficial. Because, it is known that BIPAP is more useful, although not statistically significant, in patients who have both diagnosis of ACPE and COPD. With this indication, the recommended initial CPAP value for the first hour is 5 cmH_2O and can be increased up to 15 cmH_2O according to clinical requirements. Due to CPAP is cheaper and easier than other NIV methods, it can be expected that usage of it will be expanded to prehospital area with this indication.

8.4 Use of CPAP in the Obesity-Hypoventilation Syndrome

Obesity hypoventilation syndrome is defined as coexistence of awake alveolar hypoventilation ($PaCO_2$ greater than 45 mmHg) with obesity (body mass index greater than 30 kg/m^2) and absence of other identifiable causes of hypoventilation. Generally, OSAS is present in the 90% of patients diagnosed with OHS. The estimated incidence of OHS in the population is considered to be 0.15–0.4%. The expected mortality in OHS decreases significantly with appropriate treatment. This treatment is generally nocturnal positive airway pressure therapy for ambulatory patients. One of the most commonly used treatments for this purpose is CPAP. In randomized controlled trials, the use of CPAP or BIPAP for OHS diagnosis has shown similar efficacy in short- and long-term period in term of disease control, $PaCO_2$ control and mortality [4]. Therefore, it can be used as a first line treatment especially in patients with stable OHS due to it is cheap and easy treatment method than BIPAP. A summary of CPAP titration for OHS treatment according to American Academy of Sleep Medicine can be seen in Table 8.2 [8]. The most appropriate CPAP value can be found for OHS patients with this titration method performed under polysomnography.

8.5 Use of CPAP in the Obstructive Sleep Apnea Syndrome

Epidemiological studies showed that OSAS is affect 5–15% of the population. Symptoms of daytime sleepiness (fatigue, insomnia, snoring or observed apnea) or related disorders (hypertension, atrial fibrillation, congestive heart failure, stroke, cognitive dysfunction) and five or more mainly obstructive respiratory events per

Table 8.2 CPAP titration for OHS and OSAS

A. Start CPAP with a minimum of 4 cmH_2O (higher values can be selected for patients with high BMI)
B. Evaluate the patient with 5 min intervals and increase the pressure by 1 cmH_2O if at least one of the following conditions (events) exist after 5 min
• ≥2 obstructive apneas
• ≥3 hypopneas
• ≥5 respiratory effort-related arousals
• ≥3 min of loud or unambiguous snoring
C. The maximum CPAP value is recommended as 15 cmH_2O, but can be increased up to 20 cmH_2O
D. Consider BIPAP treatment
• If the above-mentioned events continue to occur despite reaching 15 cmH_2O
• If the patient feels uncomfortable
E. Decrease the pressure by 1 cmH_2O every 10 min if the above-mentioned events have not occurred for 30 min under the last setted pressure
F. If the above-mentioned events are observed again in the pressure decrease period (section E), start increasing the pressure again in according to section B

hour of sleep during polysomnography are necessary for diagnosis of OSAS. These signs and symptoms are caused by intermittent obstruction of the upper airway during sleep. As a result, patients suffer from impaired cognitive functions, sleep patterns and reduced quality of life. The standard treatment for controlling the disease is CPAP administration. For OSAS patients, CPAP titration and determination of appropriate pressure setting are performed in sleep laboratories and the titration method is summarized in Table 8.2. The pressure value obtained by this titration method can be applied in a constant manner until the next control, there is also new method which can change the CPAP value automatically according to the autoCPAP method [3]. There was no difference in efficiency and cost between fixed value CPAP or autoCPAP method, but autoCPAP method was found to be more comfortable for patient.

8.6 Use of CPAP in the Perioperative Period

General anesthesia and surgery may cause some adverse effects in the respiratory system such as hypoxemia, decrease in lung volume, diaphragm dysfunction and atelectasis. These adverse effects can be alleviated by a simple nasal oxygen supplementation, but there is always a risk of re-intubation due to acute respiratory failure in patients after general anesthesia and surgery. However, it is known that re-intubation in the postoperative period causes an increase in the mortality of the patients. Therefore, prophylactic non-invasive mechanical ventilation (CPAP or BIPAP) during postoperative period has been shown to be effective in preventing postoperative re-intubation, especially in risky patients such as obese, elderly or

suffering from COPD, OSAS, OHS or CHF [9]. Prophylactic CPAP administration (before development of acute respiratory failure, immediately after extubation) is known to reduce the risk of developing acute respiratory failure in the postoperative period. It is also known that CPAP administration after development of acute respiratory failure reduces significantly the risk of re-intubation [6]. Initial CPAP value for the first hour can be 5 cmH_2O and can be increased up to 15 cmH_2O according to clinical requirements.

8.7 Contraindications

CPAP cannot be administered in patients who have not spontaneous breathing effort and inadequate consciousness to protect the airway. Also, patients should have sufficient inspiratory force. Other contraindications for CPAP are: presence of extreme anxiety, uncontrolled nausea and vomiting, excessive respiratory secretions, pneumothorax, severe facial burns or trauma, severe respiratory failure, respiratory arrest, cardiovascular instability.

Key Teaching Points

- The use of CPAP for many indications has expanded in the last decade.
- Nowadays, CPAP can be thought as the first choice of treatment for acute cardiogenic pulmonary edema, obstructive sleep apnea syndrome, obesity hypoventilation syndrome and postoperative period.
- In order to take benefits from the favourable effects of CPAP, appropriate patient selection is very important and the presence of contraindications should be investigated before administration.
- Due to CPAP is cheaper and easier to use, and is as effective as non-invasive pressure support ventilation, CPAP treatment needs to be further considered by clinicians in the presence of appropriate indication.

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Chapter 9
How Do Hybrid Pressure Ventilation Modes Respond to Patient's Varying Ventilatory Requirements? Insights from Respiratory Bench Simulations

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Abbreviation

VAPS Volume-assured pressure support

9.1 Introduction

Home non-invasive ventilation (NIV) is considered as a well-established treatment for patients with chronic hypercapnic respiratory failure. Traditional volume-targeted devices aimed to deliver a fixed volume set by the clinician, but cannot automatically take into account patient's varying conditions and requirements during the therapy (e.g., patient's volume change, presence of leak, etc.). Pressure-targeted ventilators aim to generate a volume by delivering bi-level pressure to patient during inspiratory and expiratory phases. This ventilatory mode improves

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patient-ventilator synchrony and leak compensation, but cannot guarantee the volume delivered to patient when the ventilatory requirement changes, such as respiratory mechanics and ventilatory drive [1, 2]. Furthermore, sleep disordered breathing events may appear during therapy. An obstructed upper airway (UA) may lead to inefficient ventilation.

Recently, volume-assured pressure support (VAPS) modes were introduced aiming to combine the features of both traditional volume-targeted and pressure-targeted ventilatory modes. These new hybrid modes are supposed to automatically adjust the delivered pressure to maintain a target tidal volume for the patient, taking into consideration patient's volume changes during the therapy. Besides, auto-adjusted expiratory positive airway pressure (EPAP) features were further introduced to VAPS modes and these features allowed the ventilator to automatically adjust the EPAP to maintain the UA patency. Also, some devices allow to set a variable backup respiratory rate alone or in combination with variable inspiratory positive airway pressure (IPAP) to achieve a target respiratory rate or a target ventilation.

The objective of the current chapter is to briefly review these new hybrid modes and to show how they react to achieve the ventilatory target by subjecting the ventilators to predefined breathing scenarios simulated by a previously reported respiratory bench model [3]. The model mainly consisted of an active lung (ASL5000 Ingmar Medical) and a Starling resistor, and was capable to mimic physiological and pathological conditions of the respiratory system as well as the UA patency [3, 4]. Detailed descriptions of the bench model are available in the online supplement.

9.2 Volume-Assured Pressure Support (VAPS) Ventilation

1. Principles and theoretical clinical benefits of VAPS ventilation

   Volume-assured modes of NIV are intended to auto-adjust the pressure support (PS) to meet patient's ventilatory needs in term of tidal volume (V_T) or alveolar ventilation which takes into account the anatomical dead space and the breathing rate, aiming to combine the benefits of pressure-targeted and volume-targeted modes. Comparing to conventional Spontaneous/Timed (ST) mode with fixed pressure support (PS) ventilation, these hybrid modes are supposed to maintain a constant tidal volume and to respond to any changes in patient's volume due to changing respiratory system properties, such as airway resistance or lung compliance, or sleep stage and posture. However, to date, there is no evidence of superiority of VAPS modes over conventional ST mode in clinical outcomes [2].

   Some commonly used VAPS modes applied in home NIV devices are listed as follows: AVAPS (PHILIPS, Murrysville, PA, USA), iVAPS (RESMED, NSW, Australia) and AutoST (LÖWENSTEIN MEDICAL, Hamburg, Germany).
2. Settings of VAPS modes

   Generally, a target tidal volume is set in the ventilator before starting the therapy. To reach this target, the ventilator provides a constant EPAP and an

automatically adjusted PS (or IPAP) within a preset range according to patient's real-time ventilation over several breaths. The EPAP ensures patient's upper airway patency and the PS (or IPAP) increases with a preset rate when patient's ventilation level drops below the target.

Discrepancies in VAPS settings between manufacturers need to be highlighted. Different from AVAPS (PHILIPS) and AutoST (LÖWENSTEIN MEDICAL), iVAPS (RESMED) targets alveolar ventilation that supposed to be equal to the portion of ventilation that reaches patient's alveoli per minute. This target is determined by the algorithm taken into account patient's height as well as the average breathing rate. When the breathing effort is absent, the algorithm adjusts both IPAP (or PS) and backup rate in order to regain the target alveolar ventilation. Accordingly, a target breathing rate needs to be set as close as possible to patient's actual breathing rate during iVAPS configuration, rather than a conventional backup rate in the ST mode [5]. Concerning this "intelligent" backup rate (iBR), the device allows the patient to trigger the ventilatory support if patient's breathing rate remains above 2/3 of the target breathing rate. Nevertheless, if patient's spontaneous breathing rate falls below this value, the device increases the backup rate to "drag" the patient to the set target value [5]. An alternative way to set iVAPS is to use "learn targets" feature available in the setting menu. This feature aims to get the patient's alveolar ventilation and average breathing rate at rest by monitoring patient's ventilatory variables. Besides, users are allowed to modify the rising rate of IPAP or PS in AVAPS and AutoST modes. This rate corresponds to the rapidity to achieve the target volume, and should be set with consideration of not only treatment efficacy but also patient comfort (in AVAPS it may be set from 0.5 to 5 cmH_2O/min; in AutoST, it can be set from 0.5 hPa/8 cycles to 1.5 hPa/cycle; and this setting is not available for iVAPS).

3. Examples: How do VAPS modes respond to a volume drop?
   – Respiratory scenario and ventilators

     To demonstrate the responses of VAPS modes to varied ventilatory needs and the resultant volumes, ventilators set with VAPS modes were subjected to a predefined breathing scenario simulated by the respiratory model described above [3]. The breathing scenario corresponded to an Obesity Hypoventilation Syndrome (OHS) patient profile with resistance and compliance equal to 3 cmH_2O/L/s and 20 mL/cmH_2O respectively. The breathing scenario started with a 5-min reference breathing of which the V_T was 500 mL, followed with a 10-min hypoventilation section where the V_T was decreased by 50% due to reduced compliance (equal to 10 mL/cmH_2O). The breathing rate was 15 breaths/min. The UA was opened during the entire scenario with a pressure applied to the pharyngeal tube at −8 cmH_2O. The curves of the simulated breathing flow and the resultant volume are shown in online supplement (Figure S1, in Data 9.3).

     Three ventilators were included: BiPAP A40 (denoted as "A40"; PHILIPS), Stella 150 (denoted as "S150"; RESMED) and Prisma VENT40 (Denoted as "V40"; LÖWENSTEIN). The ventilatory parameters in the three ventilators

were set equivalent and the VAPS modes were enabled. Main ventilatory parameters were set as following: EPAP was equal to 4 cmH_2O, and PS ranged between 5 and 25 cmH_2O (IPAP min and max = 9 cmH_2O and 34 cmH_2O respectively). The IPAP rising rates were set to 5 cmH_2O per minute for AVAPS and level 3 for AutoST. The V_T of patient was set to 400 mL for all devices because the simulated V_T was around 500 mL. Backup rate was 12 cycles/min for AVAPS and AutoST. For iVAPS this rate was set to 14 cycles/min to be close to the actual breathing rate. Besides, patient size was required for iVAPS and was set at 175 cm.

– Obtained respiratory curves

The breathing flow curves obtained with the three VAPS modes as well as the corresponding mask pressure and volume are shown in Fig. 9.1.

During the 5-min period of reference breathing, both iVAPS and AutoST delivered pressure support around 6 cmH_2O, close to the minimum PS. With an EPAP around 4 cmH_2O, the corresponding IPAP of both iVAPS and AutoST reached 10 cmH_2O. Such ventilatory support increased the volume from 530 mL (reference volume without PS) to 650 mL. Different from iVAPS and AutoST, AVAPS started with PS of 16 cmH_2O, which resulted a V_T around 950 mL; then the IPAP dropped progressively from 20 cmH_2O to 9 cmH_2O within 3 min. Consequently, the resultant volume was stabilized at 650 mL.

After the 5-min reference breathing section, hypoventilation occurred and the V_T brutally decreased to around 300 mL (Fig. 9.1 line 3, at 300th second). As response, all the devices increased immediately the PS to bring the volume back to the predefined target volume. However, the IPAP rising time, the final IPAP values and the resultant volume differed from device to device. The

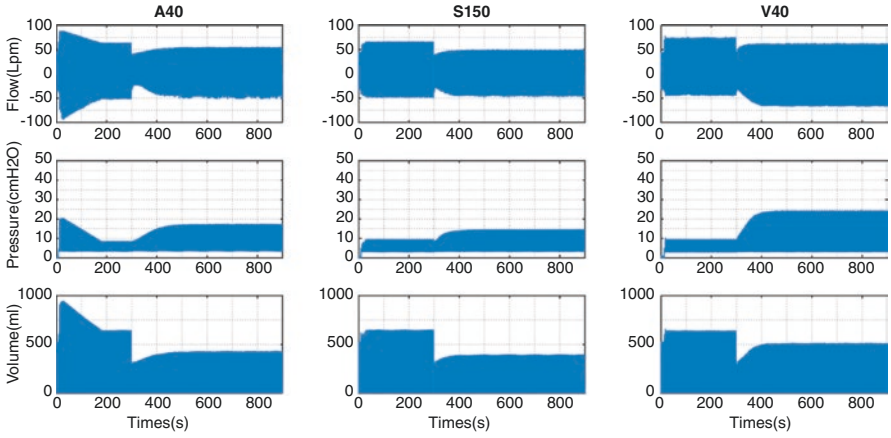

Fig. 9.1 Flow, mask pressure and volume obtained with the three volume-assured pressure support modes (VAPS). A40: BiPAP A40 (Philips); S150: Stella 150 (Resmed); V40: Prisma VENT40 (Löwenstein)

IPAP in AVAPS increased from 9 cmH_2O and finally stabilized at around 17.5 cmH_2O in 3 min. During the first 1.7 min (between 300th second and 400th second), the IPAP increased by 6.6 cmH_2O. The final volume reached 430 mL (Fig. 9.1, A40). iVAPS took about 1.7 min to adjust the IPAP from 9.1 to 14.1 cmH_2O, and the final obtained volume was 395 mL (Fig. 9.1, S150). The IPAP delivered by V40 with AutoST increased from 9.8 to 23.4 cmH_2O within 1.7 min, and accordingly, the final volume reached 510 mL (Fig. 9.1, V40).

4. Discussion on obtained respiratory curves

From the example above (Fig. 9.1), when the V_T fell because of decreased lung compliance, all the three VAPS modes were capable to react to the V_T change by adjusting the PS. Nevertheless, differences may be observed among the three devices in terms of their responses and the resultant volumes.

Regarding the response time, all the three ventilators immediately increased the PS, while the time needed to reach a stable V_T was not equal for all the ventilators. As discussed above, the IPAP rising time should be chosen with considerations, since the varying IPAP may have negative impacts on NIV tolerance and sleep quality [1]. Largely varying IPAP may cause ventilatory instability and promote periodic breathing, which may further lead to central hypopneas or apneas and consequently, arousals. These negative effects may be aggravated if IPAP rises fast [1]. Thus, setting IPAP rising rate is to find a balance between rapidity in responding to volume change and patient's comfort and sleep quality.

In the current example, the target V_T was set to 400 mL for all the three ventilators (the target alveolar ventilation in iVAPS was 3.4 L/min), while the final volumes achieved by the ventilators were different comparing to the target value. The observed inaccurate volume may be explained by several reasons. First, it should be noted that with single-limb or vented circuits, patient's ventilation estimated by the ventilator may be influenced by leaks or patient-ventilator asynchrony events. This volume is estimated from the flow delivered by the ventilator at each breathing cycle rather than from expiratory flow, since there's no patient's expiratory flow being directed back to the ventilator as in double-limb circuit configurations [1]. Manufacturers tolerate a difference up to 20% between the estimated volume and the actual value [5–7]. Second, gas standards applied by the manufacturers for the flow and volume displays are not consistent. For example, S150 expresses V_T at STPH (Standard Temperature, Pressure & Humidity: 1013.25 mbar, 21.1 °C, current gas humidity) while V40 applied BTPS (Body Temperature & Pressure, Saturated: ambient pressure + channel pressure; 37 °C, 100% relative humidity) for volume display [5, 7]. This "gas standard" corresponds to the gas conditions in which the flow or volume values are displayed. The volume of same quantity of gas molecules depends on temperature, humidity and gas type or mixture, and using different gas standards may result in a discrepancy up to 20% [8]. Last, ventilatory events during therapy such as unintentional leaks or patient-ventilator asynchrony may also cause inaccurate V_T estimation and delivery [1, 2].

9.3 VAPS Ventilation with Autotitrating Expiratory Positive Airway Pressure (EPAP)

1. Principles and theoretical clinical benefits

   During NIV, intermittent obstruction of the UA is commonly observed during sleep in patients, and the UA patency is not guaranteed and the ventilation effectiveness is impaired because of inefficient PS delivery through an obstructed UA. An automatic EPAP (auto-EPAP) is to automatically adjust the EPAP to reach a lowest but sufficient level to maintain the UA patency. This algorithm has been introduced in some ventilators with VAPS modes, and may potentially reduce the needs of manual titration with polysomnography in sleep labs. Theoretically, VAPS with auto-EPAP may deliver a lower overall pressure during ventilation and therefore improve patient's comfort and adherence of the therapy. The use of low EPAP may decrease the risk of nocturnal lung hyperinflation in Chronic Obstructive Pulmonary Disease (COPD) patients. However, long-term impacts of Auto-EPAP on clinical outcomes and adherence need to be confirmed by further studies [2].

   The VAPS modes with combined auto-EPAP are as follows: AVAPS AE (PHILIPS), iVAPS with auto-EPAP (denoted as "iVAPS AE", RESMED) and AutoST with auto-EPAP (denoted as "AutoST AE", LÖWENSTEIN). In addition to AVAPS AE, PHILIPS developed another auto-EPAP feature called "Automated Airway Management (AAM)" in their DreamStation BiPAP AVAPS (PHILIPS) device in which AVAPS AE is not available. This AAM feature does not rely on AVAPS mode and can be activated with conventional ventilatory modes alone such as ST mode. Here, AAM is discussed under the condition of ST mode with AVAPS enabled.
2. Auto-EPAP setting and upper airway obstruction detection

   For all the three VAPS modes with auto-EPAP, the EPAP range should be set according to the degree of the UA obstruction.

   To adjust automatically the EPAP in response to UA obstructions, different techniques were utilized by manufacturers to measure the UA resistance. PHILIPS integrates forced oscillation technique (FOT) in their algorithm, which imposes randomly an oscillation signal of 5 Hz during expiration (EPAP), and the device analyzes the resultant airflow to define an increased resistance or obstruction [9]. RESMED analyzes flow shapes of breathing to determine a flow limitation considered as a surrogate of UA obstruction, and an apnea is defined as alveolar ventilation below 5% of the target ventilation value [10].

   In addition, with AVAPS AE (PHILIPS), an "Auto" backup rate is available for the device to automatically adjust the backup rate near a patient's average spontaneous breathing rate.
3. Examples: How do VAPS modes with auto-EPAP respond to a volume drop with UA obstructions?
   - Respiratory scenario and ventilators

To demonstrate how VAPS modes combing the auto-EPAP feature respond to patient's tidal volume drop in the presence of UA obstructions, obstructive sleep disordered breathing patterns were added to the breathing scenario previously described for demonstrating VAPS modes. Obstructive apneas of 20 s occurred every minute during the 10-min hypoventilation section (Fig. 9.2). To generate such obstructive patterns, pressure of 15 cmH_2O was applied to the pharyngeal tube. For the rest of scenario, this pressure was set at −8 cmH_2O to maintain the UA open. Other parameters of the simulation such as tidal volume, breathing rate, and lung properties (compliance and resistance) remained same as those of the scenario described in the previous section for the VAPS. The simulated breathing flow and the resultant volume with apneas are shown in the online supplement (Figure S1 in Data 9.3).

The three ventilators mentioned in the previous section were set to VAPS modes with auto-EPAP enabled: AVAPS AE for A40, iVAPS AE for S150 and AutoST AE for V40. In addition, we included DreamStation BiPAP AVAPS device to see how AAM feature works with AVAPS (denoted as AVAPS AAM) and to have a comparison with AVAPS AE in A40 ventilator. The EPAP was set ranging from 4 to 25 cmH_2O, and the other settings were equivalent to those applied for the VAPS modes.

– Obtained respiratory curves

Figure 9.2 shows the breathing flow curves as well as the corresponding mask pressure and volume obtained with the three VAPS modes with auto-EPAP (i.e., AVAPS AE, iVAPS AE and AutoST AE). The curves of AVAPS with AAM are available in the online supplement (Figure S2 in Data 9.3).

For the 5-min reference breathing session at the beginning, similar pressure responses were observed between the VAPS modes with and without

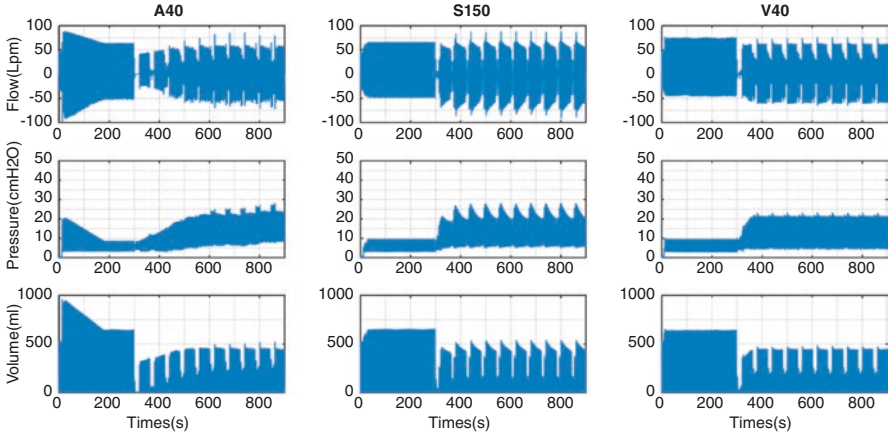

Fig. 9.2 Flow, mask pressure and volume obtained with the three volume-assured pressure support modes (VAPS) with auto-EPAP. A40: BiPAP A40 (Philips); S150: Stella 150 (Resmed); V40: Prisma VENT40 (Löwenstein)

auto-EPAP. Also, the resultant breathing flow and volume were also similar (Figs. 9.1 and 9.2).

However, the three devices responded differently to the following hypoventilation session with obstructive apneas. After the first apnea, AVAPS AE increased the PS with a similar IPAP rising rate comparing to AVAPS (Figs. 9.1 and 9.2, A40). The pressure support increased from 4.9 to 11.6 cmH_2O during 2.3 min before EPAP start increasing. And the PS was stabilized at 16.0 cmH_2O at 560th second. Note that the PS of AVAPS AE changed slightly within obstructive apneas. After 600th second, the PS delivered during apneas were slightly higher than PS when the UA was opened. Besides, the EPAP started rising during the third apnea and progressively increased during the rest of scenario. At the end, the EPAP reached to 9.0 cmH_2O. The FOT signal can be observed in the pressure curve (Online supplement, Figure S3 in Data 9.3). Consequently, the final volumes with and without obstructed UA were around 297 and 452 mL respectively.

As shown in Fig. 9.2 (S150), iVAPS AE increased PS from 5.1 to 16.5 cmH_2O during the first apnea. When normal breathing resumed, the PS was maintained at 16.5 cmH_2O for two breath cycles and then was slightly lowered back to 12.4 cmH_2O. For the successive apneas, the PS varied in a similar manner as for the first one: the PS increased rapidly during the apnea, and did not stop until 2 cycles of breathing resumed, and then decreased back (Fig. 9.2, A40). Thus, during the rest of scenario, the PS varied repeatedly within a range between 14.7 and 21.2 cmH_2O. For EPAP, this pressure increased after the first apnea by 1.9 cmH_2O, and did not significantly rise during the rest of scenario, even if apneas remained. The EPAP at the end of scenario was 6.5 cmH_2O. Consequently, the final volumes with and without obstructed UA were 301 mL and 472 mL respectively.

Regarding AutoST AE, the PS/IPAP increased in a similar way to that observed with AutoST (Figs. 9.1 and 9.2, V40). The PS increased from 5.6 to 11.1 cmH_2O during the first apnea, and the PS continued increasing and stabilized at 17.1 cmH_2O after 360th second (Fig. 9.2, V40). Similar to iVAPS AE, the EPAP increased by 1.5 cmH_2O after the first apnea, and the EPAP remained at 5.4 cmH_2O till the end of scenario. As a result, the final volumes with and without obstructed UA were 223 mL and 446 mL respectively.

The responses of AVAPS AAM to obstructive apneas were found similar to those of AVAPS AE (Figure S2 in Data 9.3). When the ventilator was turned on, the PS was 14.1 cmH_2O but decreased to 4.7 cmH_2O within 50 s during reference breathing, more rapidly than AVAPS AE. The volume of reference breathing was stabilized at 620 mL, also similar to that of AVAPS AE. Besides, the PS and EPAP varied in a similar way to AVAPS AE, and the resultant volumes with and without obstructed UA were similar to those obtained with AVAPS AE.

4. Discussion on obtained respiratory curves

The objective of combining the auto-EPAP and VAPS mode is to let the ventilator automatically adjust EPAP to overcome the UA obstructions and more

efficiently deliver PS to maintain a target volume of patient. According to bench simulation, ventilators with VAPS with Auto-EPAP have different strategies of increasing PS or EPAP to respond to obstructive events, and the effectiveness of treatment were heterogeneous.

Theoretically, when obstructions in UA occur, the ventilator should increase the EPAP until the UA is totally opened, and increasing IPAP/PS only is not an efficient way to overcome the UA obstruction [4]. Also, when the UA is obstructed, PS may not be triggered by patient's effort, and patient-ventilator asynchrony can thus be induced. However, it is tricky for an algorithm only relying on airway flow and pressure to decide which pressure should increase in a first place when patient's volume falls.

As shown in the previous section, when hypoventilation occurred, i.e., the residual volume decreased but remained above zero, all the devices immediately increased PS to maintain the target volume (Fig. 9.1). When the volume fell to zero because of apnea, pressure responses differed between devices: iVAPS AE immediately increased the PS during the obstructive event (Fig. 9.2, S150, the first apnea at 300th second), and it did not decrease until the volume largely surpassed the target V_T, which frequently due to the resume of normal breathing of the patient. This phenomenon corresponds to "Volume overshoot" in patients and was frequently observed after resolution of a pathological condition, such as obstructive apnea [1]. However, such physiological "volume overshoot" can be amplified by the fast and high-level pressure rises and abrupt hyperventilation may induce arousals and destabilize ventilatory control, and promote patient-ventilator asynchrony [1]. On the contrary, AVAPS AE and AutoST AE dealt with apneas in a more prudent manner. In our example, we observed that the PS delivered by both devices remained barely unchanged during the apneas (Fig. 9.2, A40 and V40), and PS increased with a moderate rate in presence of breaths to achieve the ventilation target.

By comparing the volumes within the last obstructive apnea for all the three device (Fig. 9.2, between 840th second and 860th second), similar volumes were found between A40 and S150 (297 mL vs. 301 mL), whereas the EPAP level of S150 was 3.5 cmH_2O lower than that of A40 (6.5 cmH_2O vs. 9.0 cmH_2O). A high-level PS could generate an appropriate volume even if the EPAP was too low to keep the UA patency. Nevertheless, the PS were delivered by the backup rate rather than triggered by patient's breaths (Fig. 9.2, S150), and these asynchronized high-level PS may induce poor ventilatory tolerance.

Aggressive PS during apneas as observed with iVAPS AE may be due to the priority of the algorithm of maintaining a target volume relative to the UA patency, but may be owing to the technique used to identify an UA obstruction. Since the detection of UA obstruction relies on breathing waveforms, PS delivery is necessary for generating a flow in order to check the UA patency. To get a rapid response to UA obstruction, this technique of detection requires a short window length for waveform analysis especially when the breathing rate is low. Otherwise, the sensitivity of detecting obstructive events in particular those of short duration can be low and "volume overshoot" may occur after apneas.

Although no device has entirely overcome the UA obstructions in our breathing scenario, FOT appeared more efficient for detecting obstructed UA leading to EPAP increase. Using FOT for UA obstruction detection did not rely on PS delivered by the ventilator, and did not affected by the PS for ventilation.

One limit of the current simulation is that we generated sudden upper airway obstruction (obstructive apnea) with a high pressure applied on the pharyngeal tube. In physiological conditions, the occurrence of the upper airway obstruction is generally a progressive and dynamic progress. An obstruction evolves from flow limitation to partial and complete occlusion. This allows ventilators to spend more time to analyze the flow waveform and to deal with the upper airway obstruction. This implies the interest of including analysis of breathing patterns such as flow limitation in the device algorithms, as such algorithms may react before the complete upper airway occlusion occurs.

It should be also highlighted that the variety and the complexity of breathing patterns and ventilatory conditions are limited in bench simulation. By simulating controlled breathing patterns with a respiratory bench model, the current chapter aims to demonstrate to readers the responses of new "hybrid" ventilatory modes to such specific patterns, and to reveal the discrepancy in the algorithms between the manufacturers. Clinical data are needed for accessing to long-term treatment data and physiologic effects of these ventilatory modes.

Key Teaching Points

- We note that the algorithms of VAPS modes differ between manufacturers, and accordingly, the treatment effectiveness of devices are different.
- Currently, there is no evidence-based superiority of VAPS modes with and without auto-EPAP over conventional ventilatory modes. Despite of the advantages claimed by the manufacturers such as simple NIV settings or "intelligent" responses to changes in patient's ventilatory requirements, conventional ventilatory modes such as ST mode should be considered prior to such fully automatic modes.

Questions and Answers

1. What are the main differences between the volume-assured pressure support (VAPS) mode and the volumetric mode (Controlled Volume)?

   (a) Different patient circuits
   (b) Different ventilatory settings (pressure settings vs. volume settings)
   (c) Measurement of patient's volume
   (d) All of the above

   Answer: (b) Different ventilatory settings (pressure settings vs. volume settings)

2. What are the main purposes of VAPS modes with auto-EPAP?

   (a) To maintain a target tidal volume for patient
   (b) To maintain the upper airway patency
   (c) To improve patient's compliance to treatment
   (d) To decrease leak

   Answer: (a) To maintain a target tidal volume for patient.
   (b) To maintain the upper airway patency

3. Which parameters are NOT automatically adjusted by the VAPS algorithm with auto-EPAP?

   (a) EPAP
   (b) IPAP
   (c) Ventilatory rate
   (d) IPAP rising rate

   Answer: (d) IPAP rising rate

4. Which statement is true?
   (a) When the patient presents obstructive upper airway events, ideally the algorithm of VAPS mode should increase the pressure support in prior to EPAP to reach the target volume.
   (b) VAPS modes show a superiority over conventional ventilatory modes (e.g., ST mode).
   (c) The expiratory volume can be estimated with VAPS mode
   (d) None of the above

   Answer: (c) The expiratory volume can be estimated with VAPS mode.

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Part II
Clinical Cases and Noninvasive Ventilation Physiology

Chapter 10
Noninvasive Ventilation Extrapulmonary Response Determinants

Aysun Dauti Isiklar

Abbreviations

AKI	Acute kidney injury
ALI	Acute lung injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
EEN	Effective enteral nutrition
ESICM	European society of intensive medicine
HFNO	High-flow nasal oxygen
IAP	Intraabdominal pressure
ICU	Intensive care unit
MODS	Multiple organ dysfunction syndrome
NIV	Non-invasive ventilation
PPV	Positive pressure mechanical ventilation
RRT	Renal replacement therapy
SD	Swallowing disorders

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10.1 Introduction

The physiological effects of mechanical ventilation are well recorded and we know that spontaneous ventilation is an exercise. Laboratory and clinical studies have shown that positive pressure ventilation (PPV) can significantly alter cardiovascular, pulmonary, neurological, renal and gastrointestinal functions. Every attempt should be made to minimize the negative effects of PPV. Therefore, understanding the physiological effects and possible complications of PPV is essential for clinicians involved in ventilator management.

10.2 Effects of Positive Pressure Ventilation (PPV) on Thoracic Functions

Positive pressure ventilation can significantly change physiological pressures in the thorax. The extent of these changes depends on the amount of positive pressure applied to the airways and the patient's cardiopulmonary status [1].

10.3 Increased Pulmonary Vascular Resistance and Altered Right and Left Ventricular Function

During high tidal volume (VT) inspiration or when a high level of PEEP is used, the pulmonary capillaries connecting the alveoli are stretched and narrowed. As a result, resistance to blood flow in the pulmonary circulation increases. This increases postventricular (RV) burden (i.e., pulmonary vascular resistance [PVR] and resting volume of RV). In normal healthy individuals, RV stroke volume is maintained against increased PVR, since RV contract function is not severely impaired. However, in patients with RV dysfunction, RV cannot overcome these increases in PVR and excessive regression of RV output occurs, leading to a decrease in RV output [1, 2].

Expansion of the RV may also force the interventricular septum to move to the left. This phenomenon usually occurs when a high image (>15 cmH_2O) is used and the patient's blood volume is depleted. When this happens, the left ventricular end-diastolic volume (LVEDV) is wound over the left ventricular (LV) stroke volume and overtake. It can be reduced because of its limited filling capacity. The septal shift may significantly reduce cardiac output in patients compromising LV function or in patients with reduced volume. In this last group of patients, intravascular volume expansion can help restore the output on the left side of the heart by restoring the LV preload [1, 2].

LV output also decreases when high VTs are used during PPV because the heart is compressed between the expanding lungs (i.e., the cardiac tamponade effect). The detectability of the left side of the heart appears to be directly related to the transmission of positive pressures from the lung to the heart. This effect is enhanced when long inspiratory times and high peak pressures are used [1, 2].

10.4 The Effect of Positive Pressure Ventilation on Coronary Blood Flow

Decreased venous return and changes in ventricular function, as well as reduced cardiac output, may result from myocardial dysfunction associated with decreased myocardial ischemia and the resulting perfusion of myocardial ischemia. The flow of blood to the coronary vessels depends on the coronary perfusion pressure. The coronary artery perfusion pressure gradient for LV is the difference between mean aortic diastolic pressure and left ventricular end-diastolic pressure (LVEDP); The perfusion pressure gradient for RV is the difference between mean aortic pressure and pulmonary artery systolic pressure.

Decrease in coronary vessel perfusion may be caused by any factor that reduces this perfusion pressure gradient. Thus, a direct effect of compression of coronary vessels caused by increases in intrathoracic pressure during cardiac output or blood pressure, coronary vasospasms, or PPV may reduce coronary perfusion and ultimately lead to myocardial ischemia.

10.5 Factors Determining Cardiovascular Effects of Positive Pressure Ventilation

The level of reduction in heart rate induced by PPV depends on a variety of factors, including lung and chest wall compliance, airway resistance (Raw), and duration and magnitude of positive pressure.

10.6 Indemnity in Individuals with Normal Cardiovascular Function

Due to compensatory mechanisms, systemic hypotension is rarely seen in people with normal cardiovascular function receiving PPV. The decrease in stroke volume normally causes an increase in sympathetic tone, which leads to an increase in systemic vascular resistance and peripheral venous pressure due to tachycardia and arterial and venous constriction respectively. In addition, some peripheral blood shunts are removed from the kidneys and lower extremities. The net effect is the maintenance of blood pressure even if there is a decrease in cardiac output**.**

It is important to understand that the effectiveness of these compensatory mechanisms in maintaining arterial blood pressure depends on the integrity of the individual's neural reflexes. Vascular reflexes may be prevented or impaired in the presence of sympathetic blockage, spinal anesthesia, moderate general anesthesia, spinal cord transection, or severe polyneuritis. In a patient with PPV initiated or ventilator mode changed, it would be wise to measure blood pressure early to ensure normal vascular reflexes are intact. The presence of normal vascular reflexes

increases the likelihood that the patient will experience a significant reduction in heart rate and blood pressure if PPV is initiated. For example, in normovolemic patients, it is unusual to see a decrease in heart output when low levels of PEEP are used (i.e., 5–10 cmH_2O PEEP). However, if higher PEEP levels (>15 cmH_2O) are used, reductions in cardiac output may occur in this patient group.

10.7 Beneficial Effects of Positive Pressure Ventilation on Heart Function in Patients with Left Ventricular Dysfunction

Although the discussion so far has focused on the negative effects of PPV, it is important to know that positive pressure may also be beneficial for patients with LV dysfunction and high filling pressures. For example, PEEP can improve cardiac function by increasing PaO_2 and improving myocardial oxygenation and performance if left LV dysfunction is caused by hypoxemia. Reductions in venous return reduce preload to the heart, thereby improving length-tension relationships and improving stroke volume in patients with ventricular overload. In addition, by increasing intrathoracic pressure, PPV transmural LV reduces systolic pressure and thus the load to the left heart [3].

10.8 Effects of Mechanical Ventilation on Intracranial Pressure and Cerebral Perfusion

The effect of positive end-expiratory pressure (PEEP) on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) has been reported by several investigators without any consensus. Acute neurological and neurosurgical patients have intracranial hypertension and hypoxemic acute lung injury. PEEP is expected to improve hypoxemia but may increase ICP and reduce CPP [4].

10.9 Renal Effects of Mechanical Ventilation

Both forms of end-organ damage ALI and acute kidney injury (AKI) usually occur in similar settings of systemic inflammatory response syndrome, shock, and developing multiple organ dysfunction. AKI is an independent predictor of mortality in ICU patients. Unfortunately, AKI can often cause a 60% mortality rate as a critical component of a multi-organ system dysfunction. In critically ill patients, AKI is part of the triad of respiratory failure requiring shock and positive pressure mechanical ventilation (PPV) [5].

Recent advances in critical care, including the implementation of lung-sparing ventilator strategies, have explained the role of inflammatory mediators of ALI and specifically ventilator-induced lung injury in AKI pathogenesis, which in some cases may be appropriately referred to as ventilator-induced kidney injury (VIKI) [6].

In 1947, PPV was first shown to affect renal function and perfusion [7]. In this first study involving healthy individuals receiving continuous positive airway pressure, various mechanisms were shown to alter cardiac output and cause changes in renal perfusion and function. The increase in intrathoracic pressure has been shown to correlate with decreased renal plasma flow during PPV, glomerular filtration rate (GFR), and urine output. This aspect of renal hemodynamics has been confirmed in part by canine studies by Qvist et al. [8]

Showed that a stable cardiac output in the PPV setting was not associated with a decrease in GFR or urine output.

The increased right ventricular afterload may lead to decreased cardiac output and reduced renal perfusion regardless of effects on venous return. Similarly, in patients with increased intrathoracic pressure (injured, stiff lungs or chest wall) or intra-abdominal pressure (morbid obesity, abdominal compartment syndrome), PPV can reduce renal blood flow by increasing renal venous pressure (reducing renal perfusion pressure). and compresses the renal vascular system leading to AKI. However, since the effects on cardiac output and renal perfusion are insufficient to fully explain the mechanism of PPV-induced oliguria and renal dysfunction, other mechanisms have been proposed to explain these events [9].

PPV has been shown to alter various neurohormonal systems such as sympathetic output, renin-angiotensin axis, non-osmotic vasopressin (ADH) release, and production of atrial natriuretic peptide (ANP). The result of all these neurohormonal pathways is decreased renal blood flow, decreased GFR, and fluid retention with oliguria (salt and water). Despite conflicting data, there is some evidence that fluid retention results from PPV-derived vasoactive substance production. These mediators shift the intrarenal blood flow from the cortex to the medulla, thereby causing more fluid retention at any level of renal perfusion [10].

ADH release in the PPV setting can be versatile. Taken together with evidence that an increase in urine osmolarity has no direct effect on PPV, it shows that ADH release is not the primary mechanism responsible for the decrease in urine output during PPV. It should not be surprising that the renin-angiotensin-aldosterone axis is affected by PPV. PPV leads to increased sympathetic tone, secondary activation of the renin-angiotensin axis, and decreased renal plasma flow, GFR and urine output. Of course, downstream stimulation of aldosterone production is among the salt-holding effects of PPV. Limited studies examining catecholamine levels and PPV did not provide a clear correlation between mechanical ventilation and hormone concentrations [11].

Suppression of ANP release has been proposed as a source of reduced urine volume and PPV-related sodium content. Of course, ANP suppression may not explain the reported reduction in PPV-induced GFR, even if it plays a role in PPV-induced sodium retention and oliguria.

The connection between AKI and lungs dates back to the 1950s when it was first assumed that patients with AKI had abnormal chest X-rays. AKI was thought to cause increased pulmonary vascular permeability and pulmonary obstruction; therefore, the term "uremic lung" was created. Since then, AKI patients have experienced the benefits of renal replacement therapy (RRT), and when the term "uremic lung" was dropped out, recent advances in understanding the complex interaction between AKI and the pulmonary system have led to rejuvenation [12].

Many of the effects of AKI are difficult to define and quantify independently, but experimental data increasingly elucidate the subclinical effects of AKI on distant organ function [13]. Uremic findings such as resistant hyperkalemia, pulmonary edema or pericarditis are associated with AKI when they develop acutely in the appropriate setting. Other uremic manifestations may have several explanations (encephalopathy, acidosis), or perhaps hidden causes of other complications (bleeding diathesis and gastrointestinal bleeding, leukocyte dysfunction and immunosuppression infection). In addition to the evidence that AKI confirms an independent role in increasing ICU mortality, it is clinically clear that AKI (including ALI and other distant organ injuries) is a major cause of morbidity and seriously complicates ICU management [13].

10.10 The Effect of Mechanical Ventilation on Liver and Gastrointestinal Functions

Mechanical ventilation causes an increase in airway pressure and, therefore, an increase in intrathoracic pressure, which can reduce systemic and intraabdominal organ perfusion. Intensive care patients rarely die of hypoxia and/or hypercarbidene, but usually develop a systemic inflammatory response resulting in multiple organ dysfunction syndrome and death. In the pathogenesis of this syndrome, gastrointestinal system and liver attracted considerable attention**.**

It was found that mechanical ventilation with high positive end expiratory pressure reduced splanchnic perfusion. The hepatic arterial buffer response is maintained, and an increased hepatic artery blood flow compensates for the decrease in portal blood flow. Despite an acute mild increase in arterial PCO_2 during protective ventilation and increased cardiac output, improvement of splanchnic and gout perfusion cannot be expected. When there was no significant increase in intraabdominal pressure without deterioration of cardiovascular function, splanchnic and gastrointestinal function remained unchanged for a short time in prone positioning. During ventilator support, spontaneous breathing improves systemic blood flow and gastrointestinal and splanchnic perfusion.

Splanchnic perfusion may change significantly when cardiopulmonary function is impaired during mechanical ventilation. PEEP has been shown to decrease at levels above 15 cmH_2O splanchnic perfusion. An acute mild increase in arterial PCO_2 during protective ventilation was observed to increase hepatic and splanchnic

blood flow in two phases. Initially, the blood flow is reduced due to sympathetic stimulation, and then the blood flow due to the direct vasodilator effect of CO_2 increases. Prone positioning of ALI patients in the absence of a markedly increasing intraabdominal pressure (IAP) does not worsen gastrointestinal and splanchnic perfusion. Periodic reduction of intrathoracic pressure achieved by maintaining spontaneous respiration during ventilator support increases cardiac output and oxygen delivery by providing a venous return to the heart and right and left ventricular filling. Maintaining spontaneous breathing during ventilator support is associated with better systemic and bowel blood flows. Based on these data, ventilator settings should be adjusted to avoid situations that may be associated with deterioration of systemic and intestinal blood flow.

10.11 Nutritional Problems During Mechanical Ventilation

In the management of patients with respiratory failure, non-invasive ventilation (NIV) reduces respiratory work and may provide a more comfortable and less sedation requirement than conventional mechanical ventilation with endotracheal tube, while preventing further deterioration of respiratory status. It appears to be beneficial in both acute and non-acute settings. A large observational French study of nutritional support in patients receiving NIV has shown that approximately 60% of the patients are fasted and only 2.6% enteral-fed during the first 2 days of treatment. The Nutrition Day ICU inspection of approximately 10,000 patients, 47% of whom underwent mechanical ventilation and 6.2% with NIV, found similar findings that 40% of the patients were hungry on the first day and 20% on the second day [14].

In addition to the fact that many ICU patients do not receive nutritional support regardless of their accepted etiology, there may be many explanations for their reluctance to provide nutritional support during NIV. NIV support may not always be successful in preventing the necessity of endotracheal intubation, and it may not be easy to predict which patients will worsen. Therefore, in general, an order per zero is given where intubation is required later. The presence of a nasogastric tube (NGT) can cause air leakage and compromise the effectiveness of NIV [14, 15].

While this problem can be overcome with special NIV masks, the port for NGT, they are not always available and are costly. Positive pressure ventilation from a face mask also causes the stomach to dilate with air. The resulting gastric distension may adversely affect diaphragmatic function, may also compromise respiratory discomfort and cause endotracheal intubation. Patients who are allowed to take an oral diet may worsen when they remove the NIV to eat and may cause a decrease in respiratory function. A retrospective observation study showed that receiving enteral nutrition during NIV was associated with respiratory complications (535,332%, $P = 0.03$) and longer NIV duration (16–8 days, $P = 0.02$). does not take enteral nutrition. The inability of NIV to relieve the patient is associated with increased mortality, which explains why physicians are reluctant to reduce the likelihood of

success by writing enteral nutritional support. NIV is also used to prevent reintubation after extubation. Oral intake during this period is known to be as low as about 650 kcal/day [15].

After extubation, swallowing disorders (SD) may weaken the return to normal food intake, and moderate/severe SD is associated with a higher rate of insufficiency, pneumonia, length of stay, and mortality. These causes may cause the physician to refrain from ordering oral/enteral nutrition in the interim period before recovery.

According to ESICM recommendations on early enteral feeding, there is a clear advantage in reducing infection complications to EEN compared with delayed enteral feeding and early parenteral feeding. The more calorie deficits a malnourished patient develops, the worse the outcome [15], and therefore malnourished patients should be fed without delay to prevent worsening of their general condition.

Technically, NIV impairs oral and enteral nutrition. If the patient is undernourished, HFNO should be considered to allow calorie and protein requirements to be met, or efforts should be made to enteral feed the patient. The use of parenteral nutrition has been recommended in patients with long-term SD who may reduce the success rate of swallowing rehabilitation by re-use of an NGT. Although parenteral nutrition is thought to be associated with worse outcomes, recent studies show that excess calories are not the path responsible for these complications. To prevent over-feeding, Siirala et al. Managed to measure rest energy expenditure (REE) in patients with a canopy that allows the determination of a calorie target with NIV [16–18].

Questions and Answers

1. A 48-years old, male patient with BMI of 43 and previously diagnosed chronic obstructive pulmonary disease is admitted to the operating room for sleeve gastrectomy operation. Peak inspiratory pressure is measured as 39 mmHg immediately after the orotracheal intubation with 7.0 mm sized endotracheal tube. The possible causes can be:

   (a) Atelectasis
   (b) Increased airway secretions
   (c) Acute respiratory distress syndrome ARDS
   (d) Surfactant deficiency
   (e) Small endotracheal tube size

   Answers: a. True; b. True; c. False; d. False; e. True

   Both obesity and general anesthesia causes atelectasis. Chronic obstructive pulmonary disease (COPD) can cause increased airway resistance due to increased airway secretion and airway inflammation. Smaller internal diameter of the endotracheal tube causes greater resistance to airflow. A 7.0 mm sized endotracheal tube is small for adult patient. Surfactant deficiency and ARDS decreases lung compliance, and are not relevant with the case presented.

2. The following conditions decrease compliance:

   (a) Obesity
   (b) Emphysema
   (c) Increased age
   (d) Pulmonary fibrosis
   (e) Kyphoscoliosis

   Answers: a. True; b. False; c. False; d. True; e. True

   Obesity and kyphoscoliosis reduces chest wall compliance. Pulmonary fibrosis increases fibrous tissue in the lung, which causes stiff lung. Emphysema causes destruction of alveolar walls, thus alveolar surface tension decreases and lung compliance increases. The structure of lung collagen and elastin changes over time, causing small increase in lung compliance.
3. The following conditions increase resistance:

   (a) decreased parasympathetic activity
   (b) lobectomy
   (c) asthma
   (d) emphysema
   (e) tonsillitis
   (f) decreased viscosity of the inspired gas

   Answers: a. False; b. True; c. True; d. True; e. True; f. False

   Airway resistance (Raw) is calculated using driving pressure (DP) and gas flow (F) (Raw = DP/F). Driving pressure (DP) is the pressure difference between the alveoli and the mouth in spontaneous breathing. Gas flow is measured during inspiration and depends on the gas viscosity, gas density, length and diameter of the airway or endotracheal tube (when artificial airway is inserted during mechanical ventilation). Acetylcholine causes direct bronchial muscle contraction, so increased parasympathetic activity increases resistance. Surgeries like lobectomy and pneumonectomy causes reduction in lung volume and this leads to increased airway resistance. Asthma causes airway hyper responsiveness and narrowing of small airways. Emphysema causes enlargement of airspaces distal to the terminal bronchiole and destruction of alveolar walls. Infections like croup, tonsillitis cause airway edema.
4. About lung mechanics:

   (a) The major components of resistance are large and medium-sized airways
   (b) Increased pCO_2 in alveolar gas increases airway resistance
   (c) Increased gas flow causes decreased airway resistance
   (d) Laparoscopic surgery increases lung compliance
   (e) Congestive heart failure decreases compliance

   Answers: a. True; b. False; c. True; d. False; e. True

5. Airway resistance (Raw) is calculated using driving pressure (DP) and gas flow (F) (Raw = DP/F). Driving pressure (DP) is the pressure difference between the alveoli and the mouth in spontaneous breathing. Gas flow is measured during inspiration and depends on the gas viscosity, gas density, length and diameter of the airway or endotracheal tube (when artificial airway is inserted during mechanical ventilation). The major components of resistance are large and medium-sized airways, and minor components are small airways and chest wall tissues. Decreased pCO_2 in alveolar gas causes bronchoconstriction via direct bronchial muscle stimulation. Increased intraabdominal pressure displaces diaphragm to the thorax, so both chest wall and lung compliance are decreased. Congestive heart failure causes pulmonary hypertension, and pulmonary venous congestion causes stiffness of the lungs, which leads to decreased compliance.

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Chapter 11
Patterns Response (Apnea, Hypopnea, Tachypnea)

Aysun Dauti Isiklar

Abbreviations

DRG	Dorsal breathing groups
ICP	Intracranial pressure
TBI	Traumatic brain injury
TV	Tidal volume
VRG	Ventral breathing groups

11.1 Introduction

There are many types of normal and abnormal breathing. Some of the patterns are Apnea, orthopnea, dyspnea, hyperpnea, hyperventilation, hypoventilation, tachypnea, Kussmaul respiration, Cheyne-Stokes respiration. Each model is clinically important and useful in evaluating patients.

Evaluation of respiratory patterns helps the clinician to understand the current physiological state of the patient. Abnormal breathing patterns indicate the possibility of the underlying injury or metabolic disorders. Early recognition of abnormal respiratory patterns may help the clinician during the early intervention to prevent further deterioration of the patient's condition [1].

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The respiratory control center is in the brain stem. It receives stimulation from central and peripheral chemoreceptors. Adjusts respiratory rate and tidal volume (TV) according to pH and $PaCO_2$.

The normal breathing cycle results from the medulla. In the medullary respiration center, there are several widely distributed neurons, called dorsal and ventral breathing groups. Separate inspiration and expiratory centers do not appear.

Bilateral dorsal breathing groups (DRG) control the respiratory rhythm by generating inspiratory impulses. The neurons in this center stimulate the motor neurons of the diaphragm and the external intercostal muscles. These nerves also extend to ventral breathing groups (VRG). Inputs from the airways, lungs, joint proprioceptors and peripheral chemoreceptors from the vagus and glossopharyngeal nerves change the respiratory pattern.

Ventral breathing groups (VRG) are also bilateral collections of inspiratory and expiratory neurons in the medulla and are active in exercise and stress. These neurons send impulses to the diaphragm and external intercostals. They also stimulate the abdominal muscles and internal intercostals through neurons in the caudal region.

The interaction between DRG and VRG generates an impulse, inspiratory ramp signal. It starts low and gradually, then increases to create a smooth inspiration effort.

Pons include two respiratory areas, called pneumotoxic and apneoustic centers. The pneumotoxic center has an inhibitory effect on the medullary. In fact, stimulation causes the end of the inspiratory effort and therefore controls the inspiratory time. Weak signals from the pneumotoxic center prolong the incidence, leading to an increase in tidal volume. The apneustic center stimulates inspiratory neurons in the medulla and inhibits expiratory neurons. Over-stimulation of this field produces long, breathtaking inspirations that are inadequately cut off from time to time. This pattern is called apneustic respiration [2, 3].

11.2 Types of Clinical Pattern Response

- Apnea is the absence of breathing. This indicates a life-threatening condition where the patient will fail quickly unless rescue breathing is initiated immediately.
- Hypopnea in decreasing volume without decreasing or increasing respiratory rate. Blood gases are normal.
- Tachypnea is a greater respiratory rate than normal for age.
- Orthopnea is also seen in heart failure. Patients cannot sit back and breathe easily. They must be in a sitting position or supported to breathe with difficulty.
- Dyspnea is the subjective feeling of the difficulty of breathing.
- Hyperventilation is more ventilation than necessary for the body's CO_2 removal. This causes a decrease in $PaCO_2$ and respiratory alkalosis. Hyperventilation can be induced by chemoreceptor stimulation due to metabolic acidosis.
- Hypoventilation is under aeration below the body's CO_2 removal. Maintaining a normal $PaCO_2$ is insufficient.

- Cheyne-Stokes is an example of crescendo-decrescendo respirations following the apnea period. This breathing habit was first described by an English Doctor John Cheyne and an Irish Doctor William Stokes. It is well defined in patients with heart failure. It is usually observed during sleep and is the result of irregular respiratory control. The presence of cardiac resynchronization therapy has implications for improving outcomes in patients with Cheyne-Stokes Respiration.
- Kussmaul respirations, first It was observed and described by Adolf Kussmaul in 1874. His observation was in diabetic patients in a coma and in the late stages of diabetic ketoacidosis. Kussmaul breaths, as defined in the classical sense, are a deep, sighing form of breathing at a normal or slow rate. Kussmaul actually called it "air hunger". This is probably the most important of abnormal breathing patterns.

Breathing patterns associated with brain injury due to mechanical ventilation and sedation may not be observed. There is a complex interaction in situations that cause brain stem injury. Autoregulation of brain blood flow is affected by the level of CO_2 in the blood. As the CO_2 increases, the brain vessels will expand and the brain vessels will narrow as they decrease. In traumatic brain injury (TBI), the brain expands and cannot swell due to the fixed volume of the intact skull. High intracranial pressure (ICP) can overcome the perfusion pressure and cause more anoxia and injury leading to brain death and/or herniation. Although hyperventilation can reduce $PaCO_2$, it causes vasoconstriction and reduces swelling/ICP, and should be avoided. The effect was short-lived. Both hyperventilation and hypoventilation should be avoided in TBI. ICP is treated with pharmacological, surgical and medically-induced coma [4, 5].

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Chapter 12
Lung Mechanics- Compliance and Resistance-Extrapulmonary Response

Aylin Özdilek

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BIPAP	Bilevel positive airway pressure
C	Compliance
COPD	Chronic obstructive pulmonary disease
DP	Driving pressure
EPAP	Expiratory positive airway pressure
e	Elastance
F	Gas flow
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
NIMV	Noninvasive mechanical ventilation
Pal	Alveolar pressure
Paw	Airway pressure

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Ppl	Pleural pressure
Raw	Airway resistance
ΔP	Pressure change
ΔV	Volume change

12.1 Introduction

Lung is an elastic structure which expands (inspiration) and collapses (expiration) during ventilation. There are different pressures that cause the air movement into and out of the lungs. *Pleural pressure* (Ppl) is the negative pressure (−5 cmH_2O) between the lungs and the chest wall and is responsible for keeping lungs open during expiration [1]. *Alveolar pressure* (Pal) is the air pressure inside the lungs and is measured 0 cmH_2O when the glottis is open, and no air is flowing into or out of the lungs [1]. *Transpulmonary pressure* (Ptp) is the difference between alveolar and pleural pressures (Ptp = Pal-Ppl) [1]. Increasing of Ptp results in inspiration and decrease of Ptp results in expiration [1].

Lung mechanics are described by two parameters: resistance and compliance.

12.2 Resistance

Frictional forces that must be overcome during breathing are defined as resistance [2]. The frictional forces can originate from airways (airway resistance) and tissues like chest wall and lungs (tissue resistance) [2, 3]. Resistance is expressed in centimeters of water per liter per second (cmH_2O/L/s) and in spontaneously breathing young adult, with a gas flow of 0.5 L/s is approximately about 0.6–2.4 cmH_2O/(L/s) [2].

12.2.1 Tissue Resistance

Tissue resistance is defined as frictional resistance originated from the tissues as they slide over each other. Tissue resistance originates from both chest wall and lungs, but the significant part is originated from the chest wall. Tissue resistance is only about 20% of the total resistance in young healthy adults [4].

12.2.2 Airway Resistance

Airway resistance is defined as frictional resistance originated from airways, that must be overcome during ventilation.

Airway resistance (Raw) is calculated using driving pressure (DP) and gas flow (F) (Raw = DP/F). Driving pressure (DP) is the pressure difference between the alveoli

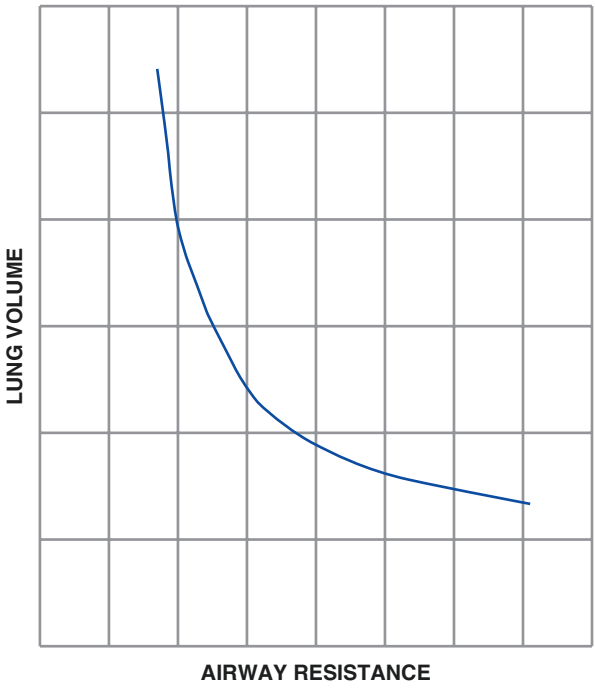

Fig. 12.1 Resistance. Reduced lung volume causes increase in resistance

and the mouth in spontaneous breathing, [4]. Gas flow is measured during inspiration and depends on the gas viscosity, gas density, length and diameter of the airway or endotracheal tube (when artificial airway is inserted during mechanical ventilation) [2].

The major components of resistance are large and medium-sized airways, and minor components are small airways and chest wall tissues [4, 5]. In mechanical ventilation, components affecting airway resistance are length, size, and patency of the endotracheal tube, and ventilatory circuit [6].

Conditions Associated with Increased Resistance:

1. Reduced lung volume: Surgeries like lobectomy and pneumonectomy causes proportional reduction in the volume of all air-containing components and this leads to airway collapse [7] (Fig. 12.1).
2. Bronchospasm: Irritants such as cigarette smoke causes increased airway resistance [4].
3. Increased parasympathetic activity: Acetylcholine causes direct bronchial muscle contraction [4].
4. Decreased pCO_2 in alveolar gas causes bronchoconstriction via direct bronchial muscle stimulation [4].
5. Airway tumors narrow airway lumen [8].
6. Infections like croup, tonsillitis cause airway edema [8].
7. Inhaled foreign bodies narrow airway lumen [8].
8. Tumor or bleeding in the neck area narrow airway lumen [8].
9. Asthma causes airway hyperresponsiveness and narrowing of small airways [8].

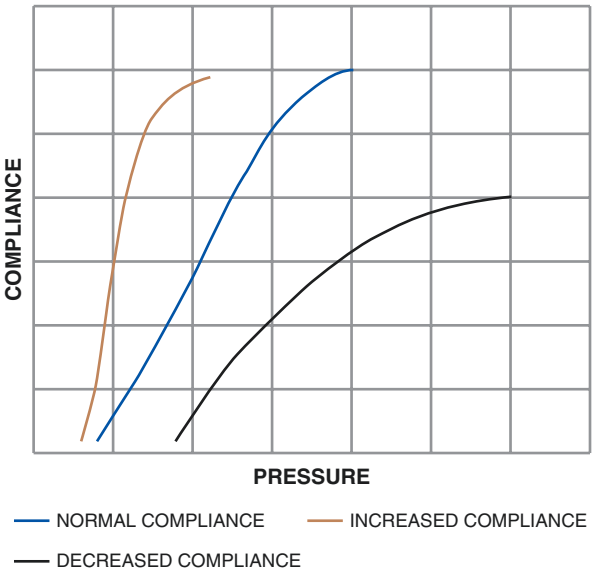

Fig. 12.2 Compliance. Compliance is defined as change in lung volume per unit change in the pressure

10. Chronic obstructive pulmonary disease (COPD) causes narrowing and inflammation of small airways [8].
11. Cystic fibrosis causes airway inflammation, mucus production and progressive lung tissue damage [8].
12. Emphysema causes enlargement of airspaces distal to the terminal bronchiole and destruction of alveolar walls [8].
13. Increased density and viscosity of the inspired gas [4].
14. Artificial airway: smaller internal diameter of the endotracheal tube causes greater resistance to flow [2].
15. Narrowing of the large extra thoracic airways: thyroid hyperplasia or tumor, paralyzed vocal cord, epiglottitis [5].
16. Anesthesia causes lung volume reduction which leads to airway narrowing [5].
17. Increased secretions narrow airway lumen [2].
18. Mucosal edema narrows airway lumen [2].
19. Interfaces used for noninvasive mechanical ventilation (NIMV): Nasal mask and nasal pillows cause higher resistance compared to oronasal, helmet and total face mask [9].

12.3 Compliance

Compliance (C) can be described as the relative ease with which the structure distends [2]. Compliance is the opposite of elastance (e), where elastance is the tendency of a structure to return to its original form after being stretched [2]. Thus, C = 1/e or e = 1/C. Both chest wall and lung compliance can affect the ventilation.

12.3.1 Chest Wall Compliance

Chest wall compliance is defined as change in lung volume per unit change in the pressure gradient between atmosphere and the intrapleural space and is about 200 mL/cmH_2O [7]. Chest wall compliance is affected by ribcage and diaphragm alterations [7]. Thus, accurate chest wall compliance can be measured when respiratory muscles are completely relaxed [5, 7].

12.4 Lung Compliance

Lung compliance (C) is defined as the change in volume (in liters) per unit change in pressure gradient (in cmH_2O) and is calculated by the following equation: $C = \Delta V/\Delta P$, where ΔV is volume change, and ΔP is pressure change [6] (Fig. 12.2). In a spontaneously breathing young healthy adult, the total compliance of both lungs is about 0.05–0.3 L/cmH_2O [1, 2, 5]. When compliance is low, lung expansion becomes difficult [6]. When compliance is high, expiration becomes incomplete and that leads to air trapping and CO_2 retention [6].

There are two different types of compliance: static and dynamic.

Static compliance is the compliance measured at a constant pressure when there is no airflow into and out of the lungs [6, 7]. Thus, static compliance can be measured more accurately in the paralyzed subject [7]. Static compliance is calculated by dividing the volume change by plateau pressure measured under these conditions [6]. When the airflow is absent, airway resistance has no influence on the compliance measurement [6]. Thus, static compliance reflects the elastic resistance of the lungs and chest wall [6].

Dynamic compliance is measured during a normal tidal breath when there is airflow into and out of the lungs [7]. Dynamic compliance is calculated by dividing the volume change by the peak inspiratory pressure [6]. Since airflow is present, airway resistance has influence on measuring the compliance [6]. Thus, dynamic compliance reflects both the airway resistance (nonelastic resistance) and the elastic resistance of the lungs and chest wall (elastic resistance) [6].

Conditions Associated with Decreased Compliance:

1. Small lung volume: Small alveoli contains less amounts of collagen and elastin, so the pressure needed to expand them increases [7].
2. Acute respiratory distress syndrome (ARDS) reduces lung compliance [2].
3. Kyphoscoliosis reduces chest wall compliance [2].
4. Surfactant deficiency: Surfactant decreases surface tension of the alveoli. Absence of surfactant causes decreased lung compliance, alveolar atelectasis, and tendency to pulmonary edema [4, 7].
5. Pulmonary venous congestion causes stiffness of the lungs [7].
6. Increased airway resistance: Bronchoconstriction reduces dynamic compliance [7].

7. Pulmonary fibrosis increases fibrous tissue in the lung, which causes stiff lung [4].
8. Alveolar edema restrains alveoli inflation [4].
9. Atelectasis causes deflation of some alveoli, which leads to decreased lung volume [4, 5].
10. Obesity reduces chest wall compliance [4, 5, 7].
11. Chest wall edema reduces chest wall compliance [5].
12. Pleural effusions reduce chest wall compliance [5].
13. Diseases of the costovertebral joints reduce chest wall compliance [5].
14. Increased intraabdominal pressure displaces diaphragm to the thorax, so both chest wall and lung compliance are decreased [7].
15. Patient position: Compared with the supine position, compliance is greater in the seated position, and is reduced in the prone position [7].
16. Tension pneumothorax reduces lung compliance [6].

Conditions Associated with Increased Compliance:

1. Emphysema causes destruction of alveolar walls, thus alveolar surface tension decreases and lung compliance increases [2, 4, 8].
2. Increasing age: The structure of lung collagen and elastin changes over time, causing small increase in lung compliance [4, 7].

12.5 Clinical Vignette

A 67-year-old, 84 kg, 173 cm male patient operated for renal cell carcinoma 2 days ago was consulted for respiratory failure. The patient was a smoker (30 cigarettes per day for 46 years) and preoperative pulmonary function test was as follows: forced vital capacity (FVC) 2600 mL (77%), forced expiratory volume in one second (FEV1) 2160 mL (84%), FEV1/FVC 116%, forced expiratory flow (FEF) 25/751,950 mL (69%). Physical examination showed respiratory rate of 38/min, Spo2 of 93, diminished breath sounds at bilateral lower lobes. Arterial blood gas analysis showed hypoxia and hypercarbia (pO_2 58 mmHg, pCO_2 57 mmHg). Crowded air bronchograms, elevation of the diaphragm and pulmonary opacification was found at thorax computed tomography. The patient was admitted to intensive care unit (ICU) for acute respiratory failure due to postoperative lung atelectasis. Bilevel positive airway pressure (BIPAP; Respironics Inc.; Murrysville, PA) with expiratory positive airway pressure (EPAP) of 7 mmHg and inspiratory positive airway pressure (IPAP) of 14 mmHg via face mask was initiated immediately after ICU admission. Arterial blood gases improved gradually, and the patient was transferred to the ward after 2 days, with respiratory rehabilitation recommendations.

Acute respiratory failure (ARF) is a common complication in surgical patients, especially after cardiac, thoracic and abdominal surgery.

Anesthesia itself reduces compliance and increases respiratory resistance [5]. Loss of muscle tone during anesthesia leads to fall of functional residual capacity (FRC). Surgery, on the other hand, decreases thoracic and diaphragmatic muscle

tone, reduces phrenic output and causes pain [10]. Thus, patients present with poor coughing and immobility after the surgery. Oxygen therapy is frequently used at ward, which complicates the atelectasis by causing *absorption atelectasis*. These factors cause formation of atelectasis and airway closure [5]. Atelectasis can occur immediately after the induction of general anesthesia and volumetric analysis of lung aeration shows that up to 20% of the entire lung may be atelectasis during general anesthesia [5]. Intraoperative atelectasis may persist after the patient is extubated and can increase the risk of acute respiratory failure and pneumonia [5, 10].

Noninvasive mechanical ventilation (NIMV) is increasingly used in the prevention and treatment of persisting postoperative atelectasis [10]. Studies showed that NIMV used for respiratory failure due to surgery increases lung aeration, improves arterial oxygenation, avoids intubation, reduces hospital and ICU length of stay, mortality and nosocomial infections [10, 11]. Thus, European Respiratory Society (ERS)/American Thoracic Society (ATS) guideline recommends NIMV for patients with post-operative ARF [11].

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Part III
Clinical Cases and Noninvasive Ventilation Pattern Response

Chapter 13
Early and Late Failure During Noninvasive Ventilation

Aslihan Gürün Kaya, Aydın Çiledağ, and Akın Kaya

Abbreviations

APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
CAP	Community-acquired pneumonia
COPD	chronic obstructive pulmonary disease
CPAP	Continue positive airway pressure
CRP	C-reactive protein
CT	Computed tomography
EPAP	Expiratory positive airway pressure
GCS	Glasgow Coma Score
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
NIV	Noninvasive ventilation
SAPS II	Simplified Acute Physiology Score II

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13.1 Introduction

In recent years non-invasive mechanical ventilation, delivered through a facial or nasal mask, has been successfully used in selected populations as an effective treatment for acute respiratory failure. However, despite recent encouraging results NIV is not always successful. Failure of NIV has usually been defined as; need for intubation because of lack of improvement in arterial blood gases and clinical parameters and death. In patients who failed NIV, a delay in intubation may lead clinical deterioration and increased mortality. Hence, the patients should be evaluated for the risk factors for NIV failure, and in the presence of risk factors, such patients should be especially be monitorized closely for a need of early intubation.

Case 1

A 53-year male patient who was admitted to the emergency department with fever and severe dyspnea, was promptly transferred to intensive care unit (ICU) with severe hypoxemic respiratory failure. The patient had a 3-day history of cough, sputum, fever and chills. Vital signs were as follows: mean arterial blood pressure 90 mmHg, pulse rate 124 beats/min, respiratory rate 26 breaths/min, and body temperature 38.8 °C. He was using accessory respiratory muscles. Simplified Acute Physiology Score II (SAPS II) was 29 and Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 16. Chest X-ray showed bilaterally opacities (Fig. 13.1). Thorax computed tomography (CT) revealed consolidations and ground-glass opacities on both lungs. Serum C-reactive protein (CRP) and procalcitonin levels were markedly elevated, 232 mg/L (0–5 mg/L) and 19 ng/mL (<0.12 ng/mL), respectively. Also, white blood cell count was 13,000/mm^3 with 73% neutrophils.

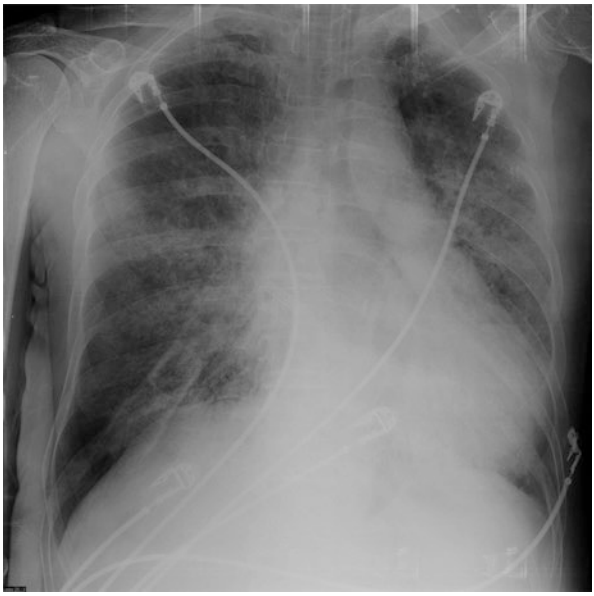

Fig. 13.1 Chest X-ray revealed bilateral heterogeneous opacities

Arterial blood gases analyses on venturi-type O_2 mask at 40% FiO_2 revealed: pH: 7.36; PCO_2: 35 mmHg; PO_2 51 mmHg; SaO_2 83%. The patient was accepted as severe hypoxemic respiratory failure due to community-acquired pneumonia and NIV was initiated using oronasal-mask. Bilevel positive airway pressure with inspiratory positive airway pressure (IPAP) of 14 cmH_2O and expiratory positive airway pressure (EPAP) of 6 cmH_2O was initiated in addition to proper medical treatment including broad-spectrum empirical antibiotic treatment. An improvement was not observed in the first hour of NIV and the IPAP and EPAP levels were gradually increased to 18 cmH_2O and 10 cmH_2O, respectively with 100% FiO_2. Despite this treatment, the patient was deteriorated and an endotracheal intubation was performed during the sixth hour of intensive care admission. A successful weaning was performed on the seventh day of invasive mechanical ventilation and the patient was discharged after 2 weeks of admission.

Case 2

A 61-year female patient with a history of chronic obstructive pulmonary disease (COPD) and bronchiectasis was admitted with cough, purulent sputum, shortness of breath. On physical examination the patient was cachectic and dyspneic. The mean blood pressure was 76 mm Hg, heart rate 122/min, temperature 39.1 °C, respiratory rate 33/min, and oxygen saturation was 77% on room air and 92% on 4 L/min oxygen with nasal cannula. Inspiratory rales was present at the basal areas of lungs on auscultation. Chest X-ray showed infiltration on bilateral lower zones and at a previous CT examination, cystic bronchiectasis was present at the lower lobes of the lung (Fig. 13.2). On laboratory findings, white blood cell count was 11,000/mm^3 with 68% neutrophils, liver and renal function tests were normal. Serum CRP level was 98 mg/L (0–5 mg/L) and procalcitonin level was 7 ng/mL (<0.12 ng/mL). Arterial blood gas analysis taken during on nasal oxygen therapy showed; pH: 7.30, $PaCO_2$: 64 mmHg, PaO_2: 58 mmHg, SaO_2: 90% and HCO_3^-: 28 mEq/L. The patient was diagnosed as exacerbation of COPD and bronchiectasis with hypercapnic

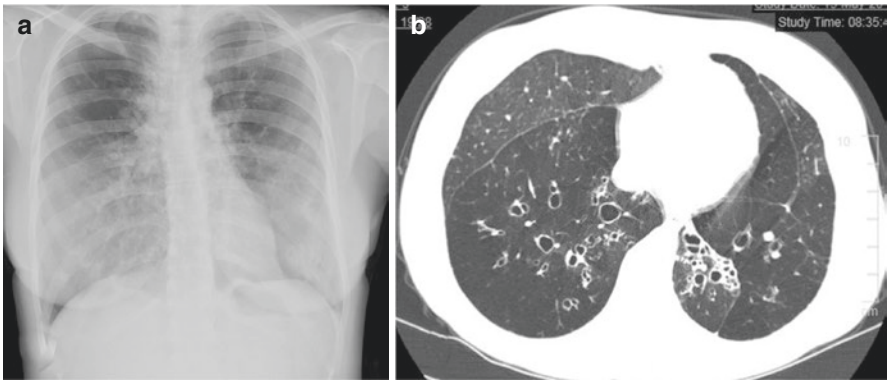

Fig. 13.2 (**a**) Chest X-ray showed infiltrations on bilateral lower zones. (**b**) Cystic bronchiectasis was present at the lower lobes of the lung on thorax CT

respiratory failure. NIV was initiated via full-face mask and bi-level positive airway pressure with inspiratory positive airway pressure (IPAP) of 14 cmH_2O and expiratory positive airway pressure (EPAP) of 5 cmH_2O. Then IPAP were titrated to 20 cmH_2O in order to achieve tidal volume of 7–10 mL/kg. In addition to NIV treatment, proper medical treatment, including clarithromycin with ceftriaxone, n-acetylcysteine and bronchodilator therapies were started. A clinical and laboratory improvement was achieved with this therapy and NIV was continued. During this therapy, the clinical findings and arterial blood gases were stable. However, the patient complained from excessive secretions and chest physiotherapy was also performed in addition to n-acetylcysteine. On the fifth day, the patient was deteriorated and $PaCO_2$ level were elevated with respiratory acidosis. The duration of NIV and levels of IPAP were increased, however, a need of invasive mechanical ventilation was developed, and the patient was intubated. During invasive mechanical ventilation, excessive secretions were aspirated and proper antibiotic therapy according to the tracheal aspirates culture was given. A clinical, radiological and laboratory improvement was observed with this treatment and the patient was successfully weaned on the fourth day of invasive mechanical ventilation.

13.2 Discussion

Noninvasive positive pressure ventilation has been shown as an effective treatment in ARF caused by various diseases. However, none of the published studies so far has reported a 100% success rate with NIV. Failure of NIV has usually been defined as a need for intubation because of lack of improvement in arterial blood gases and clinical parameters and death [1]. Although the failure of NIV may be early (up to 24 h after initiation of NIV), a late failure (more than 48 h) may also be occurred [2]. It is very important to identify patients who will fail NIV, because an inappropriate delay in intubation may cause an increase in morbidity and mortality.

The selection of appropriate patients is crucial for the optimization of NIV success rates. Predictors of NIV success or failure may be helpful in selecting patients and the reported best predictors of success of NIV are reduction in respiratory rate, improvement in pH, oxygenation and $PaCO_2$ within 1–2 h. The reported factors associated with NIV failure are: Glasgow Coma Score <11, tachypnea (>35 breaths/min), pH <7.25, Acute Physiology and Chronic Health Evaluation score >29, asynchronous breathing, edentulous excessive air leak, agitation, excessive secretions, poor tolerance, poor adherence to therapy in acute hypercapnic respiratory failure and a diagnosis of acute respiratory distress syndrome (ARDS) or pneumonia, age > 40 year, hypotension: systolic blood pressure <90 mmHg, metabolic acidosis: pH <7.25, low PaO_2/FiO_2, simplified Acute Physiology Score II >34, failure to improve oxygenation within first hour of noninvasive ventilation in acute hypoxemic respiratory failure [3]. Duan J, et al. developed HACOR score system, including heart rate, level of consciousness (Glasgow Coma Score; [GCS]), oxygenation (P/F) and respiratory rate, as a potential scoring system fort the prediction of NIV

failure regardless of diagnosis, age and severity in patients with hypoxemic respiratory failure and they reported that, the scale appears to be an effective way of predicting NIV failure in hypoxemic patients (Table 13.1) [4].

The underlying cause of respiratory failure is an important associated factor with NIV success or failure. There is strong evidence that the addition of NIV to standard medical treatment improves outcomes in patients with COPD exacerbation and in those with acute cardiogenic pulmonary edema. In the recently published ERS/ATS guideline for NIV in ARF, bilevel NIV has been recommended for patients with ARF leading to acute or acute-on-chronic respiratory acidosis (pH ⩽7.35) due to COPD exacerbation with strong recommendation, high certainty of evidence and, either bilevel NIV or CPAP for patients with ARF due to cardiogenic pulmonary oedema with strong recommendation, moderate certainty of evidence [5]. Community-acquired pneumonia (CAP) is one of the reason of ARF, and severe cases may require intensive care unit admission and mechanical ventilation. The use of NIV in patients with pneumonia is controversial due to reported high failure rates. However, in several studies, a significant reduction in intubation rate, shorter ICU stay, and lower mortality, mainly in patients with COPD has also been reported. Our Case 1 had acute severe ARF due to CAP and first we applied NIV in addition

Table 13.1 HACOR score [4]

Variables	Category	Assigned points
Heart rate (beats/min)	≤120	0
	≥121	1
pH	≥7.35	0
	7.30–7.34	2
	7.24–7.29	3
	<7.25	4
Glasgow coma scale	15	0
	13–14	2
	11–12	5
	≤10	10
PaO_2/FiO_2	≥201	0
	176–200	2
	151–175	3
	126–150	4
	101–125	5
	≤100	6
Respiratory rate (breaths/min)	≤30	0
	31–35	1
	36–40	2
	41–45	3
	≥46	4

to medical therapy, however early NIV failure was observed and the patient was intubated.

As mentioned above, the failure of NIV may be early or late. In a subgroup of patients, despite an initial improvement in arterial blood gases and clinical condition, a late failure (> 48 h) characterized with deterioration after an initial success may occur. The recognition of this subset of patients is critical because prolonged treatment of NIV may result in a delay in the time of intubation and increased mortality. Although, the factors associated with early NIV failure have been well established, the risk factors for late failure of NIV and the clinical and physiological characteristics of these patients has been evaluated in only a few studies [1, 6]. Moretti et al., studied 186 patients with COPD treated with NIV because of AHRF [1]. In their study, 74% of patients were successfully ventilated non-invasively at first and were therefore enrolled for data analysis. The authors found that, after 8.4 days (range 3–13) days of NIV 23% of patients experienced a new episode of acute respiratory failure. The occurrence of late NIV failure was significantly associated with functional limitations before admission to the respiratory ICU, the presence of medical complications and a lower pH on admission. They also reported that, these patients have a very poor in hospital prognosis, especially if NIV is continued rather than prompt initiation of invasive ventilation. In another study, performed by Carratu et al., in which 122 patients with COPD complicated by ARF and treated with NIV were enrolled, 10 (8%) patients had a late failure [6]. This subgroup of patients had a poor prognosis. In a study performed in our clinic, 93 patients with acute hypercapnic respiratory failure treated with NIV were evaluated [7]. We found that, in 25 (26.9%) patients a late failure was observed and the pretreatment high APACHE II Score and C-reactive protein level, low Glasgow Coma Score, albumin level, cough strength, bad compliance to non-invasive mechanical ventilation, the presence of bronchiectasis and pneumonia were determined as risk factors for non-invasive mechanical ventilation late failure. In our Case 2, a late failure was observed and we suggested that the presence of bronchiectasis and excessive secretions might be the reason for late failure.

In conclusion, although the use of NIV has been substantially increased in recent years, NIV is not successful in all patients with ARF. Before and during NIV treatment, the predictors and risk factors for both early and late failure of NIV should be investigated and in the presence of these factors patients should especially be monitorized closely for a need of early intubation.

Key Teaching Points

- Noninvasive mechanical ventilation is widely used in patients with acute respiratory failure and has been shown to prevent invasive mechanical ventilation.
- However, NIV is not always successful and in case of NIV failure, a delay in intubation may cause an increased morbidity and mortality.
- Although the failure of NIV may be early (first 24 h of NIV), a late failure (>48 h) may also be occurred.

- The selection of appropriate patients is very important for the success of NIV and the predictors of NIV success or failure may be helpful in selecting patients.
- Although, the factors associated with early NIV failure have been well established, there is limited data about the risk factors for late failure of NIV and the clinical and physiological characteristics of these patients.

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Chapter 14
Noninvasive Ventilation. Rebreathing

Fabrizio Rao and Elisa Falcier

14.1 Introduction

Oxygen support (O_2) and carbon dioxide (CO_2) removal are essential to ensure cellular metabolism. The intake of O_2 and the removal of CO_2 take place through the respiratory system which consists of two essential components: the gas exchange system for which the lungs and the ventilatory pump are responsible [1]. In pulmonary respiratory insufficiency the intake of O_2 is compromised to a greater extent because of the greater ability to diffuse CO_2, while in ventilatory respiratory failure both O_2 and CO_2 are altered.

If in case of pulmonary failure it is possible to apply high inspiratory fractions of O_2 or continuous positive pressure, mechanical ventilation is required in case of ventilatory insufficiency. Respiratory failure of acute ventilatory origin, regardless of the underlying pathology, can only be treated with increased ventilation through mechanical ventilation. Over the past 30 years, excellent results have been achieved through non-invasive positive pressure mechanical ventilation, which has enabled to reduce the rate of tracheal intubations in many clinical situations [2]. At the clinician's disposal there are numerous types of mechanical ventilators, more or less performing, with different ventilation modes and exhalation systems: from the circuit with valve (double limb or single limb) to the leak circuit [3, 4]. The clinician is required to know the characteristics of the ventilator and of the exhalation system

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to avoid breath rebreathing that could compromise the effectiveness of non-invasive ventilation and lead to failure.

Case Report

This is the case of a 64-year-old man, a former heavy smoker (90 pack/year), a retired insurer. History of polio at the age of 3 years with residual motor disability in the lower limbs. There is also evidence of dilated heart disease. Suffering for years from dyspnea due to mild efforts, he was admitted to the respiratory ward due to hypercapnic respiratory failure. Only the data reported in the discharge letter that show a spirometry with severe obstruction and an arterial blood gas analysis defined as "hypercarbia in labile compensation" are available. During this period of hospitalization an attempt was made to adapt to non-invasive ventilation with positive pressure in mask failed due to "poor compliance".

After 3 months the patient was admitted to emergency room of another hospital in the area due to worsening of respiratory symptoms: he presents with intense dyspnea at rest, tachycardia, in the absence of signs of pulmonary stasis, normal arterial pressure; the chest radiograph is visible in Fig. 14.1.

Arterial blood gas analysis performed in spontaneous breathing and FiO_2 0.28 showed significant hypercapnia at the limit of compensation. The patient was placed in non-invasive oxygen-enriched ventilation with a bi-level device with oro-nasal mask. Subsequent checks showed a progressive clinical and blood gas deterioration, up to the impairment of the state of consciousness, which indicated the tracheal intubation, after which the patient was transferred to Intensive Care (Table 14.1).

After intubation and deep sedation, there was a rapid improvement in the respiratory pattern and blood gases. In consideration of the positive evolution the patient was extubated after 10 h of IMV (Invasive Mechanical Ventilation) and again placed in non-invasive ventilation with an intensive care ventilator and a double limb

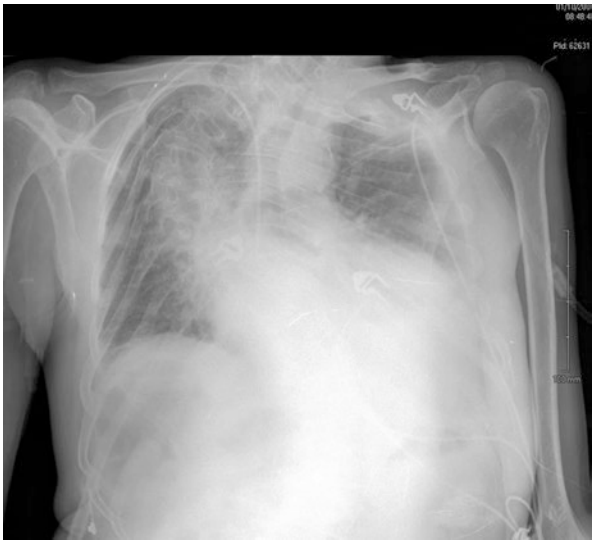

Fig. 14.1 Chest radiography

Table 14.1 Arterial blood gases in spontaneous breathing and bilevel mode

ABG	SB, FiO_2 0.28	NIV*, FiO_2 0.28, after 20 h	NIV*, FiO_2 0.31, after 21 h	NIV*, FiO_2 0.35, after 30 h
pH	7.36	7.35	7.26	7.23
$paCO_2$**	10.2	10.3	12.7	14.6
paO_2**	8.19	8.2	5.6	6.6
HCO_3^-***	41.7	42.0	43.9	46.4

*NIV parameters: BiPaP, leak ventilation, S/T mode, IPAP 15, EPAP 5, RR 12, T_i second; **KPascal; ***mmol/L; *ABG* arterial blood gases, *SB* spontaneous breathing, *NIV* noninvasive ventilation

Table 14.2 Arterial blood gases in invasive ventilation and post-extubation NIV

ABG	IMV, FiO_2 0.40	NIV* post-extubation, FiO_2 0.30, after 3 h	NIV* post-extubation, FiO_2 0.30, after 15 h	NIV**, FiO_2 0.30, after 6 h ("restrictive mode in ZEEP")
pH	7.47	7.34	7.27	7.45
$paCO_2$***	7.0	9.5	12.5	7.5
paO_2***	20.5	14.8	10.2	8.0
HCO_3^-§	33.2	36.5	40.1	37.7

*NIV parameters post-extubation ("COPD mode"): PS mode, double limb circuit, PS 16, PEEP 5, RR 14, Ciclaggio 30%; **NIV parameters post-extubation ("Restrictive mode"): PS mode, PS 14, PEEP 0, RR 12, T_i min 1.2 s, T_i max 1.4 s; ***KPascal; §mmol/L

circuit. In the following hours there was a progressive worsening of blood gas parameters as shown in Table 14.2.

In Fig. 14.2 Intensive care ventilatory setting (A "COPD mode"; B "restrictive mode").

Due to the poor clinical and arterial blood gas outcome, the setting of the ventilator was also re-evaluated considering the available anamnestic and radiological data. The patient presented severe convex right kyphoscoliosis and reported polio in the past. Based on these considerations, the setting of the ventilator was modified, hypothesizing a prevailing restrictive wall pathology which, as is known, does not predispose the patient to present a significant intrinsic PEEP: the need to set an external PEEP fell. The patient was placed in "ZEEP" (zero PEEP) and there was a rapid improvement in the values of blood gases and the clinical picture, reaching an acceptable balance in a short time.

The patient was transferred back to the respiratory ward and, after 20 days of NIV optimization and stabilization, discharged into home mechanical ventilation (HMV) with the ventilator settings and the blood gas values specified in Boxes 14.1 and 14.2.

Box 14.1 Arterial blood gases at discharge (SB, FiO_2 0.24)

pH 7.44
$paCO_2$ 7.1*
paO_2 12.0*
HCO_3^- 36.0**

*kPascal; **mmol/L

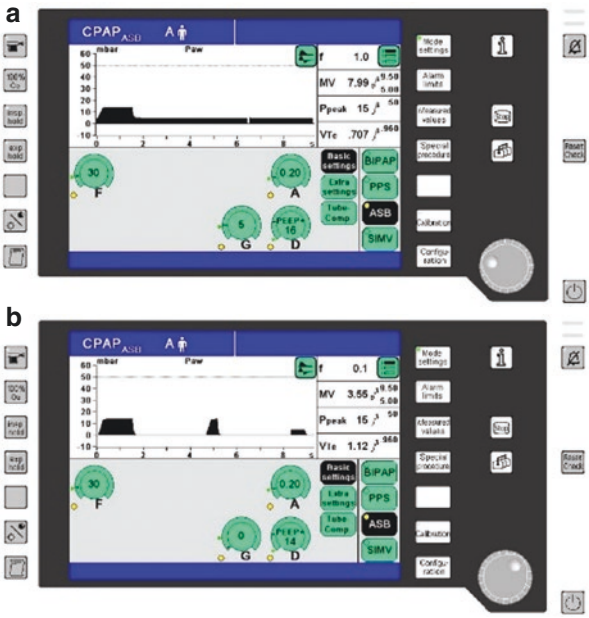

Fig. 14.2 (**a**) "COPD mode". (**b**) "Restrictive mode"

Box 14.2 Ventilation parameters at discharge

Mode PS
PS 15 cmH_2O
PEEP 0 cmH_2O
RR 12/min
T_i min 1.2 s
T_i max 1.4 s
Double limb circuit

14.2 Discussion

The presence of dynamic hyperinflation implies that the alveolar pressure remains positive throughout the expiratory phase. At the end of expiration, the presence of positive pressure inside the alveolus, is called auto positive end-expiratory pressure (auto PEEP) or intrinsic positive end-expiratory pressure (PEEPi) [5]. PEEPi and dynamic hyperinflation have been described in patients with COPD in mechanical ventilation, in which the expiratory flow limitation is a direct consequence of dynamic airway compression [6]. Further studies have suggested that, in patients with COPD with expiratory flow limitation, the application of an external PEEP during assisted mechanical ventilation can counterbalance and contribute to reducing the inspiratory load threshold imposed by the patient's PEEPi without causing further hyperinflation (see link: https://www.youtube.com/watch?v=ZCZFjj-ScJY) [7]. The external PEEP, in these cases, also makes it possible to improve the

patient-ventilator synchrony by optimizing the achievement of the trigger threshold set on the ventilator [8]. It has also been suggested that the application of an external PEEP can facilitate weaning from mechanical ventilation by reducing respiratory work and dyspnea caused by hyperinflation [9]. In the patient with wall restriction with severe kyphoscoliosis, the positive effects of long-term non-invasive ventilation have been described in numerous studies [10]. In particular, as an improvement in gas exchange, quality of life, nocturnal profile and respiratory muscle strength, as well as a reduction in the number of hospitalizations [11]. Due to the anatomical and functional characteristics of the kyphoscoliotic patient, which has reduced pulmonary compliance, the respiratory pattern is characterized by high respiratory frequencies and reduced inspiratory time in spontaneous breathing. These characteristics require particular care in ventilator setting during non-invasive ventilation. In particular, due to the reduced compliance, it is necessary to set rather high inspirator y pressures, around 20–25 cmH_2O, high sensitivity of the inspiratory trigger with short response time, an inspiratory time of 0.8–1.0 s; a external positive end expiratory pressure (PEEPe), unlike the patient with COPD, is not essential due to the absence of PEEPi, on the contrary sometimes it can cause hyperinflation [12]. In recent years there have been widespread types of mechanical ventilators called bi-level, characterized by the provision of two pressure levels, one inspiratory and one expiratory, with a circuit without an expiratory valve but equipped with a non-rebreathing system, essential to guarantee the wash-out of the patient's breath. This type of ventilator combines effectiveness and ease of use by the operator, but requires the application of a minimum expiratory pressure level of 3–4 cmH_2O, below which it is not able to guarantee the removal of CO_2 exhaled from the patient. In the case described, an EPAP level of 5 cmH_2O was decisive in causing hyperinflation, causing acute CO_2 retention and failure of non-invasive ventilation in the patient's pre-intubation phase. In the post-extubation phase, even in the presence of a high-performance intensive care ventilator with double limb circuit, the persistent application of PEEPe risked bringing the patient to new intubation. It was sufficient to reset the ventilation mode in ZEEP (zero-PEEP) to obtain a rapid drop in CO_2 levels to arterial blood gas analysis, confirming hyperinflation as the cause of the failure of the NIV in the pre-intubation phase. The acute use of a ventilator that would allow the visualization of the flow/pressure curves, in the case in question, would have allowed to quickly identify the cause of the clinical and blood gas deterioration in the course of ventilation with bilevel mode, avoiding to the patient a not necessary tracheal intubation.

Key Teaching Points

- Use in acute setting a ventilator with possibility to display the curves
- Learn to interpret curves
- Pay attention to the characteristics of the circuit and the expiratory valve
- Frame the patient from a diagnostic point of view: different ventilation settings are possible in case of severe obstruction, wall restriction, neuromuscular pathology.

Questions and Answers

1. What is the main reason to use an external PEEP in NIV in a COPD patient?

   (a) To keep alveoli open
   (b) To reduce inspiratory effort due to PEEPi (intrinsic-PEEP)
   (c) To avoid the appearance of atelectasis
   (d) To avoid air trapping
   (e) All of the above

   Answer: (b) To reduce inspiratory effort due to PEEPi (intrinsic-PEEP)

2. What is the main difficulty in the ventilation of a patient with kyphoscoliosis?

   (a) The presence of high thoracic compliance
   (b) The presence of high PEEPi
   (c) The late cycling in PSV
   (d) The early cycling in PSV
   (e) None of the above

   Answer: (d) The early cycling in PSV

3. What is the major limit in the use of ventilation in bi-level (BiPaP) with leak circuit?

   (a) Low inspiratory trigger sensibility
   (b) Low expiratory trigger sensibility
   (c) The impossibility of ventilating in ZEEP
   (d) Low leaks compensation
   (e) None of the above

   Answer: (c) The impossibility of ventilating in ZEEP

4. Which settings are indicated in NIV in a patient affected by serious kyphoscoliosis?

   (a) High inspiratory pressions (20–25 cmH_2O)
   (b) High respiratory trigger sensibility
   (c) High pressurization capacity
   (d) Minimum inspiratory time of 0.8–1.0 s
   (e) All of the above

   Answer: (e) All of the above

5. Which characteristics must a ventilator have to be used in NIV in patients with acute respiratory failure?

   (a) Possibility of setting several ventilatory modalities
   (b) Possibility of measuring inspiratory and expiratory volumes
   (c) Possibility of visualizing the pressure/flow curves
   (d) Possibility of compensating leaks
   (e) All of the above

   Answer: (e) All of the above

6. Which ventilation modality usually results more efficient in NIV in kyphoscoliotic patient?
   (a) Pressure Support Ventilation (PSV)
   (b) Assisted Pressure Controlled Ventilation (APCV)
   (c) Average Volume Assured Pressure Ventilation (AVAPS)
   (d) Sincronized Intermittent Mandatory Ventilation (SIMV)
   (e) None of the above

   Answer: (b) Assisted Pressure Controlled Ventilation (APCV)

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Chapter 15
Bilateral Pneumothorax in Neuromuscular Disease Associated with Noninvasive Ventilation and Mechanical Insufflation-Exsufflation

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Abbreviations

AVAPS	Average volume-assured pressure support
DMD	Duchenne muscular dystrophy
LVR	Lung volume recruitment
MI-E	Mechanical insufflation-exsufflation
NMD	Neuromuscular disease
PCF	Peak cough flow
VC	Vital capacity

15.1 Introduction

Neuromuscular diseases (NMD) often involve muscles of the respiratory system. Duchenne muscular dystrophy (DMD) results in progressive loss of respiratory muscle strength and death from respiratory insufficiency. A therapy to avoid these

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Table 15.1 Contraindications for use mechanical insufflation-exsufflation

Contraindications for use mechanical insufflation-exsufflation
Undrained pneumothorax
History of bullous emphysema
Known susceptibility to pneumothorax or pneumo-mediastinum
Any recent barotraumas

respiratory complications in these patients is noninvasive positive pressure ventilation (NIV) [1].

These patients with NMD have diminished peak cough flows (PCF) from inspiratory and expiratory muscle weakness. For patients with Duchenne muscular dystrophy, 90% of episodes of pneumonia and respiratory failure occur as a result of ineffective coughing during otherwise benign upper-respiratory-tract infections. In these patients, air stacking has been recommended as a method for deep lung insufflation [2]. Common examples of these adjunctive therapies are lung volume recruitment (LVR) and mechanical insufflation-exsufflation (MI-E). MI-E uses a dedicated device for delivering assisted inspiration at a set pressure followed by a rapid cycle to exsufflation at negative pressure. Because MI-E increases inspiratory capacity above a maximal spontaneous inspiration, it is important to consider the risk of pneumothorax or other overexpansion injury when prescribing this technique (see Table 15.1) [3].

Clinical Case

The authors present a case of a 35 years-old male with DMD using NIV-BIPAP (Trilogy®) 24 h/day and MI-E device (Cough Assist®) daily. The ventilator modality used was Average volume-assured pressure support (AVAPS): IPAP 26–28 cmH_2O, EPAP 10, Volume 350 mL (see Fig. 15.1). He presents to the emergency department with sudden dyspnea, chest pain and low pulse oximetry (SpO_2 77%). At admission he was using NIV but still tachypneic, had a normal blood pressure and high heart rate (BP 117/91 mmHg, HR 124 bpm). The initial arterial blood gas test showed a respiratory acidosis (pH 7.27 pCO_2 51.4 pO_2 47.4 HCO_3 23.2 $SatO_2$ 77.3%) and the chest x-ray exhibited a bilateral pneumothorax. A right 16Fr chest tube was inserted followed by insertion of a left 16Fr chest tube with partial bilateral pulmonary expansion (see Fig. 15.2). At the same time there was a change in ventilatory pressures: decreasing IPAP to 24–25 cmH_2O and EPAP to 8 cmH_2O.

He performed a lung CT-scan that showed a bilateral persistent pneumothorax with some pleural bridges (see Fig. 15.2). At this time the chest tubes were replaced by other ones connecting them to negative low suction (−10 cmH_2O) with no resolution of pneumothorax. He persisted with left bronchopleural fistula for 19 days and right bronchopleural fistula for 32 days. During hospitalization there were several attempts to reduce positive pressure achieving the lowest pressures for AVAPS: IPAP 22–20 and EPAP 4, volume 450 mL.

At discharge the patient had a small residual right apical pneumothorax and the blood arterial gas test was normal. The MI-E pressure were decreased to

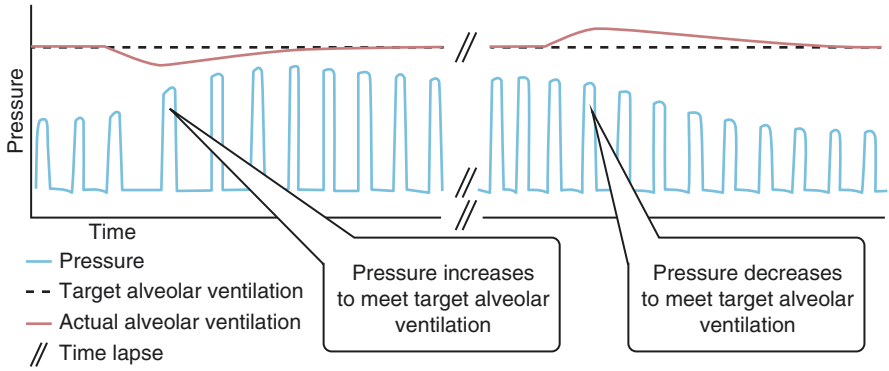

Fig. 15.1 Mode Average volume-assured pressure support example curve

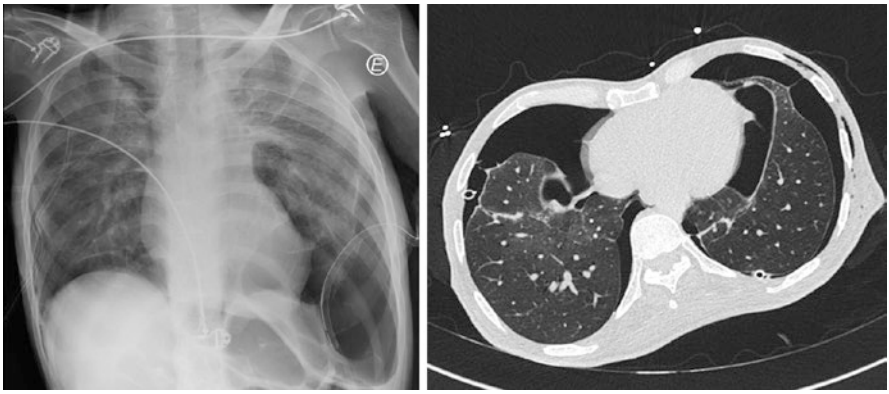

Fig. 15.2 Chest x-ray (on the left) with a right and a left chest tube with partial bilateral pulmonary expansion. Lung CT-scan (on the right) showed a bilateral persistent pneumothorax with some pleural bridges

+20/−20 cmH_2O and the patient had recommendations to use it when he had increased sputum.

Nine months after the initial presentation, the patient remains under regular follow-up, with a persistent small pneumothorax on the right, that does not affect his ventilation and oxygenation.

15.2 Discussion

DMD is known to have deterioration in pulmonary function during the late adolescence. Their vital capacity (VC) usually peaks between 9–16 year old and decreases by 5–10% per year until ventilatory support is instigated [4]. Long term NIV has

improved survival as well as quality of life in these patients. Usually for DMD, respiratory insufficiency occurs between 18 and 20 year-old. Five year survival rate of 8% was quoted if assisted ventilation was not initiated. Several large series suggested excellent long term survival rates for cases receiving NIV support with less rapidly progressive muscular dystrophies [5].

Weakness of the inspiratory muscles leads to a progressive decrease in VC, but the lung volume changes that appear in some patients with DMD are attributable to a combination of muscle weakness and alterations of the mechanical properties of the lungs and chest wall. Reduced ability to cough leads to secretion retention, predisposing to progressive respiratory morbidity [6]. MI-E is a therapy modality frequently recommended as part of the respiratory management in those with NMD. It is possible that the benefit of the technique, improving the recruitment of non ventilated pulmonary zones, and removing mucous debris, attains a more evident improvement in gas exchange rather than in breathing pattern. While the clinical utility of these techniques has been established during episodes of respiratory illness, the benefits of prophylactic use remains unclear [7].

This case represents a rare potentially life-threatening complication of NIV and MI-E, with barotrauma and bilateral pneumothorax. Considering this case, however, there were pre existing risk factors for the development of pneumothorax including the use of NIV, the use of MI-E and thoracic deformities. Suri et al. reported two cases of pneumothorax (possibly resulting from volutrauma) associated with daily use of MI-E via a cough-assist device and NIV [2].

Our patient uses NIV-BIPAP (Trilogy®) for 24 h/day and MI-E (Cough Assist®). Pneumothorax during positive pressure ventilation is predominantly caused by barotrauma when lung compliance is low. It has been observed that high peak airway pressure may be associated with pneumothorax during invasive ventilation. During chronic NIV, over-distension of regional alveolar units may be possible although steps are taken to minimize peak pressures and control volume. With MI-E the inspiratory and expiratory pressures are controlled. However, as with positive airway pressure ventilation, it is possible that during MI-E, regional variability in the lung could cause areas of over-distension leading to pneumothorax [8].

It remains unknown how often milder forms of alveolar damage, such as pulmonary interstitial emphysema or subclinical pneumothorax, occur as a consequence of NIV or MI-E. Although rare, the clinical course in our patient clearly shows that potentially life-threatening complications can develop. Another factor to consider is thoracic deformities. Scoliosis can cause unequal ventilation in the lungs with the distortion of the bronchial tree causing air trapping and thus increased risk of air leaking syndrome.

The effect of NIV on a persistent air leak is unclear, with no evidence to suggest impaired resolution. Positive pressure ventilation may contribute to the air leak but not necessarily was the main cause. Further studies are necessary to define its relationship.

The management of pneumothorax in neuromuscular patients who were dependent on chronic NIV requires special consideration. Patients with evidence of barotrauma-associated pneumothorax are managed with an immediate reduction in

ventilatory pressures and most additionally undergo chest tube. Although increased levels of supplemental oxygen are often administered, this strategy has no proven value, particularly for those already receiving high fractions of inspired oxygen. It is most likely that the absence of high-pressures and small tidal volume applied at higher frequencies may result in a rapid decrease of air leak, as showed by Ellsbury et al. in an animal model of pneumothorax [9].

LVR maneuvers or MI-E were suspended until pneumothorax was solved, but with careful monitoring to ensure retained airway secretions did not further compromise the patient. These maneuvers were typically restarted in 4–6 weeks following the pneumothorax event.

In this clinical case, it was not possible to suspend NIV due to the patient's total dependence, for that reason removing NIV was not an option. The strategy was to reduce positive pressure achieving the lowest pressures for AVAPS: IPAP 22–20 and EPAP 4, volume 450 mL.

Several methods are available in the management of persistent air leak including a surgical approach, endobronchial valve placement, medical pleurodesis or ambulatory management. In patients with chronic respiratory insufficiency and NIV dependence, it is important to consider the risk of precipitating acute respiratory failure with pleurodesis. Prolonged chest tube duration was seen, although due to the patient's deconditioning, it was decided not to proceed a more invasive therapy.

Key Teaching Points

- Neuromuscular disease (NMD) often involves muscles of the respiratory system.
- Reduced ability to cough leads to secretion retention, predisposing to progressive respiratory morbidity
- The NIV has benefits on survival and quality of life of patients with NMD.
- MI-E is a therapy modality frequently recommended as part of the respiratory management in those with NMD
- Pneumothorax is a rare complication of NIV and MI-E.

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Chapter 16
Early and Late Failure During Noninvasive Ventilation

Matthew Ballenberger and Bhusra Mina

Abbreviations

ABG	Arterial blood gas
APE	Acute pulmonary edema
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BiPAP	Bilevel positive airway pressure
CAP	Community acquired pneumonia
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary edema
FiO_2	Fraction of inspired oxygen
GCS	Glasgow coma scale
HACOR	Heart rate, acidosis, consciousness, oxygenation and respiratory rate
IMV	Invasive mechanical ventilation
IPAP	Inspiratory positive airway pressure

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mmHg	Millimeters of mercury
NIV	Noninvasive ventilation
OR	Odds ratio
$PaCO_2$	Partial pressure of arterial carbon dioxide
PaO_2	Partial pressure of oxygen
PSV	Pressure support ventilation
RR	Respiratory rate
SAPS	Simplified acute physiology score
SAPS3-CNIV	Simplified acute physiology score 3-customized NIV

16.1 Introduction

Noninvasive Ventilation (NIV) has become widely adopted as a way to effectively treat acute respiratory failure (ARF) and avoid complications associated with invasive mechanical ventilation (IMV). Physicians must be knowledgeable about how to properly assess a patient to determine if they are a good candidate for NIV and be aware of the signs of NIV failure to minimize the delay of IMV and ensure favorable patient outcomes. NIV failure has been defined as death or the need for IMV following NIV. This occurs in three different stages. Immediate failure occurs within the first hour of starting NIV, early failure occurs from the first to 48th hour, and late failure occurs after 48 h [1].

Clinical Cases
Patient A is a 65 year old male with a 50 pack/year smoking history who presents to the emergency department with shortness of breath, worsening chronic cough and dyspnea on exertion. On exam he is awake and alert, appears short of breath with accessory muscle use and has prolonged expiration with diffuse wheezes. Labs are significant for a normal white blood cell count, an arterial blood gas (ABG) shows a pH of 7.2 with a partial pressure of arterial carbon dioxide ($PaCO_2$) of 55 millimeters of mercury (mmHg) suggestive of acute respiratory acidosis. His chest x-ray is shown in Fig. 16.1a. Patient B is a 74 year old female with a recent influenza infection who presents with fever and a productive cough. Her temperature is 39 °C, respiratory rate (RR) is 32, oxygen saturation is 84% on 6 L of oxygen via nasal cannula. She is awake and alert and he has decreased breath sounds in the left upper and right lower lobes with scattered rhonchi. Her chest x-ray is shown in Fig. 16.1b.

16.2 Immediate Failure

A recent literature review found that 15% of NIV failure occurs within the first hour of use. The major causes of failure within this timeframe include a weak cough reflex or excessive secretions, hypercapnic encephalopathy, coma, intolerance of treatment, psychomotor agitation and patient-ventilator asynchrony [1]. A number

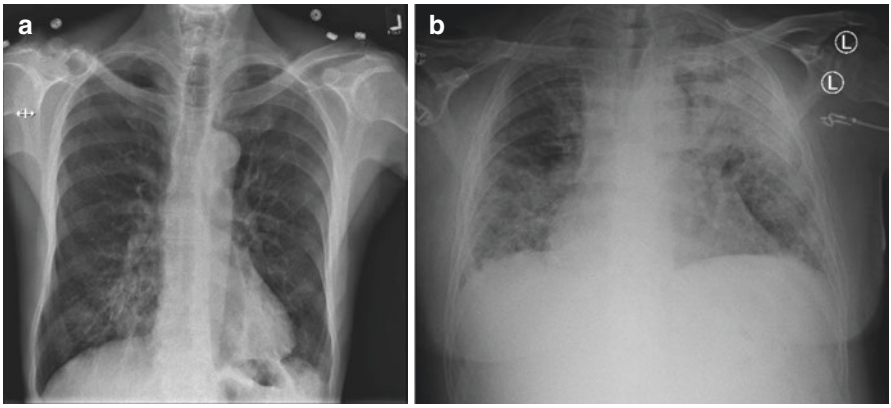

Fig. 16.1 Part (**a**) shows the chest x-ray of patient A who is diagnosed with a COPD exacerbation. Part (**b**) shows a chest x-ray of patient B who is diagnosed with multifocal pneumonia

of these problems can be prevented with proper evaluation before initiating therapy and by simple troubleshooting with ventilator interface or settings.

16.2.1 Should These Patients Receive a Trial of NIV?

In order to minimize the risk of failure or developing complications, every patient should be properly assessed for eligibility to receive NIV safely. Indications for NIV use include patients who have dyspnea, tachypnea, accessory respiratory muscle use, paradoxical abdominal "belly" breathing, $PaCO_2$ >45 mmHg and pH <7.35 [1, 2]. Contraindications for NIV therapy are depressed neurological status such as coma or seizures, inability to protect the airway or clear secretions, upper airway obstruction, severe upper gastrointestinal bleeding or recent gastroesophageal surgery, recent facial surgery or trauma, refractory interface excessive air leaks, untreated pneumothorax, excessive vomiting or high risk of aspiration, hemodynamic instability, cardiopulmonary arrest or multiorgan failure [1–3].

16.2.2 Initiating NIV: Location

When starting a patient on NIV, it is important to consider the location in which it will be initiated. Ideally, the patient should be in a setting where they can be constantly monitored for signs of failure and prompt intubation is readily available. If the cause of ARF can be determined, etiologies with high rate of NIV failure, such as acute respiratory distress syndrome (ARDS), severe pneumonia or asthma attacks should be treated in such high monitored settings without exception [2].

16.2.3 Initiating NIV: Settings and Interface

One of the major reasons for NIV failure is patient intolerance of therapy, which can be caused by ventilator asynchrony, air leaks, and interface discomfort. When initiating NIV, there are numerous settings to choose from to deliver respiratory support which can affect patient tolerance. Continuous positive airway pressure (CPAP) delivers continuous positive pressure throughout the respiratory cycle and does not assist with inspiration. Bilevel positive airway pressure (BiPAP) provides an increased inspiratory positive airway pressure (IPAP). The higher pressures supplied during inspiration helps to overcome the difference in pressures during inspiration and expiration. Pressure support ventilation (PSV) is one method of delivering BiPAP, which triggers the initiation of the IPAP vent by a change in pressure [3].

Choosing which settings are best when starting NIV is dependent on the setting, providers experience and etiology of ARF. If physicians are inexperienced with adjusting or starting NIV settings, CPAP is a viable option in certain circumstances, such as ARF caused by cardiogenic pulmonary edema (CPE) as this has been shown to be as efficacious for treatment as BiPAP [4]. If providers are experienced, BiPAP is an option for most etiologies of ARF as it has been shown to decrease work of breathing and transpulmonary pressures. PSV is often well tolerated, but it can cause air leaks that can lead to significant ventilator-asynchrony and therefore patient discomfort and intolerance. This occurs when there is an air leak that inhibits a sufficient change in pressure to trigger the ventilator to initiate the IPAP. If this happens, the patient can be optimized by adjusting mask size or changing the interface, such as from a nasopharyngeal mask to a full face mask. If leaks persist, the IPAP pressure settings can be decreased or set to an inspiratory time-limited cycle to maximize patient tolerance [3].

Clinical Cases Continued
Patient A is diagnosed with hypercapnic respiratory failure due to an acute COPD exacerbation. He has no contraindications for NIV and is admitted to medical telemetry and started on BiPAP. Patient B is found to have acute hypoxic respiratory failure due to multifocal pneumonia. This diagnosis infers a high risk for failure and she is admitted to the medical ICU for monitoring. She also has no contraindications for NIV and is placed on BiPAP.

16.3 Early Failure

The majority of NIV failure, around 65%, occurs from the first hour to 48 h. Studies differentiate between hypoxemic or hypercapnic respiratory failure within this period. Hypoxemic respiratory failure can be caused by multiple etiologies such as ARDS, CPE and pneumonia. The most studied cause of hypercapnic respiratory failure treated by NIV is chronic obstructive pulmonary disease (COPD), though other etiologies include asthma and neuromuscular disorders [1].

Arterial blood gas can be useful as a predictor of NIV failure. One of the factors affecting NIV failure for hypoxemic ARF is the ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2). A limited number of studies have shown an association between a low PaO_2/FiO_2 (<150) at presentation for patients with community acquired pneumonia (CAP) and ARDS, representing severe hypoxemia with poor gas exchange. A more robust association has been made with values obtained after 1 h of NIV treatment, representing a failure of NIV to improve gas exchange and correct hypoxemia. Additional factors associated with early failure of NIV for hypoxemic ARF include increased respiratory rate at 1 h of treatment and delay between admission and NIV use. For patients with hypercapnic respiratory failure, arterial pH can be useful in determining the likelihood of NIV failure. Arterial pH inversely correlates with $PaCO_2$, so a low pH can indicate retention of CO_2. Although recent studies have suggested that low initial pH values (<7.25) may indicate a risk for NIV failure, a stronger association has been found with values obtained at 1 h of treatment. As with hypoxemic respiratory failure, this suggests that severity of illness at initial presentation is not as important as indicators obtained after a short term of treatment. Additionally, a RR at presentation and at 2 h after initiation of NIV can be useful in predicting failure. A RR >35 breaths per minute at presentation is associated with NIV failure with an odds ratio (OR) of 2.5 and increases to nearly 5 if the RR remains elevated at 2 h after starting treatment [1].

Disease severity scores have previously mixed results in being associated with NIV failure, though recent studies have shown a more consistent correlation. Higher SOFA, APACHE II and SAPS II scores have been associated with failure in patients with hypoxemic ARF from sepsis, pneumonia and hematological malignancies. These disease severity scores have shown inconsistent results in predicting NIV failure in hypercapnic patients [1].

Clinical Cases Continued

Patient A and B have been on NIV for 1 h. A repeat ABG for patient A shows his pH has gone from 7.2 to 7.35 and $PaCO_2$ decreased from 55 to 45 mmHg. He continues to feel short of breath and has increased work of breathing. The patient has shown significant improvement in her pH and $PaCO_2$ which suggests that the patient is lower risk for NIV failure and therapy is continued. Patient B is on an FiO_2 of 0.8 and an ABG shows her oxygen saturation is 87% and PaO_2 is 55. His PaO_2/FiO_2 is 69 indicating he is at high risk for failure. She continues to show signs of respiratory distress with an elevated respiratory rate of 26, and has a persistent air leak (Fig. 16.2). The patient is intubated to improve oxygenation.

16.4 Late Failure

Although there is no standard among studies indicating the cutoff for late failure, this period can be considered to start after the 24–48 h period following initiation of NIV and accounts for nearly 20% of failures. The majority of studies for failures

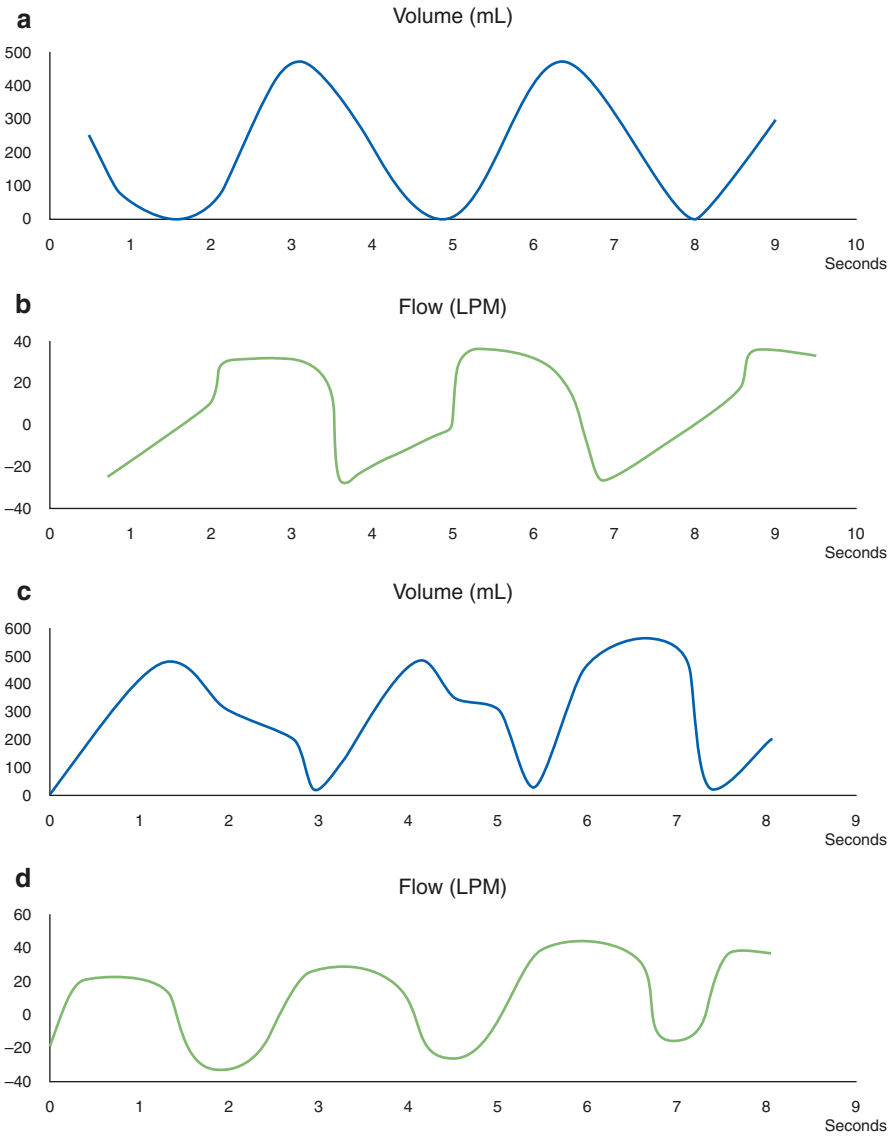

Fig. 16.2 Parts (**a** and **b**) show volume and flow tracings respectively for a patient with a well fitted face mask interface without any appreciable air leak. There is a gradual return to a volume of 0 milliliters (mL) and the flow tracing shows a consistent return to −25 an exhalation. Parts (**c** and **d**) show the volume and flow tracings respectively for patient B with a persistent air leak. There is a sudden drop to 0 mL on exhalation and the peak flow on exhalation gradually approaches 0 liters per minute (LPM)

within this period have focused on hypercapnic respiratory failure. This group has higher rates of failure if they have sleep disturbance or experience delirium. For COPD patients, failure during this period has been associated with low functional status and low pH at presentation. Patients with pneumonia have a higher rate of failure during this period. $PaCO_2$ and pH values have been found to improve at similar rates in success and failure groups which indicates the need for continued monitoring for patients even after they have a good initial response, as late failure is associated with high mortality [1].

Clinical Cases Continued

Patient A is maintained on BiPAP for 48 h. He fails attempts at transitioning the patient to nasal cannula. On the second night, the patient adamantly refuses the BiPAP stating the mask is uncomfortable and prevents him from sleeping. He is placed on nasal cannula and maintains a normal oxygen saturation. The next morning the patient is lethargic and difficult to arouse. An ABG shows a pH of 7.12 and $PaCO_2$ of 74. He is promptly intubated to improve ventilation and protect his airway.

16.5 Predictive Scores

Recently, physicians have attempted to establish a simple calculation that can accurately predict the outcome of a trial of NIV. Since delaying treatment can result in clinical deterioration, physicians must be able to obtain the data points quickly and easily calculate a score to guide therapy. Two scores have been developed to help guide physicians' decision making with treatment. The heart rate, acidosis, consciousness, oxygenation and respiratory rate (HACOR) score helps predict the likelihood of NIV failure in hypoxemic respiratory failure [5]. The SAPS 3-Customized NIV (SAPS3-CNIV) is used to predict hospital mortality with NIV use [6] (Table 16.1).

The HACOR score ranges from 1 to 25. Patients with a score >5 at 1 h of treatment was associated with a sensitivity of 72.6%, specificity of 90.2%, positive

Table 16.1 Predictive score variables

HACOR score [5]	SAPS3-CNIV [6]
1. Heart rate	1. SAPS3 (20 variables)[a]
2. Arterial blood pH	2. Hemoglobin
3. Glasgow coma scale (GCS)	3. $PaCO_2$
4. PaO_2/FiO_2	4. Lactate
5. Respiratory rate	5. Do not resuscitate (DNR) orders
	6. Etiology of respiratory failure

[a]SAPS3 variables: age; length of hospital stay before admission to ICU; department patient arrived from; diagnosis; use of vasoactive drugs; acute or planned admission; reason why patient is admitted to ICU; acute or planned surgery; type of surgery; infection at admission; GCS; serum bilirubin, creatinine and pH; temperature; heart rate; blood pressure; leukocyte and platelet count; PaO_2/FiO_2; location [7]

predictive value of 87.2%, negative predictive value of 78.1%, and diagnostic accuracy of 91.8% for NIV failure. A score of ≤5 was associated with an NIV failure rate of 18.4% and hospital mortality of 21.6%. A score >5 had a failure rate of 87.1% and hospital mortality of 65.2%. This score can easily be calculated using data that can quickly be acquired, but it only applies to hypoxic patients and has not been evaluated for hypercapnic respiratory failure. The HACOR score has only been tested in one single center study and requires further external trials for validation [5].

The SAPS3-CNIV is an expanded version of the SAPS3. It utilized multiple variables to predict hospital mortality following NIV. In addition to an elevated SAPS3 score, DNR orders and elevated lactate (>2 mg/deciliter) are associated with elevated risk of mortality. Previous diagnosis of COPD, APE and hemoglobin levels >10.7 g/deciliter reduce mortality risk ($p < 0.05$) [8]. This score can be used for both hypercapnic and hypoxic respiratory failure. The limitation of this score is that it requires a large number of data points that can take time to acquire, which can delay calculation therefore limiting its usefulness. This score additionally requires further studies to support its validation, as initial external studies have failed to reproduce its predictive value [6].

16.6 Discussion and Practical Implications

NIV is a useful tool that can be used to effectively treat ARF and avoid the complications associated with IMV. To prevent NIV failure within the first hour of use, patients should be evaluated to determine if they are a good candidate for NIV treatment. Patients can be considered if they show clinical signs of respiratory distress or develop hypercapnia or acidosis [1, 2]. Physicians should avoid using NIV if a patient shows signs of a depressed neurological status, is unable to protect their airway, is vomiting, cannot tolerate the facemask interface or has a persistent air leak. It should also be avoided if the patient is severely ill, showing signs of being hemodynamically unstable or having organ failure [1–3]. NIV is generally more efficacious at treating hypercapnic respiratory failure with the exception of hypoxic respiratory failure from cardiogenic pulmonary edema [4]. If initiating NIV for patients with ARF from etiologies that are at high risk for failure, the treatment should be started in a setting where the patient can be very closely monitored and IMV can be promptly initiated, such as in an ICU [2].

Patient's should be closely monitored during the first 24 h after initiating NIV as this is the period with the highest rate of treatment failure. Although data points at presentation such as a high RR, low arterial pH values or low PaO_2/FiO_2 can help predict failure, the most robust predictor of treatment failure during this period is failing to show an improvement in these parameters at 1–2 h after initiating NIV treatment [1]. The clinical implications of these findings are important as it suggests that it is critical to closely monitor patients in the first hours after initiating NIV. A failure to show improvement clinically or with laboratory values suggests that NIV

is not adequately addressing the patient's pathology. These parameters should be tracked closely as initiating NIV can potentially mask the severity of a patient's illness. Patients receiving NIV for greater than 24 h require continued monitoring as failure during this period is associated with a high rate of mortality. Late failure can occur despite improvement in laboratory parameters and patients who experience sleep disturbances or delirium should be closely monitored as they are at high risk for treatment failure in this time period [1].

When employing NIV therapy for ARF, it is imperative that physicians select and monitor patients very carefully throughout the duration of treatment. Physicians must identify signs of treatment failure, such as worsening clinical status, failure to show improvement in symptoms or correction of abnormal laboratory values. If physicians fail to identify these signs of failure and delay response by either adjusting NIV settings or considering IMV, it places the patient at risk for increased morbidity and mortality that may easily be avoided with early intubation.

Key Teaching Points

- To prevent immediate failure with NIV, patients should be adequately screened for contraindications. If patients have a diagnosis of pneumonia, acute respiratory distress syndrome, or de novo respiratory failure, they should be monitored very closely as these etiologies have a high risk of NIV failure
- Patients with hypoxemic respiratory failure who present with and continue to have a low PaO_2/FiO_2 (<150) after 1 h of NIV treatment have a high likelihood of failure.
- Patients with hypercapnic respiratory failure who present with and continue to have a low pH (<7.25) after 1 h of NIV treatment have a high likelihood of failure.
- Patients should be monitored closely for late NIV failure as failure in this stage occurs independently of corrections in PaO_2/FiO_2 and low pH.
- Scores such as the SAPS3-CNIV and HACOR score may be helpful in predicting failure and risk of mortality with NIV treatment

Questions and Answers

1. Which of the following are indications for initiating NIV?

   (a) Patient complaining of shortness of breath
   (b) Arterial pH >7.45
   (c) Accessory respiratory muscle use
   (d) $PaCO_2$ <35 mmHg
   (e) All of the above

   Answer: (c) Accessory respiratory muscle use

2. Which of the following are contraindicated to initiating NIV because they will likely lead to NIV failure?

   (a) Severe upper GI bleed
   (b) Recent facial surgery
   (c) Refractory air leak
   (d) Hemodynamic instability
   (e) All of the above

   Answer: (e) All of the above
3. A patient presents with pneumonia and is initiated on NIV. Which of the following is the most sensitive predictor of NIV failure?

   (a) RR >25
   (b) O_2 sat of <88% on room air
   (c) PaO_2/FiO_2 <150 at start of NIV
   (d) PaO_2/FiO_2 <150 after 1 h of NIV
   (e) All of the above are equal predictors of failure

   Answer: (d) PaO_2/FiO_2 <150 after 1 h of NIV
4. A patient presents with a COPD exacerbation and is initiated on NIV. Which of the following is the most sensitive predictor of NIV failure?

   (a) RR >25
   (b) Serum pCO_2 >55
   (c) Arterial pH <7.25 at initiation of therapy
   (d) Arterial pH <7.25 after 1 h of NIV
   (e) All of the above are equally sensitive to predict NIV failure

   Answer: (d) Arterial pH <7.25 after 1 h of NIV
5. Which of the following evaluation tools have shown to be predictive of hypercapnic respiratory failure?

   (a) SOFA
   (b) APACHE II
   (c) SNAPS II
   (d) HACOR
   (e) None of the above

   Answer: (e) None of the above
6. Which of the following evaluation tools have shown to be predictive of hypoxic respiratory failure?
   (a) SOFA
   (b) APACHE II
   (c) SNAPS II
   (d) HACOR
   (e) None of the above

   Answer: (d) HACOR

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Part IV
Noninvasive Ventilation Interaction, Monitoring and Methodology

Chapter 17
Patient Ventilator Asynchrony

Alejandro Úbeda Iglesias, Irene Fernández Burgos, and Rosario Ana Torcuato Barrera

Abbreviations

COPD	Chronic obstructive pulmonary disease
EPAP	Expiratory positive airway pressure.
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure.
MV	Mechanical ventilation
NIV	Noninvasive ventilation
PEEP	Positive end expiratory pressure
PEEPi	Intrinsic PEEP
TV	Tidal volume

Case Clinic

A 61-year-old woman with chronic obstructive pulmonary disease (COPD) was admitted to hospital due to an acute exacerbation of her lung disease. After 6 days of ward stay, *Klebsiella pneumoniae* was isolated in bronchoaspirate. Three days after the diagnoses of nosocomial pneumonia, patient was admitted to the intensive care unit (ICU) in a situation of hipercapnia. Oxygen saturation (SpO_2) 80% with non-rebreathing reservoir mask at fraction of inspired oxygen (FiO_2) 100%. Clinical exploration showed sweating, tachypnea and superficial breathing. The patient was

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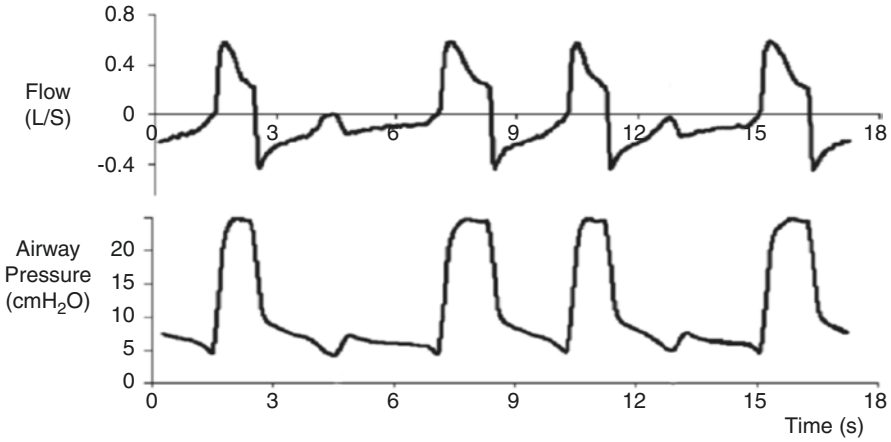

Fig. 17.1 Ineffective trigger asynchrony: the pressure curve shows a curve smaller than the others which pressure is not enough to trigger the ventilator. It translates in a decreased respiratory flow, shown in the flow curve

connected to a NIV ventilator, with an oro-nasal mask, in BIPAP mode with parameters: IPAP 14 cmH_2O, EPAP 7 cmH_2O, FiO_2 0.4, inspiratory ramp 120 ms. After 12 h of therapy, when trying to decrease inspiratory pressure, patient's respiratory rate increases up to 40 breaths per minute with the respiratory curve showed below (Fig. 17.1).

Parameters were modified to: IPAP 10 cmH_2O, EPAP 5 cmH_2O, FiO_2 0.3, inspiratory ramp 100 ms. After 2 h, the asynchrony was solved and the NIV could be removed after 36 h.

A large number of patients admitted to the ICU for acute respiratory failure require noninvasive mechanical ventilatory (NIV) support. The ventilator can contribute to successful treatment of respiratory failure by allowing the underlying disease to recover. Patient-ventilator asynchrony leads to unnecessary imposed muscle loading and may appear clinically as a patient who is fighting the ventilator. This may lead to unnecessary administration of sedation, NIV failure, need of invasive mechanical ventilation and ICU stay.

17.1 Trigger Asynchrony

1. **Ineffective trigger**

   Also known as "missed triggering" or "wasted effort". It is the most frequent type of asynchrony. Patient effort to initiate a breath is unrecognized by ventilator. Airway's pressure drops, flow changes simultaneously during expiration and it is not followed by a ventilatory cycle. It indicates that patient's effort is not detected by the ventilator. A negative pressure ≥0.5 cmH_2O is observed and flow

increases. The higher the level of assistance, the higher are the numbers of ineffective effort. It may occur during both the inspiratory and expiratory cycles. The presence of ineffective effort is detected on ventilator graphics by a downward concavity of the flow/time waveform with a simultaneous upward concavity of the pressure/time waveform [1].

2. **Double triggering**

   In this type of asynchrony, two consecutive ventilator cycles occur (triggered by the patient) separated by an expiratory time lower than one-half of the mean expiratory time. The patient's effort is not completed at the end of the first ventilator cycle and triggers a second ventilator cycle. On the ventilator's graphic (Fig. 17.2a) it shows: as one respiratory phase has ended, the next one starts immediately. Hyperinflation may occur as tidal volumen (TV) is twice dispensed. This type of asynchrony takes place due to patient's high ventilatory requirements or an inappropriate inspiratory time (low TV, low pressure support, ventilator set inspiratory time too short). It is frequent in patients with severe lung injury and increased respiratory drive [2].

3. **Auto-triggering**

   It is defined as a cycle delivered by the ventilator without a prior airway pressure decrease, which indicates that the ventilator delivered a breath that was not

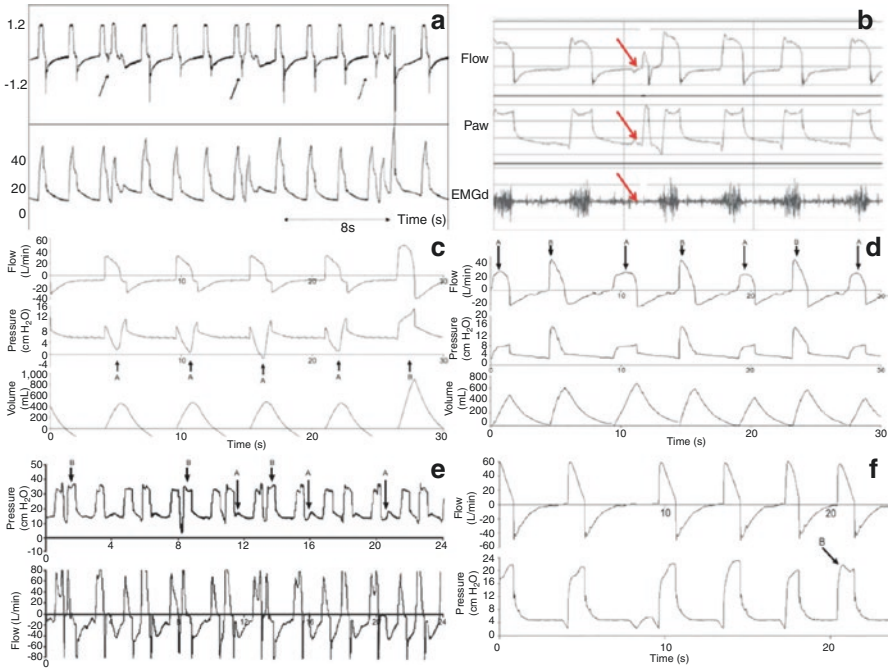

Fig. 17.2 Types of asynchrony. (**a**) The first waveform is the flow one (L/s) and the second one the pressure (cmH_2O). The arrows indicate where the double-trigger asynchrony occurs. (**b**) Auto-triggering. (**c**) Low flow asynchrony. (**d**) High flow asynchrony. (**e**) This curves show a patient who is experiencing premature cycling (arrows A) and double-triggering (arrows B). (**f**) Delayed cycling

triggered by the patient [2]. Since a drop in airway pressure or a flow signal is used to trigger the ventilator, airways leaks or strong cardiac oscillations can reach the triggering threshold of the ventilator in the absence of patient's effort and provoke the insufflation of repeated extra breaths. More than one breath occurring in a single patient effort (Fig. 17.2b) [3].

17.2 Flow Asynchrony

1. **Low flow**
   After trigger has been activated, respiratory muscles continue working. Pressure curve can be decreased during inspiration (Fig. 17.2c) [4, 5].
2. **High flow**
   Pressure curve shows a peak at the beginning (Fig. 17.2d). This asynchrony can be corrected by decreasing flow [4, 5].

17.3 Cycle Asynchrony

1. **Premature cycling**
   Ventilator's set inspiratory time is too short for the patient. Patient's inspiratory effort can still happening eventhough ventilator's inspiration is already over (Fig. 17.2e) [4, 5].
2. **Delayed cycling**
   Ventilator's set inspiratory time exceeds patient's neural inspiratory time. Patient ends inspiration before the ventilator does. It can activate expiratory muscles when the ventilator continues dispensing volumen during inspiration. Most frequent causes are an inappropriate timing cycling setting and airleaks. COPD and asthma are risk factors for delayed cycling (Fig. 17.2f) [4, 5].

Key Teaching Points

- Asynchrony is associated with patient discomfort, higher dose of sedation, prolonged ICU stay and even increased mortality.
- NIV use continues to increase and clinicians should understand the causes of asynchrony during NIV as well as potential remedies.
- Recognising patient-ventilator asynchrony during NIV by visual inspection of the ventilator waveforms is difficult.

Questions and Answers

1. Which is the most frequent type of asynchrony during noninvasive mechanical ventilation?

   (a) Ineffective trigger.
   (b) Double triggering.
   (c) Auto-triggering.
   (d) Premature cycling.
   (e) Delayed cycling.

   Answer: (a) Ineffective trigger
2. Patient-ventilator asynchrony may lead to all the following situations, EXCEPT…

   (a) Unnecessary administration of sedation.
   (b) NIV failure.
   (c) Need of invasive mechanical ventilation.
   (d) Unnecessary imposed muscle loading.
   (e) Increase patient comfort.

   Answer: (e) Increase patient comfort
3. When there is a cycle delivered by the ventilator without a prior airway pressure decrease, what kind of asynchrony do we have?

   (a) Ineffective trigger.
   (b) Double triggering.
   (c) Auto-triggering.
   (d) Premature cycling.
   (e) Delayed cycling.

   Answer: (c) Auto-triggering
4. When ventilator's set inspiratory time is too short, patient's inspiratory effort can still happening eventhough ventilator's inspiration is already over. This asynchrony is called:

   (a) Ineffective trigger.
   (b) Double triggering.
   (c) Auto-triggering.
   (d) Premature cycling.
   (e) Delayed cycling.

   Answer: (d) Premature cycling
5. When ventilator's set inspiratory time exceeds patient's neural inspiratory time, patient ends inspiration before the ventilator does. This asynchrony is called:

   (a) Ineffective trigger.
   (b) Double triggering.
   (c) Auto-triggering.
   (d) Premature cycling.
   (e) Delayed cycling.

   Answer: (e) Delayed cycling

6. When two consecutive ventilator cycles are triggered by the patient separated by an expiratory time lower than one-half of the mean expiratory time, we could have…
   (a) Ineffective trigger.
   (b) Double triggering.
   (c) Auto-triggering.
   (d) Premature cycling.
   (e) Delayed cycling.

   Answer: (b) Double triggering

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Chapter 18
Patient Ventilator Asynchrony

Lazzeri Marta and Spadaro Savino

Abbreviations

AI	Asynchrony index
ASV	Adaptive support ventilation
BPM	Beats per minute
CF	Cardiac frequency
COPD	Chronic obstructive pulmonary disease
EAdi	Electrical activity of diaphragm
FEV_1	Forced expiratory volume in the first second
GCS	Glasgow coma scale
GOLD	Global initiative for chronic obstructive lung disease
IBP	Invasive blood pressure
ICU	Intensive care unit
MV	Mechanical ventilation
NAVA	Neurally adjusted ventilatory assist
NIV	Non-invasive ventilation
PAV	Proportional assist ventilation
PAW	Airway pressure;
PEEPi	Intrinsic positive end-expiratory pressure

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PSV	Pressure support ventilation
PVA	Patient ventilator asynchrony
PY	Pack year
RR	Respiratory rate
TV	Tidal volume

18.1 Introduction

In the last decades the Non-invasive ventilation (NIV) has gained importance as first-line treatment of Acute Respiratory Failure (ARF), due to its less-invasiveness when compared to mechanical ventilation (MV). However, patients experiencing NIV failure have a considerable risk of mortality, higher than those treated with invasive MV. Therefore, it is relevant to accurately identify which patients could benefit from NIV therapy and to manage all potentially reversible causes of NIV-failure, which rate of failure remains high, close to 40% in observational studies [1].

The failure of non-invasive ventilation (NIV) may be due to different variables such as patient's compliance (i.e. tolerance to the interface chosen and its adherence to the skin), or other objective factors as the consciousness state, severe hypoxemia, hemodynamic instability, difficulty to cough; further, there is an important role played by poor patient-ventilator interaction and consequently patient-ventilator asynchrony (PVA) [2, 3]. The term "asynchrony" indicates the lack of coordination between the ventilator cycling and the patient effort. It has been known that asynchronies increase the work of breathing and the risk of weaning failure; consequently, patients with higher percentage of asynchronies have higher rate of tracheostomy and higher risk of ICU or hospital mortality [3]. The rate of asynchrony is commonly defined by an Asynchrony Index (AI), calculated dividing the asynchrony breaths by the total of breaths; patients that have AI $\geq$10% are considered to suffer from severe asynchrony [4]. Asynchronies have been first classified taking into account the phase of the respiratory cycle and recently the classification has been revised depending on the extent of the disturbance of coordination, as (1) major: ineffective triggering, auto-triggering, double-triggering; and (2) minor: premature or anticipated cycling, prolonged or delayed cycling, triggering delay [5].

Ineffective triggering is the most frequent asynchrony and it develops when the patient's effort is not assisted by the ventilator; it should depend on low ventilator trigger sensitivity, weakness of inspiratory effort or high intrinsic positive end-expiratory pressure (PEEPi). Auto-triggering asynchrony type occurs when the ventilator delivers an assisted breath that is not triggered by the patient. It happens for instance when airways leaks are present or sometimes deep cardiac oscillations can reach the trigger threshold and lead the ventilator insufflation. Double triggering occurs when the ventilator inspiratory time is shorter than the patient' one, so that the patient previous ineffective inspiratory effort triggers the following ventilator act. These major asynchronies are represented in Fig. 18.1.

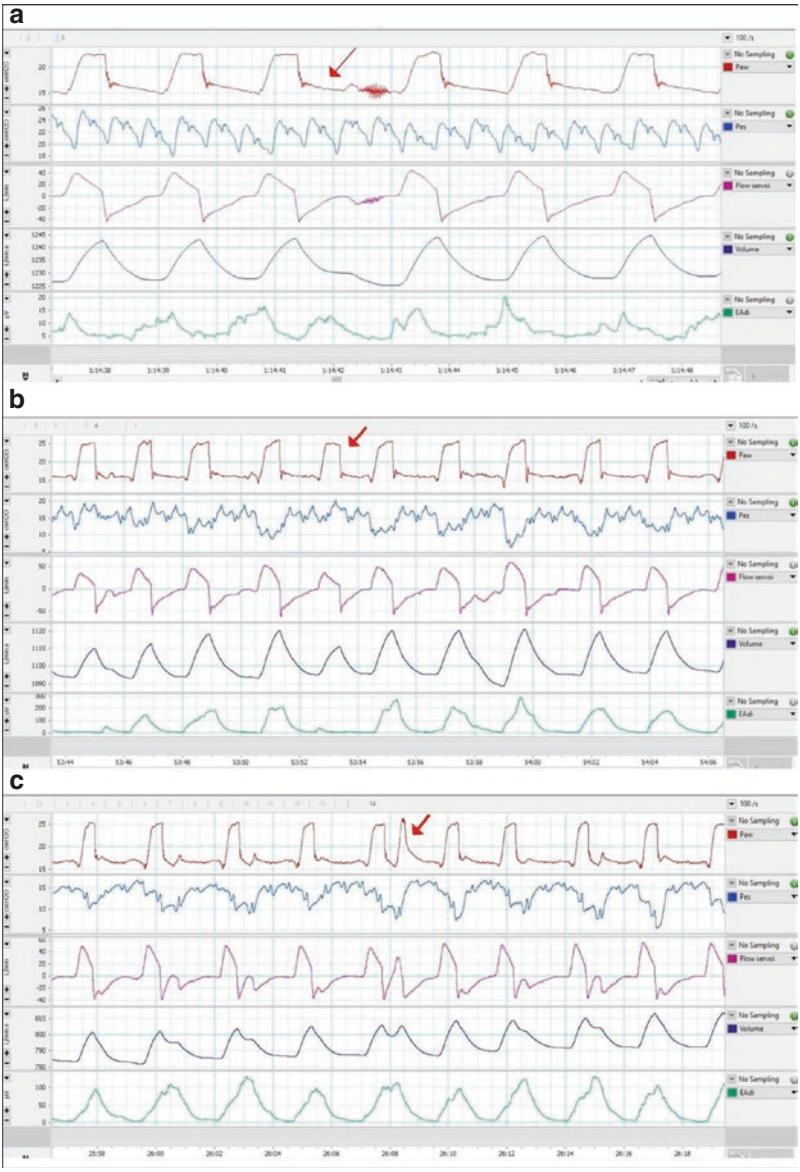

Fig. 18.1 This image shows the three major kinds of patient ventilator asynchrony during invasive mechanical ventilation. The first on the top (letter **a**) referred to **ineffective triggering**. Looking at the EAdi waveform you can see that one of the patient inspiratory effort is not too powerful to be assisted by the ventilator. The red arrow shows the missing act on the airway pressure waveform. The second image (letter **b**) shows the **auto-trigger**: note the respiratory act on the airway pressure waveform (red arrow) and the missing act on the corresponding EAdi waveform. The last image (letter **c**) represents the **double-trigger**: the same ineffective patient effort (EAdi waveform) generates two ventilator respiratory cycles. The red arrow shows the inspiratory act delivered by the ventilator on the same patient effort (EAdi waveform)

Recently, Sinderby et al. proposed a NeuroSync Index: a standardized and automated method to quantify asynchronies based on EAdi continuous monitoring. It was found to be correlated to manual analysis methods and it increased the sensitivity of detecting asynchronies compared to previous indices [4].

Despite analysis methods to detect asynchronies, for health-care professionals working in ICU is challenging to recognize PVA from waveform analysis however it is not impossible if they are properly trained to. For this reason diaphragmatic electromyography and esophageal pressure measurements have been considered the useful methods to detect asynchronies [3].

Clinic Case

We report a case of a 78-year old female, ex-smoker (pack years >60) affected by COPD (stage 2 of GOLD classification, post-bronchodilator FEV_1 of 0.7 L (54%), exacerbation history >2 per year leading to hospitalization), asthmatic bronchitis, osteoporosis and with abdominal aortic aneurysm in follow up. She was admitted in ICU after pelvic and bladder traumatic injury due to accidental event. At the admission to the Emergency Department the patient was awake and space-time oriented, complained about abdominal and left side pain. Respiratory rate (RR) was in physiological range (RR 16–17 b/m) and there were no signs of subcutaneous emphysema, but she had low blood pressure (90/45 mmHg) and tachycardia, she had bleeding wounds on the forehead and on the scalp, moreover she presented hematuria. The pelvic radiographs showed a stable fracture of the pubic symphysis; the CT scan showed hemoperitoneum and traumatic bladder rupture. The patient was suddenly conducted to emergency operatory room to suture the bladder, and at the end of the surgery she was admitted in ICU. After the source bleeding control the hemodynamic stability was reached and the patient was extubated on the second day of ICU. The blood gas analysis after extubation showed a chronic respiratory acidosis and a mild hypoxia (pH 7.39, $PaCO_2$ 52 mmHg, HCO_3^- 31 mmol/L, BE 4 mmol/L, PaO_2 69 mmHg) despite 3 L for minute of oxygen administered by standard nasal cannula. She presented forced expiration and wheezing at rest. Simultaneously with the subjective dyspnea complained by the patients she had tachycardia (HR 130 bpm) and worsening of peripheral saturation (SpO_2 from 94% to 87%). Due to persistent tachypnea and hypoxemia (PaO_2 62 mmHg), we decided to perform helmet NIV (Fig. 18.2). The choice of helmet as interface was obligated because of the wounds in her head and, moreover, helmet has been largely recognized to be comfortable and to reduce intubation rate compared with the mask especially in patients with COPD exacerbation [7].

Mild intravenous sedation was started to treat patient's agitation, with improvement of patient-ventilator interaction. The ventilator (Maquet® Servo-I, Getinge Group, Gothenburg, Sweden) was set in PSV (i.e. pressure support 8 cmH_2O + PEEP 8 cmH_2O), FiO_2 60%, to obtain a tidal volume of about 440 mL (6–7 mL/kg of ideal body weight). The others parameters were: P Peak: 17 cmH_2O, P Mean: 10 cmH_2O, TV: 440 mL, RR: 16–17 b/m, P_{01} –4 cmH_2O. After 1 h of helmet-NIV the blood gas analysis data showed: pH 7.37, $PaCO_2$ 50 mmHg, HCO_3^- 32 mmol/L, BE 4 mmol/L, PaO_2 72 mmHg, PaO_2/F_iO_2 ratio 120. After 6 h in helmet-NIV the PaO_2/F_iO_2 ratio improved until 170.

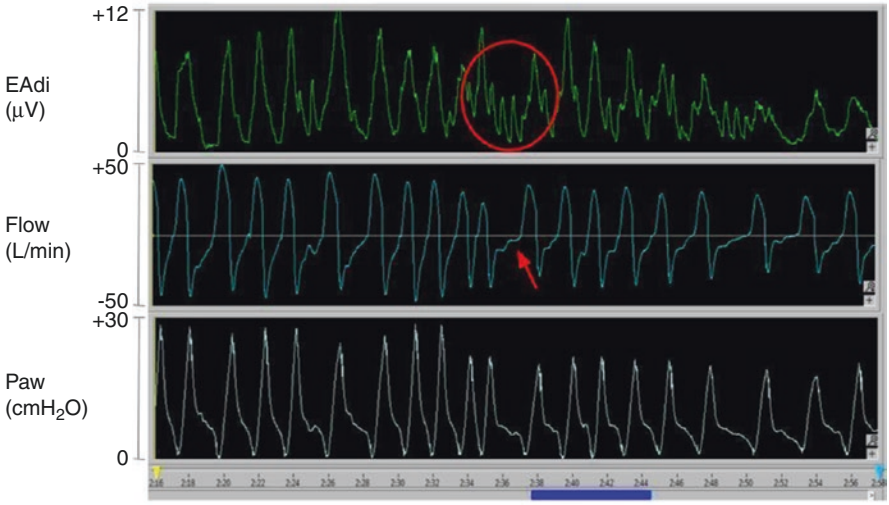

Fig. 18.2 The patient during helmet NAVA-NIV

During the third day patient developed fever (T° 38C) with tachycardia, hypertension, drowsiness, tachypnea and intolerance to the helmet-NIV. The blood gas analysis parameters got worsening: pH 7.32, $PaCO_2$ 65 mmHg, HCO_3^- 28 mmol/L, BE 2 mmol/L, PaO_2 62 mmHg, P/F ratio 103. A deeper analysis of flow waveform suggested the occurrence of many asynchronies such as ineffective triggering, with occasionally double-triggering; both remained despite changing in trigger sensitivity or flow cycling; furthermore, diaphragm dysfunction was assessed basing on ultrasound evaluation of thickening fraction less than 20%, indicating a worsening of diaphragm contractility.

Considering the patient's clinical presentation, the blood gas analysis parameters and the ultrasound evaluation we were extremely closer to the threshold of NIV failure, but taking into account the high asynchrony rate and the diaphragmatic dysfunction, we decided to perform the last attempt before proceeding with invasive ventilation: a catheter was placed to measure the electrical activity of the diaphragm (EAdi) (16 French/125 cm; Maquet®, Getinge Group, Gothenburg, Sweden) in order to improve patient-ventilator interaction and diaphragm monitoring. The Eadi catheter was placed using the positioning tool provided by the manufacturer and the ventilator was equipped with NAVA module.

Briefly, NAVA mode is a kind of ventilation which provides respiratory support proportional to electrical activity of the diaphragm (Eadi); in this way the neural activity of the diaphragm is the trigger captured by the ventilator to assist the patient effort.

We set the NAVA trigger at 0.7 μV, the default cycling at 70% of the peak electrical activity of the diaphragm, whereas the NAVA gain was set to obtain a target of minute ventilation of 6–8 mL/kg of predicted body weight. PEEP level was left unchanged compared to those applied during PSV (i.e. 8 cmH_2O). Flow, pressure

Fig. 18.3 This figure shows, from the top to the bottom, EAdi, Flow and Airway Pressure (Paw) waveforms. You can see, in the red circle above the EAdi waveform, two weak patient inspiratory efforts that cannot generate a valid respiratory act. Looking at the flow waveform, the red arrow shows a notch on the track corresponding to the untriggered act. This kind of asynchrony is known as **ineffective triggering**, the most common one

and Eadi waves were acquired from the recording system (NAVA tracker Maquet®, Getinge Group, Gothenburg, Sweden). The EAdi waveform confirmed the suspect of ineffective triggering asynchrony as shown in Fig. 18.3.

After about 2 h, the asynchronies reduced, together with patient's subjective dyspnea. Moreover, adequate therapy was administered to treat fever and agitation. After 48 h of NAVA-NIV all the blood gas analysis parameters improved: pH 7.39, $PaCO_2$ 45 mmHg, HCO_3^- 30 mmol/L, BE 3 mmol/L, PaO_2 106 mmHg, P/F ratio 260. The respiratory rate was in the normal range and the respiratory dynamic was not paradoxical. In addition, probably due to patient-ventilator synchrony, the diaphragm efficiency improved and the thickening fraction reached 33%. Thus, we decide to interrupt the NIV therapy and replace it with a standard venturi mask until ICU discharge that happened 2 days later.

In conclusion, this clinical case showed an improvement of patient-ventilator interaction, gas exchange and patient comfort by using NAVA NIV through helmet rather than NIV alone, according to previous studies [3, 6, 7]. However, the reduction of asynchronies during NAVA NIV can play a role to decrease the diaphragmatic dysfunction, probably due to improvement in neuro-ventilatory and neuro-mechanical efficiency [8].

PVA is reported in literature to occurred in 80% of patients receiving NIV [4]. In this chapter, we summarized the problems regarding the correct detection of asynchronies and, even if dedicated software have been developed for this aim, none of them is compatible with routine clinical use.

Different strategies can reduce the incidence of PVA both during invasive and non-invasive ventilation [4]:

- *Avoid overassis*tance, increasing patient respiratory drive by diminishing the inspiratory pressure support in order to decrease the rate of ineffective triggering;
- Reducing tidal volume and minute ventilation mostly in COPD patients to minimize PEEPi, determinant for ineffective triggering;
- Promote the use of proportional assist ventilatory mode as NAVA, PAV (Proportional Assist Ventilation) and ASV (Adaptive Support Ventilation). These modalities can play a role in reducing PVA but only NAVA can be applied during NIV;
- Inspiratory trigger sensitivity should be optimized because low inspiratory trigger threshold may cause auto-triggering, in contrast, high inspiratory trigger threshold may result in ineffective triggering;
- *Avoid deep sedation* and long-lasting sedative drugs, mostly during NIV;
- *Correct choosing of the right interface* during NIV to avoid air leaks.

Key Teaching Points

- NIV has gained importance as first-line treatment of ARF; however, NIV failure is associated with greater risk of mortality when compared to the more invasive MV. Therefore, clinicians efforts should target the prevention of NIV-failure
- An important role of NIV failure is played by poor patient-ventilator interaction and patient-ventilator asynchrony, correct assessment of asynchronies can be challenging or even impossible with standard ventilator monitoring
- Measurement of diaphragmatic electrical activity has been considered a useful method to detect or even prevent asynchrony
- Avoid overassistance, reducing tidal volume and minute ventilation, optimize inspiratory trigger sensitivity, avoid deep sedation and correct choosing of the right interface, these are all helpful strategies to reduce PVA
- Considering our clinic case, NAVA-NIV prevented NIV failure improving comfort, patient-ventilator interaction and it led to a successful weaning compared to NIV alone

Questions and Answers

1. What kind of proportional ventilation modality can be helpful in reducing asynchronies during NIV?

   (a) Proportional Assist Ventilation (PAV)
   (b) Neurally Adjusted Ventilatory Assist (NAVA)
   (c) Adaptive Support Ventilation (ASV)

   Answer: (b) Neurally Adjusted Ventilatory Assist (NAVA)
2. How asynchronies have been recently classificated and which is the most common one?

   (a) (1) Major: ineffective triggering, auto-triggering, double-triggering; and (2) minor: premature or anticipated cycling, prolonged or delayed cycling, triggering delay. The most common is ineffective triggering
   (b) (1) Major: premature or anticipated cycling, prolonged or delayed cycling, triggering delay; and (2) minor: ineffective triggering, auto-triggering, double-triggering. The most common is triggering delay
   (c) (1) Major: ineffective triggering, auto-triggering, double-triggering; (2) minor: premature or anticipated cycling; and (3) uncommon: prolonged or delayed cycling, triggering delay. The most common is: double-triggering

   Answer: (a) (1) Major: ineffective triggering, auto-triggering, double-triggering; and (2) minor: premature or anticipated cycling, prolonged or delayed cycling, triggering delay. The most common is ineffective triggering
3. Which strategies can be applied to reduce patient-ventilator asynchrony?

   (a) Avoiding deep sedation and choosing the correct interface.
   (b) Optimizing inspiratory trigger sensitivity and avoiding over assistance
   (c) All of the above

   Answer: (a) All of the above
4. Which of the following sentences about NAVA is false?
   (a) It is a volume-target pressure support mode with automatic adjustment of pressure support according to the spontaneous respiratory rate
   (b) It is a mode of mechanical ventilation where the ventilator is controlled directly by the patient's own neural control of breathing
   (c) It is a kind of ventilation which provides respiratory support proportional to electrical activity of the diaphragm (Eadi); in this way the neural activity of the diaphragm is the trigger captured by the ventilator to assist the patient effort.

   Answer: (a) It is a volume-target pressure support mode with automatic adjustment of pressure support according to the spontaneous respiratory rate.

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Chapter 19
Clinical Cases in Non Invasive Ventilation: Pressure Waveform

Ana Cláudia Vieira and António Miguel Silveira

Abbreviations

AI%	Asynchrony index
COPD	Chronic obstructive pulmonary disease
NIV	Non invasive ventilation
PEEPi	Intrinsic positive end-expiratory pressure

19.1 Clinical Cases in Non Invasive Ventilation: Pressure Waveform

19.1.1 Standard Clinical Case

A male patient, 72 years old, former smoker (90 pack-year) with a medical history of type II diabetes, arterial hypertension and chronic obstructive pulmonary disease with severe obstruction, multiple exacerbations (with hospital admissions,

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including one episode of invasive mechanical ventilation) and type 2 respiratory insufficiency, on supplementary oxygen and non invasive ventilation (NIV) at night, was brought to the emergency department with dyspnea at rest, cough with purulent sputum and fever (temperature of 39 °C maximum). At observation he was conscious and alert, tachycardic (120 bpm), hypertensive (140/90 mmHg) and had fever (38.5 °C). He was using his accessory muscles (intercostal, supraclavicular) with oxygen saturations of 87% under his domiciliary non invasive ventilator (PSV mode; IPAP 20; EPAP 6; respiratory backup rate 14; maximum inspiratory time 0.8–1.4 s; rise time 3; low ventilator trigger sensitivity) with adjuvant supplementary oxygen (2 L/min). At pulmonary auscultation he had crackles in the right basal hemithorax.

The exams performed at emergency department showed a respiratory acidosis (pH: 7187; $PaCO_2$: 122.9 mmHg; PaO_2: 69.3 mmHg; HCO_3: 45.6 mmHg; SaO_2: 87.2%), the blood tests leukocytosis and an elevated C-reactive protein and the chest radiograph showed an opacity at the base of the right lung, suggestive of pneumonia.

Under NIV, the patient was restless and anxious, due to poor patient–ventilator synchrony and the pattern on the pressure waveform was suggestive of ineffective triggering, leading to an increase in ventilator trigger sensitivity and a decrease in the maximum inspiratory time (to 0.5–1 s) with improvement in arterial blood gases (pH: 7338; $PaCO_2$: 82.7 mmHg; PaO_2: 58.2 mmHg; HCO_3: 43.4 mmHg; SaO_2: 86.8%). Despite that, the patient remained, somewhat, uncomfortable and, combined with the pressure waveform pattern, double triggering was detected leading to an increase of IPAP level to 22 mmHg, with achievement of patient ventilator synchrony.

In the following questions, choose the correct answer:

1. **One of the reasons to explain ineffective triggering in this case is:**

   (a) High inspiratory trigger threshold
   (b) Low intrinsic positive end-expiratory pressure (PEEPi)
   (c) High respiratory drive

2. **When the patient had poor patient-ventilator synchrony and ineffective triggering was detected, we could identify in the pressure waveform:**

   (a) Two cycles separated by a very short expiratory time
   (b) An increase in airway pressure near the end of the inspiratory phase
   (c) An airway pressure drop caused by the inspiratory effort of the patient without the delivery of pressure from the ventilator

3. **Double triggering can be identified:**

   (a) In the pressure waveform by two mechanical cycles triggered by the patient, separated by a very short expiratory time
   (b) Frequently, in patients with low respiratory drive
   (c) Mostly in patients with a sufficient level of pressure support

4. **If auto-triggering occurred it could be because of (choose the incorrect answer):**

   (a) Air leaks
   (b) Low trigger sensitivity
   (c) Changes of airway pressure not caused by patient effort

   Answers: 1. (a); 2. (c); 3. (a); 4. (b)

19.2 Discussion

The most important aim when instituting noninvasive mechanical ventilation is to decrease patients' work of breathing. The most effective unloading of the inspiratory muscles is obtained when the ventilator cycles are in synchrony with patient's respiratory rhythm. Nevertheless, asynchronies may appear at several points during the respiratory cycle [1]. Patient ventilator asynchrony is a mismatch between patient and ventilator assisted breaths and the ventilator's ability to meet the patient's flow demand [2].

Poor patient–ventilator interaction and synchrony during non invasive ventilation (NIV) can cause discomfort, agitation, increased work of breathing and worsening of gas exchange.

We can identify these asynchronies trough ventilator waveform observation, complex mathematical algorithms or using the electrical activity of the diaphragm or esophageal pressure. The gold standard for measuring patient ventilator asynchronies is the phrenic neurogram and esophageal balloon catheter but it is less feasible in clinical practice, a source of discomfort to the patient and contributes to air leaks. The phrenic neurogram senses diaphragmatic muscle contraction (patient inspiration) through invasive sensory probes. The second measure is correlated with pleural pressure and is obtained from the esophageal balloon catheter. In routine clinical practice, visual inspection of the ventilator screen is the commonest method adopted. Waveform analysis is conducted by visually detecting particular morphological changes and is the most available and least invasive measure for patient-ventilator asynchronies interpretation at the bedside.

Clinically relevant asynchronies are present in up to 60% of patients doing noninvasive ventilation. Pressure/time and flow/time waveform analyses require a trained eye. Since asynchronies are common and complex, clinicians need to be knowledgeable regarding waveform analysis to detect ineffective patient ventilator interaction [2]. We can use the asynchrony index (AI%) to evaluate the rate of asynchrony. This is calculated by dividing the asynchronous breaths by the overall breath count. Values of AI% $\geq$10 are associated with worsened patients' outcomes (for example high levels of inspiratory pressure can be associated with and increased index).

In this chapter we will learn how to interpret asynchronies through pressure waveform analysis.

We can classify patient–ventilator asynchronies as major (ineffective triggering, auto-triggering, and double triggering) and minor (premature cycling, prolonged cycling, triggering delay).

Ineffective triggering (wasted efforts) is the most common asynchrony and occurs because an inspiratory effort is not assisted by the ventilator. There are various factors that can contribute to this event, particularly low respiratory drive, low ventilator trigger sensitivity or high intrinsic positive end-expiratory pressure (PEEPi). A high incidence of ineffective efforts during long term non invasive ventilation is associated with a poorer nocturnal oxygen gas exchange [3]. Ramsay et al. used parasternal electromyography to assess types and prevalence of asynchronies during long term NIV and nearly 80% of patients had an AI% ≥10. Ineffective efforts were the most common asynchrony [4]. Lower levels of inspiratory support decrease the rate of ineffective triggering (increases patient respiratory drive). In fact, in patients with airway obstruction, reducing tidal volume and minute ventilation improves patient–ventilator synchrony because it decreases auto or PEEPi that can also contribute to ineffective triggering. Due to a high PEEPi and when pressure triggering is used, the patient cannot decrease his airway pressure below PEEPi and the inspiratory effort is ineffective. High inspiratory trigger thresholds may also result in ineffective triggering. In the presence of ineffective efforts we will have an airway pressure drop in the pressure waveform (Fig. 19.1) caused by the inspiratory effort of the patient (decreasing the airway pressure) and, a change in the expiratory flow (which tends to return to zero due to the inspiratory effort of the patient) without the delivery of pressure from the ventilator [1, 5].

Auto-triggering occurs when the assistance that the ventilator delivers is not related to the patient's spontaneous effort. During mechanical ventilation triggering of the ventilator should result from inspiratory muscles contraction. However, changes in airway flow/pressure because of cardiac oscillations, water in the circuit, air leaks can be erroneously interpreted as triggering efforts. Auto-triggering, most often, occurs with low respiratory drive and frequency and when dynamic hyperinflation is absent. Zero flow can occur for some time during expiration, just before the next inspiration, making the system vulnerable to triggering from changes of airway pressure not caused by patient effort. Therefore, a greater sensitivity of the triggering system programmed on the ventilator also increases the risk of auto-triggering. Auto-triggering shows in the pressure waveform, a lack of airway pressure drop or variations in the flow waveform at the beginning of the inspiratory phase (Fig. 19.1).

Double triggering is characterized by two mechanical cycles triggered by the patient, separated by a very short expiratory time. It is more common in patients with low respiratory compliance receiving pressure support ventilation or patients with high respiratory drive. It is associated with an insufficient level of pressure support, and results in an inspiratory effort retriggering the ventilator after it has discontinued pressurization [5, 6]. We can identify this asynchrony in pressure waveform in the presence of two cycles separated by a very short expiratory time (Fig. 19.1).

Premature cycling is related to the end of the ventilator insufflation before a patient's effort has finished (patients with low compliance) and delayed or

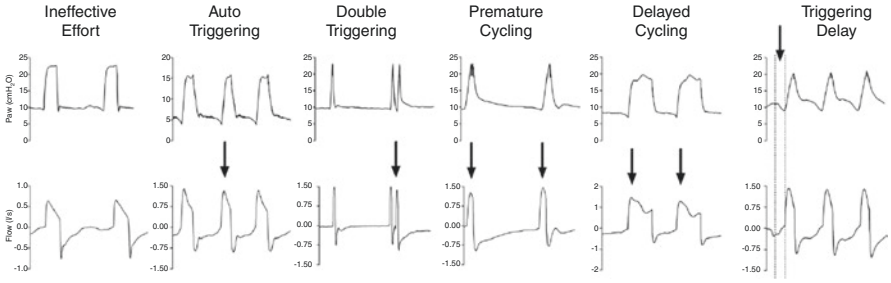

Fig. 19.1 Waveforms of airway pressure (Paw) and flow for each type of patient–ventilator asynchronies. Arrows highlight the asynchronous events. (From: Eugenio Garofalo, Andrea Bruni, Corrado Pelaia, Luisa Liparota, et al. (2018). Recognizing, quantifying and managing patient-ventilator asynchrony in invasive and noninvasive ventilation. *Expert Review of Respiratory Medicine*, 12(7):557–567)

prolonged cycling is the opposite, which means it happens when the patient's inspiration has ceased and mechanical assistance continues (patients with higher resistance and normal or elevated lung compliance, like in patients with chronic obstructive pulmonary disease or in presence of air leaks). Premature cycling produces a decrease in airway pressure, which can be seen immediately after the end of the inspiratory phase and delayed cycling is evidenced in the pressure waveform as an increase in airway pressure near the end of the inspiratory phase (Fig. 19.1).

Finally, triggering delay corresponds to a prolonged time between patient's respiratory effort and ventilator support initiation [5]. In pressure waveform before ventilator support there is a pressure drop caused by the inspiratory effort of the patient (Fig. 19.1).

In NIV, air leaks represent the most important contributors to asynchrony. The development of software capable of detecting and compensating for air leaks has promoted a better patient–ventilator interaction during NIV, lowering the occurrence of auto-triggering, ineffective efforts, and late cycling. It is also crucial to choose the right interface to avoid excessive air leaks. Interestingly, the study conducted by Carlucci et al. suggested that the occurrence of asynchrony does not differ between patients with obstructive or restrictive disease [7].

Key Teaching Points

- Asynchronies may appear at several points during the respiratory cycle.
- We can identify these asynchronies by ventilator waveform observation.
- We can classify patient–ventilator asynchronies as major (ineffective triggering, auto-triggering and double triggering) and minor (premature cycling, prolonged cycling, triggering delay).
- Ineffective triggering is the most common asynchrony and occurs because an inspiratory effort is not assisted by the ventilator.
- In NIV, air leaks represent the most important contributors to asynchrony.

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Chapter 20
Pressure Waveform. Clinical Interpretation - Acute Respiratory Failure in COPD

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Abbreviations

COPD	Chronic obstructive pulmonary disease
EPAP	Expiratory positive airway pressure
IPAP	Inspiratory positive airway pressure
NIV	Non invasive mechanical ventilation
PCV	Pressure control ventilation
PEEP	Positive end expiratory pressure
PS	Pressure support
PSV	Pressure support ventilation
PVA	Patient ventilator interaction
VCV	Volume controlled ventilation

Case Report

A 77 years old man, ex-smoker for about 45 years (Pack/years 68) suffering from chronic ischemic cardiopathy treated whit PTCA+STENT and systemic blood hypertension, COPD GOLD D whit prevalence of emphysema alterations in therapy whit inhaler extra fine triple therapy.

He reports weight loss and low-grade evening fever, lasting for some months. He arrived from the emergency room in order to be under our observation because of a

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worsening of the dyspnea, a no-tolerance for NIV, and breath rate 38, use of accessory muscles of breathing, productive cough whit white sputum, body temperature of 38.5 °C, arterial blood gas analysis at the entrance in Oxygen 2 L/min whit nasal cannulas (PO_2 47 mmHg, PCO_2 65 mmHg; Ph 7.35; HCO_3^- 35.9 mmol/L), the chest X-Ray showed "extended thickening on right hemithorax whit minimal homolateral pleural effusion" (Fig. 20.1a).

Blood test showed neutrophilic leukocytosis GB 25.76 (10^3/μL) NEU 11.95 (10^3/μL), PCR 11.5 mg/dL VES 120 mm 1 h, procalcitonin 0.02 μg/mL. ECG: sinus tachycardia HR 112 bpm.

Echocardiography: dilated left atrium. Ejection fraction 60%. PAPs 30 mmHg. TAPSE 18 mm. Slight pericardium effusion (5 mm).

The patient was treated whit NIV and nasal mask (Fig. 20.1b) vented in BILEVEL whit addition oxygen 1 L/min whit the following settings: IPAP pressure 10 cmH_2O, EPAP pressure 4 cmH_2O, Breath Rate 14, inspiratory time 1 s, flow trigger sensitivity 2 L/min, flow cycle sensitivity 55%, rise time 3, tidal volume 660 mL. Whit this setting saturation improved 92%, HR 108 bpm. After half an hour a new EGA was PO_2 90 mmHg, PCO_2 65 mmHg; Ph 7.29; HCO_3^- 35.9 mmol/L. The compliance was not optimal with a lot of various phases of ventilation interruption. (Fig. 20.1d) The analysis of the ventilation curves graphic downloaded from the mechanical ventilator showed a complete patient's asynchrony and most of the respiratory acts were not supported, showing an important desynchronization especially when the

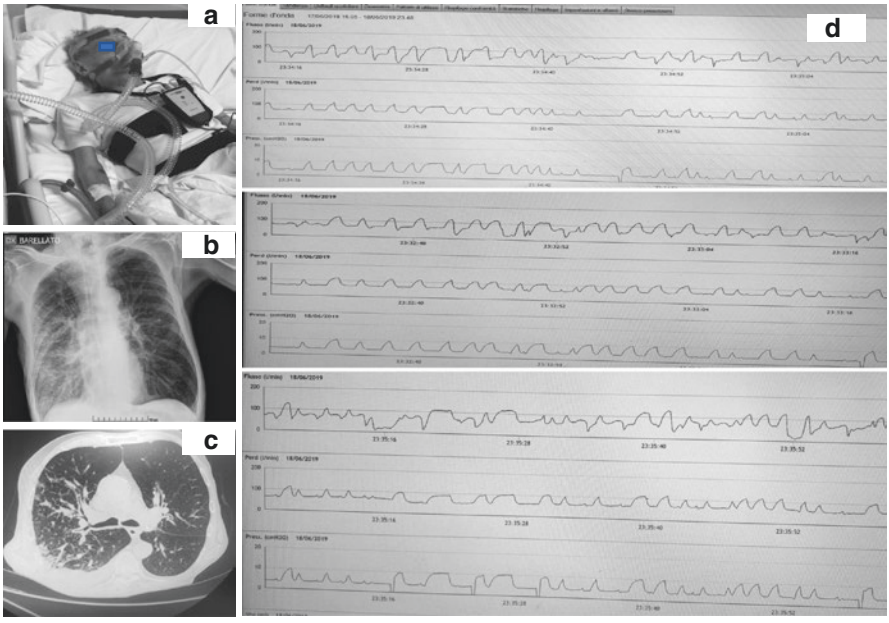

Fig. 20.1 (**a**) Chest X-ray. (**b**) Patient in NIV with nasal mask. (**c**) Particular of chest CT. (**d**) Dyssynchrony: ineffective effort, Flow asynchrony, leaks, double trigger

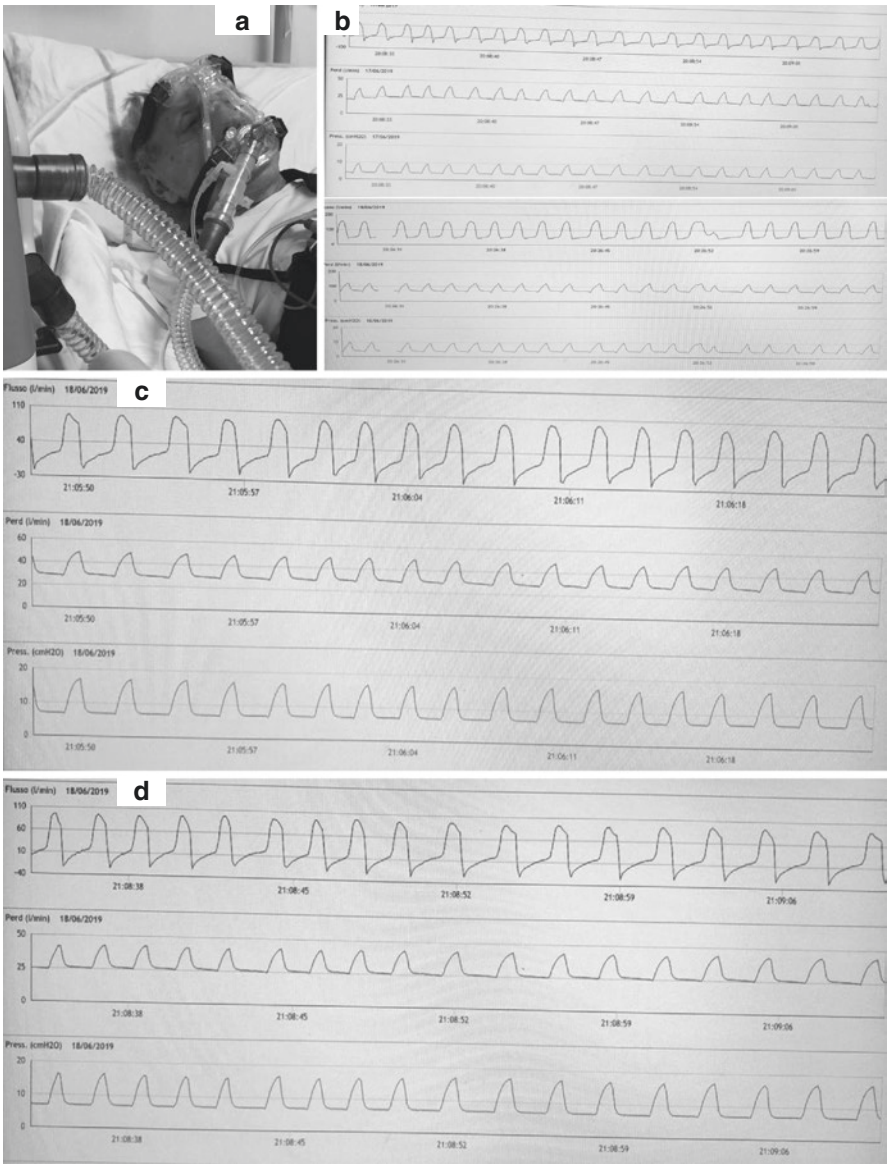

Fig. 20.2 (**a**) The patient in NIV with full face mask. (**b–d**) Waveforms after parameter modification

leaks increased. The patients were informed of the need to be changed interface and the circuit ventilation mode whit whisper and full-face mask without integrated leak. (Fig. 20.2a) The setting is also changed during graphic visualization in: IPAP pressure 16 cmH_2O, EPAP pressure 6 cmH_2O, Breath Rate 14, inspiratory time 1 s, flow trigger sensitivity 2 L/min, flow cycle sensitivity 55%, rise time 3, tidal volume

660 mL. We noted that the patient's breathing rate was always high 32 bpm ad we decided to make the flow trigger sensitivity by going from 2 to 4 L/min. (Fig. 20.2b) The analyses of the curves graphic highlighted unassisted respiratory acts, unsatisfactory inspiratory flow and this presence of double-trigger, and furthermore during the expiratory phase of the graphic we noticed fluctuations corresponding to the movement of the bronchial secretions. We decided to change the setting again as follows IPAP pressure 18 cmH_2O, EPAP pressure 7 cmH_2O, Breath Rate 14, inspiratory time 1 s, flow trigger sensitivity 2 L/min, flow cycle sensitivity 55%, rise time 3, tidal volume 660 mL. After about 10 min the BR is reduced to 10 while the inspiratory time to 0.8 s. there is a slight improvement in respiratory acidosis. Always guided by the analysis of the curves graphic and the clinic conditions of the patient, whit the reduction of the accessory respiratory muscles activity and the improvement of the compliance and an improvement of the saturation, we decided to change the setting IPAP pressure 20 cmH_2O, EPAP pressure 7 cmH_2O, (Fig. 20.2c, d) Breath Rate 10, inspiratory time 0.8 s, flow trigger sensitivity 2 L/min, flow cycle sensitivity 55%, rise time 3, tidal volume 660 mL, in addition oxygen 1 L/min whit a worked improvement in saturation 94% and in EGA (PO_2 74 mmHg, PCO_2 54 mmHg; Ph 7.41; HCO_3^- 33 mmol/L).

A bacterial sputum culture test was negative. Chest computed tomography (CT)/PET showed a solid neoplastic lesion in the right hilum of lung (26 × 33 mm) and large lymph nodes in different areas: right supraclavicular-retroclavicular and mediastinum (Suv max is 10.77) (Fig 20.1c). We decided to undergo him to biopsy of right supraclavicular lymph node and the anatomopathological findings of metastasis from neuroendocrine tumor of lung.

20.1 Discussion

Noninvasive positive pressure ventilation (NIV) is the first-line intervention for patients suffering from acute exacerbation of chronic obstructive pulmonary disease (COPD) and secondary respiratory acidosis, reducing intubation rate and mortality. In this case, and generally, the main objectives of NIV include supporting satisfactory levels of gas exchange and reducing respiratory effort until the clinical state is resolved or compensated. (Fig. 20.3a, b).

Often, when NIV is performed, ventilatory parameters are determined empirically taking into account the underlying disease, patient toleration while awake and changes produced in diurnal arterial blood gas. The clinical intention should be optimal patient-ventilator interaction, with an equilibrium between patient inspiratory effort and ventilator triggering, ventilatory demand and delivery of flow and tidal volume, and between the interruption of patient inspiration and cycling of the device. (Fig. 20.4a, b).

When we treated a patient with NIV, we have a non-hermetic system that causes involuntary leaks, so the ventilator-lung interaction cannot be imagined as a unique model because of the presence of a variable resistance expressed essentially by the

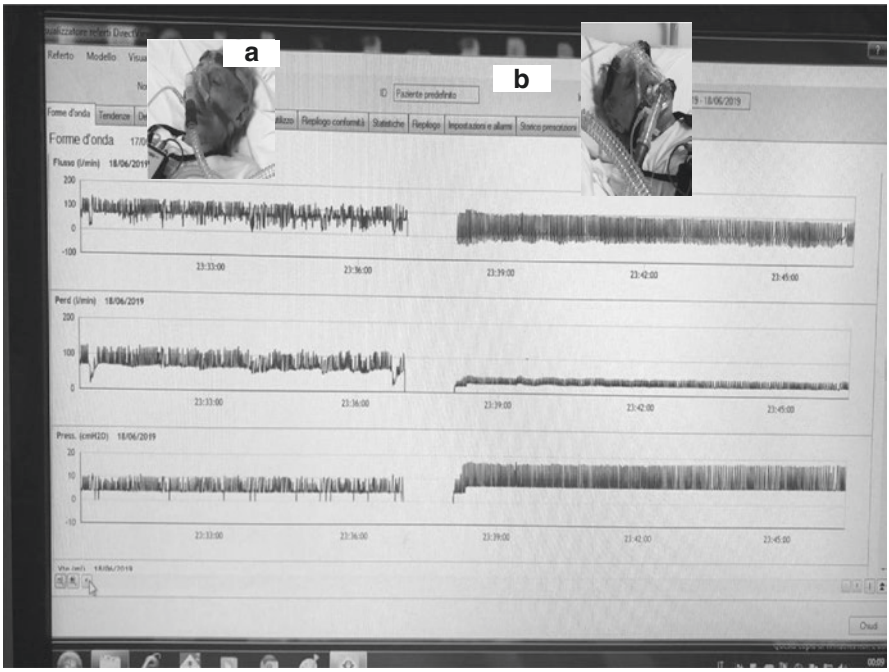

Fig. 20.3 (**a**, **b**) Progressive modifications parameter NIV and interface

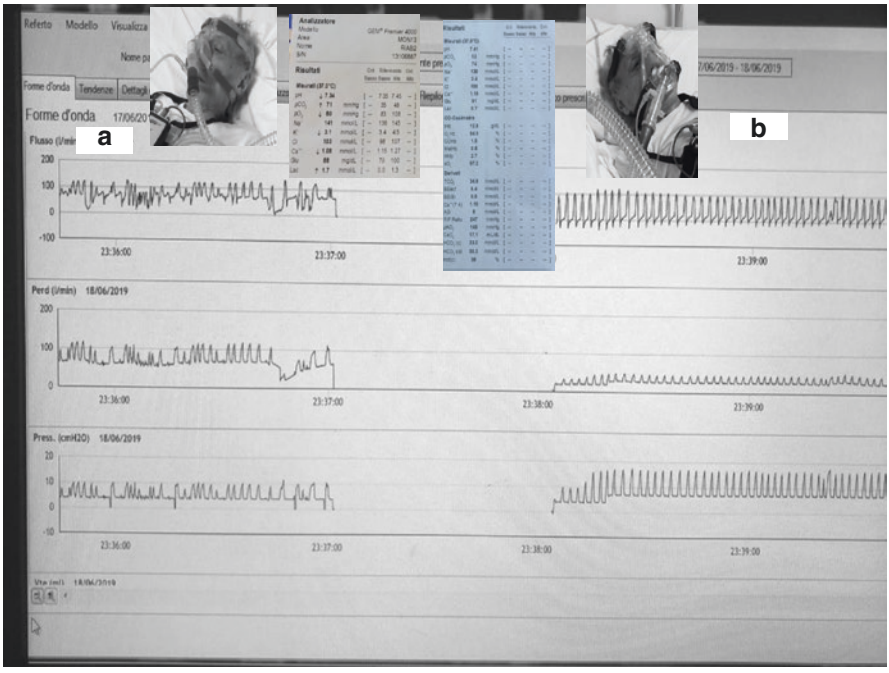

Fig. 20.4 (**a**, **b**) Improvement of respiratory parameters after resolution of leaks and NIV adjustment

upper airway. Both conditions may compromise the delivery of an acceptable tidal volume. Respiratory mechanics influence the type of patient-ventilator asynchrony, depending on neural inspiratory time and ventilator settings [1].

20.2 Waveform Analysis

COPD has been estimated usually associated with asynchrony, especially in the presence of auto-positive end-expiratory pressure (auto-PEEP), which limits ventilator triggering and favors the frequent ineffective efforts. By analyzing the volume, flow, and pressure waveforms on the mechanical ventilator display, it is possible to recognize the most frequent types of patient-ventilator asynchrony, which are those correlated to triggering, those about cycling, and those related to flow.

Pressure and flow waveforms show the interactions between the mechanical breath and the respiratory mechanics and patient's work, and researches have proved them to be a handy tool for identifying asynchronies. Some authors demonstrated that the real-time analysis of pressure and flow waveforms during NIV was correlated with a different ventilator setting compared to the standard ventilation, leading to a more rapid pH normalization in patients needing NIV for COPD exacerbation, with a faster $PaCO_2$ reduction in the first 6 h of ventilation [2, 3].

The inception of the patient's expiration can be identified simply on the flow and pressure waves. On the waveforms, the start of the patient's inspiration can be recognised as a swift negative deflection in pressure tracing with a sudden positive deflection of flow, whereas, on the flow curve, a positive deflection can be recognised, even if the flow is still negative. So, the patient's inspiratory activity can be identified even when it is not identified or assisted by the ventilator.

The underlying respiratory disease can favor a certain type of asynchrony, the presence of different pathologies makes the coexistence of multiple asynchronies possible. An obstructive respiratory mechanics profile seems to be more related with delayed cycling asynchrony, complicated by short neural inspiratory time. A restrictive respiratory mechanics profile, with longer neural inspiratory time, improves premature cycling events during pressure support ventilation (PSV).

No best interaction between patient and ventilator can have wide-ranging physical and psychological outcomes, including discomfort and anxiety, dyspnea and lung injury. These outcomes on the patient may often go undetected by healthcare staff, with nurses and physicians undervaluing the sensation of breathlessness and reduced respiratory function or impair oxygenation as reported by the patients during a spontaneous breathing trial. Some asynchronies are usually linked with a patient's low respiratory drive and/or too much ventilator support such ineffective efforts, delayed cycling, auto-triggering; others are correlated with a high respiratory drive and low ventilator support, such as early cycling and double-triggering.

Patient-ventilator asynchrony (PVA) occurs when there is an incongruity between the patient's inspiratory time and the mechanical breath or when the flow delivered by the ventilator is inadequate.

PVA determine clinical effects and is associated with unsatisfactory outcomes, such as distress, dyspnea, worsening of pulmonary gas exchange, enhanced respiratory effort, diaphragmatic injury, decreased quantity and quality of sleep, increased use of sedation and use of neuromuscular blockade, with an enlarged duration of NIV and increased mortality [4].

Dyssynchronous breathing or ineffective effort has been shown to produce increases in transpulmonary pressure, potentially leading to ventilation-associated lung injury [5].

Thille and colleagues systematically tested ventilator setting optimization in patients on PSV with an ineffective triggering index higher than 10%; they assessed two different levels of PEEP (0 vs. 5 cmH_2O) and then the effect of PS reduction by steps of 2 cmH_2O or reducing insufflation time by increasing the cycling-off by steps of 10%. They showed that the most effective way to decrease ineffective efforts was to reduce over-assistance by decreasing pressure support: they were eliminated in two-thirds of the patients [6]. Optimizing inspiratory time allowing smaller tidal volume was also an efficient way to decrease ineffective efforts. A relevant mechanism related to the genesis of PVA in COPD is dynamic hyperinflation. Dynamic hyperinflation might be a result of a too-short expiratory time, which can be the case with high breath frequency, or high IPAP, levels. Dynamic hyperinflation enhances the work of breathing and might induce ineffective effort, as inspiratory resistance has to be overcome before the patient can produce a negative inspiratory flow to trigger the ventilator.

Ineffective efforts are the most common asynchrony in patients undergoing mechanical ventilation, accounting for at least 60% of asynchronous breaths. Ineffective efforts can be identified in the flow waveform. Ineffective efforts during mechanical inspiration abruptly increase inspiratory flow, whereas, during expiration, they result in an abrupt decrease in expiratory flow.

Rate asynchrony happen when a patient's respiratory rate and the ventilator rate are not synchronized. It occurs during the end of the patient's inspiratory phase and the beginning of the expiratory period, thus causing asynchrony between the patient's and ventilator's rate. Causes of rate asynchrony may be air hunger or neurological injury, increasing spontaneous rate.

The consequences of the addition of a high backup frequency on respiratory muscle unloading were individually distinctive. On the one hand, adding a great backup might produce optimal muscle unloading, without effectively regulating ventilation, and with little PVA. On the other hand, a too high backup frequency might be disadvantageous, also concerning respiratory muscle unloading.

20.3 Pressure Support Level

The correct pressure is essential for reducing the inhalation effort and improve synchronization during this phase; the inspiratory flow should be adjusted to balance the demand inspiratory. Factors impacting the rate of pressurization are the level of

ventilatory support, the amount of time required to reach the pressure target, the compliance and resistance of the respiratory system and the patient inspiratory effort. A higher level of pressure support has been associated with ineffective inspiratory efforts and an improvement in the level of assistance is necessary to solve the problem.

NIV with high inspiratory pressures might be needed to produce an optimal respiratory muscle comfort and an optimal correction in gas exchange in stable hypercapnic COPD patients.

However, excessive levels of pressure support should be avoided; over-assistance, as under-assistance may generate asynchronies. High pressure support can worsen hyperinflation, leading to difficult triggering and late cycling to expiration. When this type of asynchronies are identified on ventilator waveforms, physicians should think a modification in the level of pressure support. On the other hand, it must be accentuated that, if slow pressurization could strengthen inspiratory work, an excessive peak flow could also produce adverse effects as it may increase the sensation of dyspnoea, induce double triggering and lead to high peak mask pressure, favoring leaks.

Flow asynchrony: flow asynchrony may be caused by either too fast or too slow flow and may happen with either flow-targeted breaths or with pressure-targeted breaths. For pressure-targeted breaths, rise time can be evaluated by observing the pressure and flow waveforms. Short rise time may cause a pressure spike near the beginning of the pressure waveform (overshoot). The flow received by the patient is lower than his ventilatory request, typically occurring when the flow is set by the operator and cannot be increased by patient spontaneous inspiratory time, when it is longer than patient neural inspiratory time. Inadequate inspiratory flow can also happen during pressure control ventilation (PCV) and PSV when the levels set are not sufficient to produce the flow request by the patient. The corrective strategy can match a decrease in ventilatory request as in case of improvement of fever, anxiety, pain; an increment in flow delivery by means of appropriate adjustments for each mode, examining patient satisfaction and use of accessory respiratory muscles, as well as the structure of the pressure waveform. In patients on volume controlled ventilation (VCV), changing to PCV or PSV, which have a free flow, can be a good alternative.

In addition, in PCV and PSV, an increase in rising time directly changes flow delivery early after the respiratory cycle is triggered; the shorter rise time, the higher the flow delivery and the faster the initial pressurization of the system; a rapid rise time is suggested in patients with disease that determine air hunger. Excessive flow asynchrony occurs because of too much delivery of inspiratory flow. In some cases, excessive pressurization may occur, characterizing an overshoot of the flow in PCV or PSV. A good solution is decrease flow delivery by lowering the set value in VCV or by reducing the utilized pressure over PEEP or increasing the rise time in PCV and PSV.

20.4 Leaks

Unintentional leaks are common in NIV. Leakage may be absent or smallest when the patient is awake but during sleep as a result of the reduction of voluntary control and reduced muscle tone we can recognize higher leaks. Leaks can take place at the mouth (as an inpatient with a nasal mask) or between the skin and the mask, and air could also be collected in the oropharyngeal reservoir and even flow into the digestive tract (internal leaks) [7]. Teschler et al. reported that large leaks could occur without obvious opening of the mouth as air escaped through a corner of the closed mouth. Mask leaks may cause ineffective efforts and auto triggering as the ventilator is unable to detect the patient's inspiratory effort, and delayed cycling, as the ventilator does not cycle to exhalation once the flow remains below a certain level [7]. The inspiratory flow curved in the absence of leaks shows a very rapid increase in flow, reaching an early peak, followed by a progressive decrease until cycling. If there are leaks, the inspiratory flow curve reveals a typical two-slope part, with an initial quick growth followed by a slower increase in the flow until cycling happens. An increment in inspiratory time may also occur in the case of flow cycling. It may be due to a progressive increase of the ventilator turbine to compensate for leaks. Ventilator flow increases to compensate for a drop-in pressure, but leaks result in decreased tidal volume.

An increment in flow amplitude during insufflation can also be detected in case of improved inspiratory efforts of the patient corresponding to inspiratory pressurization. In that phase, the rise in insufflation flow amplitude is associated with an increase or disappearance in thoracic and abdominal belt signal amplitudes.

20.5 Inspiratory Trigger

Classically, NIV devices have two kinds of triggers. The pressure-trigger, existent prevalently in old ventilators, is based on drop-in proximal airway pressure and needs a closed circuit. The flow-trigger, present in almost all modern ventilators, is based on detection of inspiratory flow in the presence of continuous flow washing out the circuit during expiration. An appropriate inspiratory trigger setting supports the beginning of the breath and reduces the patient's work of breathing. Flow trigger is valued better than pressure trigger because it is more sensible to the patient's effort and does not need negative pressure to be produced in the circuit to trigger the ventilator; A small quantity of flow entering the inspiratory valve is enough.

Moreover, the adaptable inspiratory trigger is a possibility immediately accessible in most home ventilators. Some of these also recommend automated complex trigger algorithms in which the flow-time waveform is utilized to trigger the ventilator. Leaks may significantly influence trigger function, either by inhibiting the detection of patient inspiratory effort (leading to ineffective inspiratory effort) or by simulating an inspiratory flow (when using flow triggering) or moving the EPAP

level below the trigger threshold (when using pressure triggering), both conditions being capable of leading to auto-triggering.

Clinically, the patient inspiratory effort can be sensed by touching the chest or abdomen, observing that a ventilator-delivered breath does not accompany the movement of the chest or abdomen. To solve an ineffective triggering, the sensitivity should be set as high as possible. When auto-PEEP associated with dynamic hyperinflation is noted, one can attempt to raise PEEP slowly monitoring the resolution or attenuation of asynchrony, unusually exceeding 10 cmH_2O, or decreasing the pressure support level or to reduce inspiratory time in VCV.

Double triggering is when ventilator produce two consecutive breaths in answer to patient respiratory muscle effort. In this case, neural inspiratory time is more extended than the ventilator inspiratory time. Usually, the first trigger is from the patient effort.

Auto triggering occurs when a patient receives a mechanical breath in the absence of inspiratory effort. This event is due to artifacts in the ventilator; it improperly recognizes a flow or pressure fluctuation in the circuit as being patient involuntary respiratory muscle effort, such as the existence of condensate in the circuit, or the transmission of intrathoracic pressure variations because of cardiac activity due to systolic ejection.

Reverse triggering happens when patient inspiratory muscle effort emerges from reflex mechanisms triggered by mechanical insufflation with a ventilator-controlled breath.

20.6 Cycling from Inspiration to Expiration

Cycling should correspond with the end of patient effort. During mechanical ventilation switching from inspiration to expiration can be time-cycled or flow-cycled. In flow-cycled modes, cycling happens as inspiratory flow reduces to a defined percentage of the peak inspiratory flow, which is assumed to indicate the end of inspiratory effort.

The criteria applied to end inspiration may have a clinically important effect on the quality of ventilation. Moreover, when flow cycling is applied, leaks may also limit switching into expiration because, in an attempt to sustain pressure, the flow rate is supported above the level at which cycling into expiration occurs. Both these conditions may influence to patient-ventilator expiratory asynchrony. In older ventilators cycling into expiration was set at 25% of peak flow, but more modern ventilators offer adjustable values. In patients with obstructive disease, intrinsic positive end-expiratory pressure (iPEEP) can decrease the useful trigger threshold leading to a significant delay between the beginning of patient inspiratory effort and ventilator triggering or even to ineffective efforts. In this case, is necessary to apply an external PEEP may counterpoise iPEEP, improving patient-ventilator synchrony.

20.7 Expiratory Asynchrony

Each patient requests a customized setting based on respiratory mechanics. During the expiratory phase, asynchrony may be due to the presence of auto-PEEP, that can be identified by the evaluation of flow waveform (flow does not reach zero). Trigger problems related to auto-PEEP may improve with applied external PEEP, approximately equal to 80% of auto-PEEP. Expiratory asynchrony can be recognised as the delay in the relaxation of the expiratory-muscle activity before the subsequent mechanical inspiration. There is an overlay between expiratory and inspiratory phase. In expiratory asynchrony, termination of ventilator flow happens either before or after the patient ends the inspiratory effort. Tassaux et al. studied ten intubated COPD patients with flow-cycle settings of 10, 25, 50, and 70% of peak inspiratory flow. Increasing the flow-cycle setting to greater than 25% of peak inspiratory flow decreased the duration of pressurization; diminished delayed cycling without inducing premature cycling; and decreased intrinsic PEEP, trigger delay, the magnitude of inspiratory effort needed to trigger the ventilator, and the number of non-triggered breaths [8]. Conversely, reducing the cycling pattern to less than 25% worsened patient-ventilator asynchrony. It demonstrated the need for continuous monitoring and adjustment of the flow-cycling criterion to optimize patient-ventilator interaction.

20.7.1 Delayed Cycling

The ventilator produces a breath with a longer inspiratory time than is wanted by the patient, that is, the ventilator can do to improve these asynchronies by directly regulating the inspiratory time setting. During PSV, the ventilator cycles to expiration when flow decreases to a set percentage of peak inspiratory flow. Insufflation tends to be longer with higher levels of pressure support and with increased airflow resistance. Higher levels of pressure support result in a higher peak flow that may shorten the neural inspiratory time, contributing to a mismatch between a long mechanical insufflation and a short neural inspiratory time. In COPD and asthma patients the shorter expiratory time contributes to worsening hyperinflation. Moreover, over assistance results in hyperventilation, hypocapnia, respiratory alkalosis, reducing respiratory drive and perpetuating the mechanism.

Premature cycling happens when the ventilator completes the inspiratory flow sooner than desired by the patient; that is, the inspiratory ventilator time is shorter than the patient neural inspiratory time.

In PSV mode, the principal strategy is to improve the cycling threshold percentage of peak flow, which can habitually be fixed between 5 and 70%. To improve premature cycling, the threshold should be reduced, and, to alter delayed cycling, the limit should be enhanced. In COPD patients, for the reason that their increased airway resistance, the reduction in the flow delivered by PSV is slighter. This

asynchrony can be modified by adjusting the cycling level, which is usually pre-set at 25%, to higher values, such as 45–55%.

20.8 Conclusion

In summary, patient in NIV presents different characteristics and disease that can predispose to the onset of multiple and complex asynchronies. It is important to try to recognize and minimize PVA to promote compliance with the NIV and therapeutic benefit. The choice of ventilatory mode and of ventilator settings are determinants that influence the incidence of asynchrony. The regulation of the ventilator during noninvasive PSV is often complex since the altered respiratory mechanics of COPD patients (that is, the elevated resistance and compliance and intrinsic positive end-expiratory pressure (PEEPi), concomitantly with the presence of air leaks, may profoundly interpose with the synchrony between the machine and the patient.

Once the clinician has recognised the patient's action and asynchronies by looking at ventilator waveforms, there are several interventions that can efficiently resolve the problem.

Cause of external interference has to be reduced (i.e., circuit leaks, secretions, circuit occlusions, and disconnections), because they can manage to variations in the waveforms and thus to misunderstanding. Furthermore, clinicians have to estimate the consequences of ventilator settings on the development of asynchrony and change them accordingly to improve synchronization. These cycling delays and ineffective inspiratory efforts are two of the usual forms of asynchrony.

In patients supporting prolonged pressure-support ventilation, cycling was found to be limited in more than 50% of the patients' breaths. When at the bedside, clinicians can improve the problem of cycling delays by varying the expiratory trigger sensitivity according to what they observe on the ventilator monitor. Otherwise, they can set the ventilator to open the expiratory valve as soon as a rapid variation from fast to slow is recognised in the reduction of the inspiratory flow. The interpretation of waveforms by the specialist eye is a good way of recognizing asynchronies and only the systematic practice of ventilator signals on display may help denote these asynchronies and at the same moment in driving the operator in his choice to change the settings.

Questions and Answers

1. The end of the life decision-making process about the intervention should consider:

   (a) Firstly the family members' preferences and wishes
   (b) The patient's preferences and desires if competent
   (c) The physicians can decide a caring plan without a discussion with the patient and the family members
   (d) None of the above
   (e) All of the above

   Answer: (b) The patient's preferences and desires if competent

2. The dosage of the morphine in patients at the end of life are treated with NIV?

   (a) It may be increased
   (b) It may be reduced
   (c) The NIV use does not modify the dose of the morphine
   (d) None of the above
   (e) All of the above

   Answer: (b) It may be reduced

3. In patients at the end of life with solid malignancies, the treatment with NIV in a safe setting?

   (a) It is not necessary
   (b) It is not beneficial
   (c) It is helpful for the patient
   (d) There is no relation between the setting and end of life treatment with
   (e) None of the above

   Answer: (c) It is helpful for the patient

4. If NIV does not guarantee the right comfort?

   (a) It should not be suspended
   (b) It should be suspended, and the use of the HFNC should be considered
   (c) The invasive mechanical intubation is an option although the patient refused it
   (d) The physicians may decide the best intervention
   (e) All of the above

   Answer: (b) It should be suspended, and the use of the HFNC should be considered

5. At the end of life, the ventilator setting is different from the configuration of the other treatment diseases?

   (a) Yes, it necessary a different modality and setting
   (b) No, it is the same
   (c) It is essential to start with a higher level of PEEP
   (d) None of the above
   (e) All of the above

   Answer: (b) No, it is the same

6. The discussion about the ethical aspects should be?
   (a) A critical component of the caring planning
   (b) The ethical aspects are well considered in recent guidelines
   (c) The ethical elements don't refer to the possibility that the NIV prolongs the suffering
   (d) All of the above
   (e) None of the above

   Answer: (a) A critical component of the caring planning

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Chapter 21
Intensive Care Unit Ventilators Some Aspects in Noninvasive Mechanical Ventilation

Ebru Ortac Ersoy

Abbreviations

COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
ICU	Intensive care unit
NIV	Non invasive ventilation
PC-BiPAP	Pressure control, bilevel positive airway pressure
PEEP	Positive end expiratory pressure

21.1 Introduction

The standard management for patients in the ICU suffering from severe acute respiratory failure is becoming increasingly to consider NIV as a first option. In order to decide whether therapy with NIV is indicated, a careful analysis of both the type and the underlying cause of respiratory failure is necessary [1]. The success of NIV in the acute setting, is dependent on proper patient selection, interface, and ventilator capabilities with regard to leak management and auto-triggering. The choice of a ventilator may be crucial for the success of NIV in the acute setting, because intolerance and air leaks are significantly correlated with NIV failure especially in acute respiratory failure [2, 3].

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In this section two acute respiratory failure patients (First COPD exacerbation, and second acute de novo respiratory failure because of pneumonia and multiple malign metastases) will be discussed and recommendations for NIV with ICU ventilators will be written.

Case 1

A 66-year-old man with a history of end-stage COPD, having been intubated within the last month for a similar exacerbation, arrived by ambulance to our Emergency Department. The chief complaint was severe difficulty breathing which came on gradually. Initial assessment noted tachypnea with nasal flaring and purse lipped breathing, as well as bilateral wheezing and wet cough.

This patient is well known to our staff with multiple prior admissions. He has home mechanical ventilation as BiPAP–ST and is having long term oxygen therapy. Based on history, it was anticipated that this patient would be intubated and admitted to the ICU.

He had a smoking history of 1 pack per day for the past 47 years. On examination he appears cachectic and in severe respiratory distress. His neck veins are mildly distended. Lung examination reveals a barrel chest and poor air entry bilaterally, with severe inspiratory and expiratory wheezing. Heart and abdominal examination are within normal limits. Lower extremities exhibit scant pitting edema. He has beard. Arterial blood gas examination reveals respiratory acidosis (PH: 7.25, $PaCO_2$: 86 mmHg, PaO_2: 55 mmHg, SaO_2: 85%) although he was using his home ventilator for 24 h before admission (In acute illness CO_2 rebreathing occurred).

In ICU NIV began with ICU ventilator. The setting of NIV was as below:

On NIV mode spontan-CPAP was began with ΔPsupp: 18 mmHg PEEP: 5 mmHg, FiO_2: 60%, ramp: 0.40 ms.

On this settings, patient became confused and apneas occurred. He could not trigger the ventilator. Arterial blood gases became more acidotic (PH: 7.21 $PaCO_2$: 90 mmHg, PaO_2: 70 mmHg, SaO_2: 92%). We thought leak occurred because of his beard. Although the ICU ventilators have leak compensation, if the leak reaches above 80% this can be problem for triggering the ventilator and apnea occurred. Both severe respiratory acidosis and leak from mask patient became more sick. His mouth and nose dried. We shaved the beard and changed the ventilator mode to PC-BiPAP, added heated humidifier and settings was made as below:

PEEP: 5 mmHg, FiO_2: 60%, ramp: 0.10 ms, Pressure support: 18 mmHg, respiratory rate: 15/min, I/E ratio: 1/2, Trigger sensitivity: 2 L/min.

Arterial blood gases improved (PH: 7.37 $PaCO_2$: 55 mmHg, PaO_2: 78 mmHg, SaO_2: 94%).

Case 2

A 30-year-old man with acute respiratory failure due to pneumonia admitted to ICU. He has multiple pulmonary metastasis because of malign mesenchymal cancer. On examination he appears in severe respiratory distress. He was tachypneic.

His arterial blood gases reveals hypoxic respiratory failure (PH: 7.48, $PaCO_2$: 28 mmHg, PaO_2: 55 mmHg, SaO_2: 85%). NIV started with ICU ventilator.

The initial setting was as below:

Fig. 21.1 Pressure controlled ventilation as; PEEP: 5 mmHg, FiO_2: 55%, ramp: 0.40 ms, Pressure support: 12 mmHg, respiratory rate: 12/min, İnspirium time: 1.7 s, Trigger sensitivity: 2 L/min. On this settings autotriggering was seen on waves (first). We increased the respiratory rate to 29/min. Patient ventilator synchrony occurred (Second) although 73% leak

On NIV mode spontan-CPAP was began with ΔPsupp: 16 mmHg PEEP: 5 mmHg, FiO_2: 60%, ramp: 0.10 ms, Trigger sensitivity: 2 L/min.

On this settings he became tachypneic and ventilator waves reveal double triggering. Although leak compensation of ICU ventilator, we thought that it is due to leak (64%) from mask. We increased trigger sensitivity to 4 L/min and tighten the mask. On this settings apnea occurred. Patients NIV settings were revised. Mode changed to pressure controlled ventilation as; PEEP: 5 mmHg, FiO_2: 55%, ramp: 0.40 ms, Pressure support: 12 mmHg, respiratory rate: 12/min, İnspirium time: 1.7 s, Trigger sensitivity: 2 L/min. On this settings autotriggering was seen on waves. We increased the respiratory rate to 29/min. Patient ventilator sencrony occured (Fig. 21.1) although 73% leak. Because leak compensation of ICU ventilator is good enough.

21.2 Discussion

Here the cases with acute respiratory failure due to COPD exacerbation and *de novo* respiratory failure treated with ICU ventilators in NIV modes were described.

Even if any ventilator can be theoretically used to start NIV both in acute and chronic respiratory failure, success is more likely if the ventilator is able to (a) adequately compensate for leaks; (b) let clinician continuously monitor patient-ventilator synchrony and ventilator parameters due to a display of pressure-flow-volume waveforms and a double-limb circuit; (c) adjust the fraction of inspired oxygen (FiO_2) to assure stable oxygenation; and (d) adjust inspiratory trigger sensitivity and expiratory cycling as an aid to manage patient-ventilator asynchronies [3, 4].

In first case we used ICU ventilator for NIV in COPD exacerbation for decreasing CO_2 levels and avoiding CO_2 rebreathing. Patient had hypercapnia although using home ventilator. Because he had high respiratory rate and one limb circuit of home NIV, he rebreated CO_2. Using two limb circuit ventilator can avoid CO_2 rebreathing especially in patients with tachypnea. It is important to use two limb circuit in patients with high arterial CO_2 levels.

Types of ventilators have been commonly used for NIV in acute settings are regular ICU ventilators (with no NIV capabilities or algorithm), ICU ventilators with NIV algorithm, and dedicated NIV ventilators. ICU ventilators are more powerful and have more adjustable features (trigger type and sensitivity, slope of pressurization, cycling criteria) and monitoring capabilities [4, 5].

New generation ICU ventilators has good leak compensation, which allows a partial or total correction of air leak-induced patient-ventilator asynchrony, even with large amount of leaks. If leak flow reaches the trigger threshold, auto-triggering occurs. On the other hand, if the leak is large enough, the ventilator may not detect respiratory efforts, or patient can not start the respiration leading to miss-triggering or apnea as in our first patient. Additionally, leaks can lead to aerophagia, odynophagia, dry mouth, eye irritation, and nasal symptoms, and noise may result, all of which reduce therapeutic compliance [5]. In acute settings both in *de novo* respiratory failure and acute on chronic respiratory failure, using ICU ventilators for NIV can be more successful because of patient–ventilator synchrony (leak compensation), monitoring patient, avoiding CO_2 rebreathing (two limb circuit).

The ventilators may automatically decrease trigger sensitivity according to the level of leak to avoid auto-triggering, but as the leak decreases, the trigger sensitivity increases. This can lead to miss-triggering, particularly if the change is larger than the inspiratory effort. If the change in leak is smaller than the inspiratory effort, miss-triggering is unlikely, though higher patient effort is required to reach this threshold [6]. In acute respiratory failure with air hunger as in our second patient because of patients high respiratory rate autotriggering can be occurred and increasing ventilator respiratory rate can solve the problem.

In acute respiratory failure, NIV algorithms provided by ICU ventilators can reduce the incidence of asynchronies because of leaks, thus confirming bench test results, but some of these algorithms can generate premature cycling.

Key Teaching Points

- In acute respiratory failure especially patients with high CO_2 levels and high respiratory rate NIV with ICU ventilators with an O_2 blender and dual limb circuit is more appropriate than only NIV ventilators
- ICU ventilators have dual limb circuit for avoiding CO_2 rebreathing. In patients with COPD exacerbation dual limb circuit has an advantage in lowering CO_2.
- NIV with ICU ventilators can avoid patient ventilator asynchrony in acute settings by leak compensation but there is a wide range of heterogeneity among ICU ventilators in the leak compensation algorithms.

- Too sensitive trigger, especially if flow based, may induce auto triggering during NIV with substantial air leaks and, consequently, ventilator dyssynchrony due to unwanted efforts.
- NIV algorithms mostly improve ICU ventilator performance in NIV, however, modifications still have to be carried out to prevent triggering and cycling asynchrony.

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Part V
Clinical Cases in Noninvasive Ventilation: NIV in Procedures Applications

Chapter 22
Non Invasive Mechanical Ventilation and Echocardiographic

Dusanka Obradovic and Uros Batranovic

Abbreviations

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ATS	American Thoracic Society
BGA	Blood gas analysis
BNP	Brain natriuretic peptide
COPD	Chronic obstructive pulmonary diseases
CPAP	Continuous positive airway pressure
CPH	Chronic pulmonary hypertension
CRP	C reactive protein
CTPA	Computed tomographic pulmonary angiography
DOT	Domiciliary oxygen therapy
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction

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ERS	European Respiratory Society
HDU	High Dependency Unit
ICU	Intensive Care Unit
IVS	Interventricular septum
LMWH	Low molecular weight heparin
LV	Left ventricle
NIV	Noninvasive ventilation
PE	Pulmonary embolism
PEEP	Positive end-expiratory pressure
PPV	Positive pressure ventilation
PRV	Pulmonary vascular resistance
RF	Respiratory failure
RV	Right ventricle
RVSP	Right ventricular systolic pressure
TAPSE	Tricuspid annular plane systolic excursion
TEE	Transesophageal echocardiography
TRV	Tricuspid regurgitation velocity
TTE	Transthoracic echocardiography
TV	Tricuspid valve
VCI	Vena cava inferior

22.1 Introduction

Noninvasive ventilation (NIV) is generally accepted therapeutic procedure for the patients with acute and chronic respiratory failure (RF). Indications for the NIV in patients with RF (acute or chronic) are defined according to the latest guidelines [1]. The indications with the strongest level of recommendations are exacerbation of chronic obstructive pulmonary disease (COPD) with hypercapnic acidosis and cardiogenic pulmonary edema. Other indications for patients with acute RF (ARF), according to the ERS/ATS guidelines have conditional recommendation (Table 22.1).

The diagnostic procedures revealing the suspected cause of the RF in patients on NIV are usually restricted to bedside procedures. Among them echocardiography is one of the most used in everyday practice. There are two types of echocardiographic examinations with various imaging modalities and techniques. Point of care transthoracic echocardiography (TTE) as noninvasive, readily available procedure is emerging as an important bedside diagnostic toll in acute setting (Fig. 22.1). Due to the proximity of the esophagus, transesophageal echocardiography (TEE) provides more accurate information about heart structure and function even in patients with suboptimal TTE visualisation, but it is invasive, more costly and is considered as valuable complementary tool.

TTE gives us the information about the size of the cardiac chambers, wall thickness, systolic and diastolic function of the ventricles, about morphology and function of the valves, presence of thrombus in cardiac chambers etc. Thus, in patients

Table 22.1 Conditional recommendations for using NIV in patients with ARF [1]

Indications for using NIV in patients with ARF	Certainty of evidence	Recommendation
Acute asthma exacerbation	/	No
Immunocompromised patients	Moderate	Conditional
Postoperative patients	Moderate	Conditional
Palliative care	Moderate	Conditional
Trauma patients	Moderate	Conditional
Pandemic viral illness	/	No
Post-extubation in high risk group (prophylaxis)	Low	Conditional
Post-extubation RF	Low	Conditional
Weaning in hypercapnic patients	Moderate	Conditional
Prevention of hypercapnia in acute exacerbation of COPD	Low	Conditional

Fig. 22.1 Application of transthoracic echocardiography in patient treated with NIV

treated with NIV, TTE can provide very valuable information about the cause of RF e.g. ventricular dysfunction, pericardial effusions with tamponade, pulmonary embolism, acute valvular regurgitation etc. Uncertain etiology of respiratory failure and/or hypotension in critically ill patient is an example where the clinical question can be answered with TTE [4].

Case Presentation No 1: Pulmonary Embolism

A 45 years old female patient presented in the emergency department with clinical signs of RF and suspected diagnosis of severe acute exacerbation of COPD (AECOPD). She was treated for 20 years for COPD and she is on DOT (domiciliary oxygen therapy) for 5 years. During that period she had six AECOPD episodes requiring hospitalization. Echocardiography performed during recent hospitalization revealed signs of the chronic RV pressure overload consistent with chronic cor pulmonale: enlargement of right ventricle (end-diastolic RV/LV diameter <1.0) with abnormal RV wall thickness (0.6 cm), moderate tricuspid regurgitation with peak tricuspid regurgitation velocity (TRV) 3.6 m/s, estimated right ventricle

systolic pressure (RVSP) 52 mmHg, tricuspid annular plane systolic excursion (TAPSE) 17 mm.

At admission to the High Dependency Unit (HDU) the patient was tahi-dyspnoic, cyanotic, with positive hepatojugular reflux, hemodynamically stable, with sinus tachycardia on the ECG and with respiratory acidosis in blood gas analysis (BGA) (pH 7.30). Chest X ray revealed the hyperinflation with basal adhesions on both sides, without lung infiltrations. The patient was treated with bilevel oronasal positive pressure (Maquet Getinge group, Rastatt, Germany) and TTE was performed at the beginning of the NIV. The echo findings revealed signs consistent with acute-on-chronic right ventricle (RV) pressure overload with reduced RV systolic function (Fig. 22.2). Right ventricle was dilated (end-diastolic RV/LV diameter >1.0) with RV hypokinesia and positive Mc Connell sign. Interventricular septum was flattened, moderate to severe tricuspid regurgitation was revealed with the peak tricuspid regurgitation velocity (TRV) 4.17 m/s, estimated right ventricular systolic pressure (RVSP) 80 mmHg (vena cava inferior-VCI diameter was 23 mm, with <50% of collapse with a sniff), pulmonary artery acceleration time (Pacc) was 50 ms, tricuspid annular plane systolic excursion (TAPSE) 12 mm.

The value of D Dimer was extremely elevated (10.000 ng/mL). As the pulmonary embolism (PE) was suspected, low molecular weight heparin (LMWH) in therapeutic doses was started. Patient was treated with standard therapeutic protocol (inhalations of beta 2 agonist, corticosteroids) for AECOPD. Control BGA revealed the worsening respiratory acidosis (pH 7.27), with mental status change and patient was intubated and transferred to the intensive care unit (ICU). Diagnosis of PTE was confirmed with computed tomographic pulmonary angiography (CTPA) and LMWH treatment was continued as patient was hemodynamically stable. After 48 h the BGA improved, patient was weaned from the mechanical ventilation, treated with NIV the following 2 days and transferred to the general ward with oxygen therapy.

This is a typical case of pulmonary embolism as “the greatest masquerader” in internal medicine. Considering the BGA findings, patient received appropriate initial treatment for AECOPD. Acute PE was suspected based on TTE findings of acutisation of CPH with RV failure.

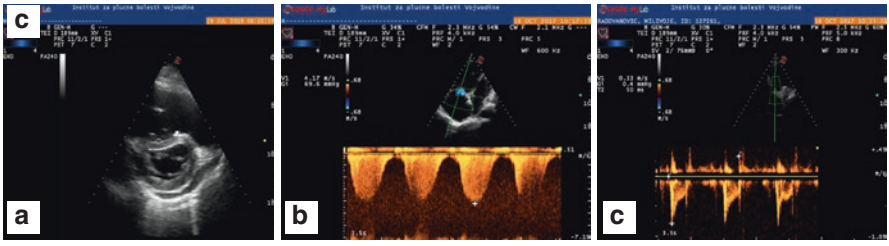


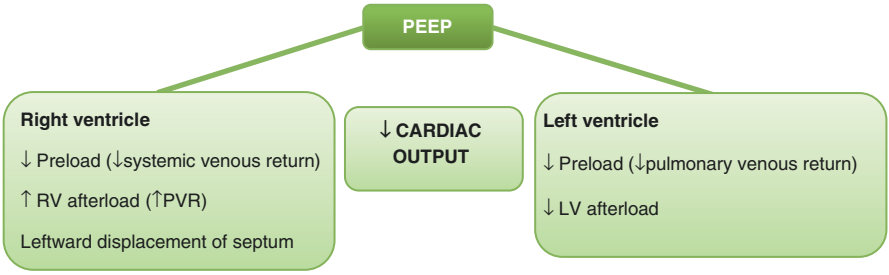
Fig. 22.2 Echocardiographic signs of chronic pulmonary hypertension acutisation (**a**) flattened interventricular septum, (**b**) tricuspid regurgitation velocity, (**c**) pulmonary artery acceleration time-Pacc)

TTE is usually the initial imaging diagnostic tool used for cardiac function assessment in acute conditions, especially in cardiac emergencies. Findings on the echocardiography are influenced by many specific pathophysiological changes in critically ill patients. These changes are connected to the volume status of the patient, metabolic status, mechanical ventilation (invasive or noninvasive) with different modes of ventilation, treatment with the inotropes and vasopressors, pulmonary disorders (pneumothorax, pleural effusions, acute respiratory distress syndrome-ARDS etc.), treatment with the extracorporeal membrane oxygenation-ECMO [2].

Regarding the use of echocardiography in patients who are treated with NIV, one has to be aware that positive pressure ventilation (PPV) has influence on hemodynamic parameters of the heart. Hemodynamic parameters should be interpreted in light of changes in transmural pressure (difference between intraventricular and intrapleural pressure). Positive pressure ventilation and applied PEEP (positive end-expiratory pressure) change the determinants of cardiac output e.g. preload, contractility and afterload (Scheme 22.1). PEEP influence the venous return by decreasing it and preload decreases. Afterload depends on the transmural pressure. In the case of applied PEEP intrapleural pressure increase, so the afterload of left ventricle (LV) decreases. Regarding the RV, afterload increase because of the increase in the pulmonary vascular resistance (PVR) (compression on the pulmonary vessels which leads to an increase of the transpulmonary arterial pressure) [3].

The usually measured echocardiographic parameters are also influenced by PEEP. In a prospective study conducted by Au et al. [4], 107 patients with obstructive sleep apnea were included. The patients were on CPAP (continuous positive airway pressure) therapy and TTE was performed 15 min before and after starting CPAP. The results of this study showed significant changes in heart dimensions and LV and RV systolic function, without changes in diastolic function. The clinically significant changes in VCI diameter and VCI variability were found as the changes in tricuspid regurgitation velocity. The authors recommended alternative methods for predicting right heart pressure.

The main indirect findings on RV pressure overload in pulmonary embolism are the consequences of acutely increased pulmonary artery/right heart pressures, but with low overall sensitivity for the diagnosis of pulmonary embolism of about



Scheme 22.1 The influence of applied PEEP on the cardiac output

50–60% [2]. Moreover, acute cor pulmonale may also develop as a consequence of AECOPD. In our case, although we observed worsening in comparison with the echocardiographic findings from recent hospitalization, our suspicion of pulmonary embolism was not based only on echocardiographic findings, but also on the clinical presentation and D-dimer test results. Nevertheless, according to our experience, echocardiographic examination is still useful in patients on NIV, especially if the patient is not transportable, when TTE may be the only immediately available and appropriate imaging investigation.

Case Presentation 2: Septic Cardiomyopathy

Male, 45 years old patient was admitted to the HDU due to chest discomfort accompanied with cough, fatigue and fever for 3 days. In past medical history patient had myocardial infarction with preserved ejection fraction (EF) treated with the primary coronary intervention 2 years ago. Patient presented with signs of respiratory distress, he was tachycardic, normotensive, with hypoxemia in BGA. Physical examination revealed diffuse expiratory wheezes. The diagnosis on the admission was cardiogenic oedema and CPAP (Maquet Getinge group, Rastatt, Germany) was started, with PEEP 5 cmH_2O. TTE was done immediately after the CPAP was started and showed reduced ejection fraction of 40% with global hypokinesia. ECG findings, except sinus tachycardia, were unremarkable, the values of cardiac biomarkers were inconspicuously elevated (high sensitive troponin and creatine kinase slightly elevated, MB fraction within normal range), and NT pro-BNP (N-terminal pro-brain natriuretic peptide) was slightly elevated. Procalcitonin and CRP (C-reactive protein) were elevated. Lactate level was also very high (8 mmol/L). Chest X ray revealed massive pleuropneumonia in right lower lobe. Antibiotics and fluid therapy with crystalloids were initiated. Patient started to deteriorate and was transferred to the intensive care unit (ICU) due to refractory hypotension and worsening hypoxemia requiring intubation and mechanical ventilation. The diagnosis of septic shock was established, vasopressors and inotropes were initiated with lung protective volume-controlled mechanical ventilation. Repeated TTE shown worsened EF of 25% with no changes in cardiac biomarkers. ECG was also unremarkable. The diagnosis of septic cardiomyopathy was established. Despite all implemented therapeutic procedures patient died. According to the autopsy report, no changes were found on epicardial coronary arteries.

Echocardiography has proven to be an important alternative to invasive hemodynamic measurements for the initial, non-invasive hemodynamic assessment in the acute setting. Echocardiography is also the best bedside method to assess cardiac function repeatedly and heart ultrasound is increasingly used for initial hemodynamic monitoring to guide fluid therapy**.**

Septic cardiomyopathy occurs in 60–80% of patients with septic shock according to the results of transthoracic echocardiography [5]. Routine coronarography is not indicated as TTE is noninvasive and less expensive method for evaluation of LV function especially in critically ill patients, like in the patients with sepsis and septic shock. In clinical practice the diagnosis of septic cardiomyopathy is not straightforward since all reference values for cardiac function parameters are normalized to

afterload values of healthy volunteers. In distributive shock afterload is strikingly reduced, and therefore ejection fraction in septic shock is considered a measure of afterload, more than a measure of contractility. This explains why correction of LV afterload by norepinephrine may unmask septic cardiomyopathy [6].

On the other hand, the influence of mechanical (noninvasive or invasive) ventilation on the LV and RV function is well known [3]. PEEP decreases LV afterload as a consequence of increased intrapleural pressure by lowering LV transmural pressure. Moreover, LV compliance is decreased via effects of PEEP on the interventricular septum (IVS) (leftward shift of the IVS).

If the patient has a septic cardiomyopathy, the positive pressure ventilation may reduce LV stroke volume with unpredictable effect on RV function. This is the reason why serial evaluations have to be done in critically ill patients, not just as diagnostic tool but also as a guidance for the hemodynamic therapy.

Case Presentation 3: NIV in Patient with Microcellular Carcinoma and Endocarditis

Patient 37 years old, male, presented in emergency department with respiratory deterioration, tachycardia, hypotension, regurgitant heart murmur in right parasternal part of the thorax and fever. The patient has malignant diseases (microcellular carcinoma) in the left lung confirmed by bronchoscopy 6 months ago. He was treated with chemotherapy 2 weeks ago. He is also i.v. drug user and allergic to Penicillin. The BGA revealed hypoxemia, on the chest X ray no changes were found comparing with the findings from 1 month ago (tumor in left lower lobe, with mediastinal lymphadenomegaly). NIV was started as a palliative therapeutic procedure (CPAP, Maquet Getinge group, Rastatt, Germany) with total face mask. The inflammatory biomarkers were elevated (CRP 300 mg/L, procalcitonin 8 ng/mL). Blood cultures were obtained and TTE was performed. Oscillating mass on tricuspid valve was seen and diagnosis of endocarditis was suspected. Patient were transferred to the ICU. As the transesophageal echocardiography (TEE) was indicated, the Janus mask (Biomedical srl, Florence, Italy) was applied, with the special hole for endoscopic probes. TEE revealed a vegetation on the tricuspid valve. Empiric antibiotic therapy (vancomycin 30 mg/kg bid) was started and patients was ventilated noninvasively until the BGA were improved. Blood cultures (3 samples) were positive for Staphylococcus aureus. Cardiac surgery was not considered because patients had serious contraindications for surgery (congestive heart failure, fungal infection, persistent sepsis, recurrent septic emboli, conduction disturbances caused by septal abscess). After 72 h patient improved, he was afebrile, hemodynamically stable, and transferred to the general ward where he was treated with oxygen therapy and antibiotics for 4 weeks. Patient was discharged from hospital after 2 months and continued with oncology treatment.

Transoesophageal echocardiography (TEE) is very important cardiovascular imaging modality. It provides more accurate information than TTE in several specific conditions and areas, like cardiac surgery, interventional cardiology, anesthesia etc. General indications for TEE are evaluation of cardiac structure and function when the TTE is nondiagnostic, intraoperative TEE, TEE for guidance of

transcatheter procedures and in critically ill patients. Specific indications are connected to the need for the detailed evaluation of prosthetic heart valves, open heart and thoracic aorta surgical procedures, for the patients where the TTE images are compromised because of the mechanical ventilation, chest wall deformities, injuries, when the endocarditis is complicated with paravalvular abscesses etc. [7]. TEE can be performed in the patients on NIV with appropriate interface. Regarding the sedation guidelines by non-anesthesiologist [8], they propose a moderate sedation when TEE is performed, because the profound sedation can aggravate the vital signs, so they should be monitored continuously.

In our case presentation the TTE maybe was sufficient for endocarditis diagnosis, but concerning the fact that the patient is an i.v. drug user, endocarditis of the native valve can be complicated with paravalvular abscess. This can be overlooked, especially in patients ventilated with positive pressure ventilation, when the TTE images are often compromised.

Key Teaching Points

- Echocardiography can reveal many of respiratory failure causes
- TTE should be performed in all patients on NIV
- The findings on echocardiography in patients treated with NIV have to be analyzed with consideration of the influence of the positive pressure ventilation on the hemodynamic and echocardiographic parameters
- Use TEE in specific indications, do not use TEE routinely in patients on NIV
- If the TEE is performed do not sedate patient profoundly

Questions and Answers

1. Which is the main reason to perform echocardiography in patients treated with NIV:

   (a) To assess size of cardiac chambers
   (b) To assess systolic and diastolic heart function
   (c) To assess morphology and function of the heart valves
   (d) All of the above

   Answer: (d) All of the above
2. In patients treated with NIV echocardiography can help us to:

   (a) Reveal the cause of respiratory insufficiency
   (b) Modify therapy
   (c) Modify NIV settings
   (d) All of the above

   Answer: (d) All of the above

3. Positive pressure ventilation and applied PEEP influence hemodynamic parameters by:

   (a) Decreasing preload of the right ventricle
   (b) Decreasing afterload of the right ventricle
   (c) Improving cardiac output
   (d) Increasing afterload of the left ventricle

   Answer: (a) Decreasing preload of the right ventricle
4. In patient with septic shock and established coronary artery disease, presenting with cardiogenic oedema and with applied NIV we can see:

   (a) Changes of in the right ventricular systolic pressure
   (b) Changes in the left ventricular ejection fraction induced by septic cardiomyopathy and reduced afterload
   (c) Changes in the aortic flow velocity
   (d) Changes in the mitral flow velocity

   Answer: (b) Changes in the left ventricular ejection fraction induced by septic cardiomyopathy and reduced afterload
5. Transeosephageal echocardiography is indicated in patients treated with NIV with:
   (a) Myocardial infarction
   (b) Pulmonary embolism
   (c) Endocarditis with suspected paravalvular abscess
   (d) Pericardial effusion

   Answer: (c) Endocarditis with suspected paravalvular abscess

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Chapter 23
Lung and Diaphragm Ultrasound for Monitoring Patient's Ongoing Non-invasive Mechanical Ventilation

Eva M. Tenza-Lozano

Abbreviations

AChR-Ab	Autoantibodies against the acetylcholine receptor
BIPAP	Bilevel positive airway pressure
CPAP	Continuous positive airway pressure
CT	Computerized tomography
DE	Diaphragmatic excursion
DT	Diaphragm thickness
EPAP	Expiratory positive airway pressure
FiO_2	Fractional inspired oxygen
HCO_3	Bicarbonate
ICU	Intensive Care Unit
IPAP	Inspiratory positive airway pressure
IV	Intravenous
LUS	Lung ultrasound
NIMV	Non-invasive mechanical ventilation
O_2	Oxygen
pCO_2	Arterial carbon dioxide tension
pO_2	Arterial oxygen tension
TI	Thickening fraction

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Real Case Clinic

23.1 Introduction

We present the case of a 52-year-old female was admitted to hospital with a 2-day history of fluctuating weakness in the arms and shoulders and generalized fatigue. She also complained of ptosis, diplopia, dysphagia and dysarthria. There was no evidence of respiratory insufficiency at admission. The patient was attended by a neurologist in the Emergency Department and admitted to an Intensive Care Unit (ICU). Serologic test (autoantibodies against the acetylcholine receptor, AChR-Ab) and electrophysiologic studies confirm the diagnosis of myasthenic crisis. Microbiological culture was negative. Pyridostigmine, Methylprednisolone and Immunoglobulin therapy was administered.

23.2 Complementary Explorations

- Hemogram: Hemoglobin 16.7 g/dL, Hematocrit 48%, 6800 leukocytes/mm^3 (neutrophils 83%), platelets 267,000/mm^3.
- Biochemistry: glucose 121 mg/dL, creatinine 0.9 mg/dL, sodium 141 mEq/L, potassium 4.1 mEq/L, C-reactive protein 30 mg/L, procalcitonin 3 μg/L, total bilirubin 0.7 mg/dL, HbA1C 10.0 g/L, B12 vitamin 3132 pg/mL, negative antinuclear antibodies, anti DNA antibodies 31.9, IgA 230 mg/100 mL (normal 70–390), IgG 900 mg/dL (normal 650–1500), IgM 200 mg/dL (normal 40–345), IgE 165 mg (normal 0–100), C3 100 mg/dL (normal 83–177), C4 32 mg/dL (normal 15–45), TSH 10.2 μU/mL. T4 2.0 μg/dL, T4L 1.0 ng/dL, T3 72 ng/dL
- Gasometry at admission: pH 7.42, pO_2 70 mmHg, pCO_2 37 mmHg, HCO_3 24 mmol/L, lactate 1.6 mmol/L.
- Electrocardiogram: sinus rhythm at 74 beats per minute.
- Ac anti-AChR positive.
- Chest CT scan (computerized tomography) in the second day: consolidation pattern in the right lung base (pneumonia), didn't show evidence of thymoma or thymus hyperplasia.
- Electromyography done by repetitive nerve stimulation at 3 hertz shows a decrement ranging from 10 to 34% confirming myasthenia gravis (ocular and deltoid muscles) (Fig. 23.1).

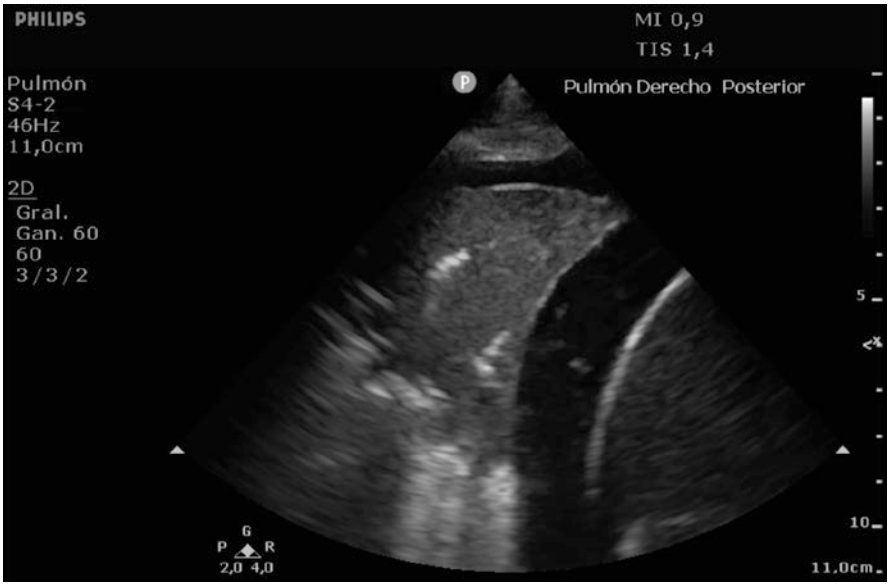

Fig. 23.1 Lung ultrasound corresponding to consolidation pattern in the basis of right lung

23.3 Discussion

In the second day in ICU the patient developed respiratory failure. Non-invasive mechanical ventilation (NIMV) was therefore commenced (BIPAP Vision, Respironics) with initial an inspiratory positive airway pressure (IPAP) of 15 cmH_2O with an expiratory positive airway pressure (EPAP) of 5 cmH_2O and FiO_2 of 0.6%. Respiratory function stabilized with improvement in gas exchange. Lung Ultrasound (LUS) revealed a lower-right lobar-type pneumonia that was confirmed in chest CT, and amoxicillin and clavulanic acid were given at a dose of 1 g three times a day for 7 days. Microbiological culture of sputum was negative. Episodes of sputum retention were treated with chest physiotherapy and tracheal suction via a nasopharyngeal airway.

The requirement for NIMV was continuous at first; periods of only a few minutes without it resulted in hypoxia. The ventilatory settings varied little during this period (IPAP 10–15 cmH_2O, and EPAP 5–7 cmH_2O and FiO_2 0.5–0.8%). Between days 4 and 6, the patient tolerated periods of continuous positive airway pressure (CPAP) and periods breathing oxygen via a high flow oxygen delivery facemask.

Lung and diaphragmatic ultrasounds were performed on days 2, 5, and 7. For LUS we used a convex probe with the patient in the supine position. On day 2, we observed pulmonary consolidation pattern in the right lung base on LUS. The consolidation pattern appeared as a tissue-like echotexture (hepatization) and hyperechoic punctiform images, corresponding to air bronchograms. Penetration of gas into the bronchial tree of the consolidation during inspiration produces an

inspiratory reinforcement of these hyperechoic punctiform images, is the so-called dynamic air bronchogram. In the following days, there was an improvement in the consolidation pattern, predominantly pattern of A-lines, probably due to the resolution of pneumonia with antibiotic treatment. LUS is an effective tool in the follow-up of pneumonia [1].

In the case of diaphragm ultrasound to measure DE (diaphragmatic excursion) we used a convex probe that we will place below the right costal margin (hepatic window), between the mid clavicular line and the anterior axillary line. We placed the ultrasound beam in the medial, cephalic and dorsal direction, so that it reached perpendicular to the posterior diaphragmatic dome (Fig. 23.2). In B mode we obtained a general view and then we changed to the M mode, and we observed the diaphragmatic movement like a hyperechoic sinusoidal wave that ascended in the inspiration and descended in the expiration. The height of the curve is the displacement or diaphragmatic excursion. In the first diaphragm ultrasound (day 2) we observed a DE less than 5 mm (Fig. 23.2). Some authors consider that DE smaller than 10–15 mm indicates the presence of diaphragmatic dysfunction [2, 3],

In diaphragm ultrasound we measured TI (thickening fraction) with a line probe that we placed in the right hemidiaphragm, in the zone of apposition of the diaphragm, on the midaxillary line between the eighth and tenth intercostal spaces, with the patient in a semi-decubitus position (20°–40°). First, we observed the diaphragm in M-mode as a hypoechoic structure between two echoic lines (the diaphragmatic pleura and the peritoneal membrane) with a hypoechoic band in the middle (diaphragm) (Fig. 23.3). We measured the diaphragmatic thickness at the end of expiration and inspiration. Under normal conditions it's greater in inspiration and lower in expiration. To calculate TI we used the following formula: TI = [(Thickness at the end of inspiration − Thickness at the end of espiration)/ Thickness at the end of espiration] × 100. The thickness of the diaphragm in non-forced expiration in ventilated patients is 2.4 ± 0.8 cm, values below 2 cm indicate atrophy [4]. A TI lower than 20–30% is related to diaphragmatic failure. In our

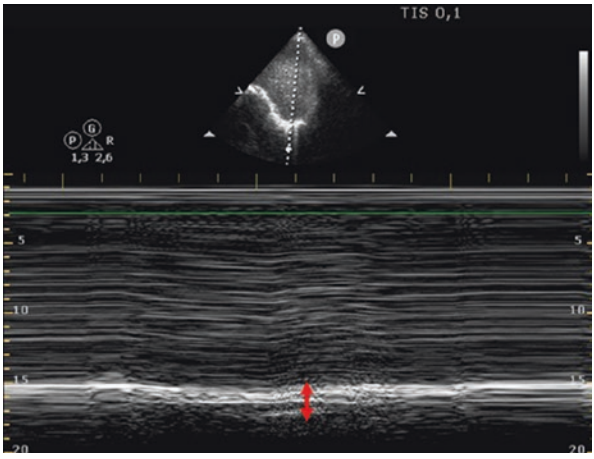

Fig. 23.2 Diaphragm ultrasound in M-mode. Diaphragm Excursion (red arrow), we can observe the absence of diaphragmatic movement which indicates diaphragmatic dysfunction

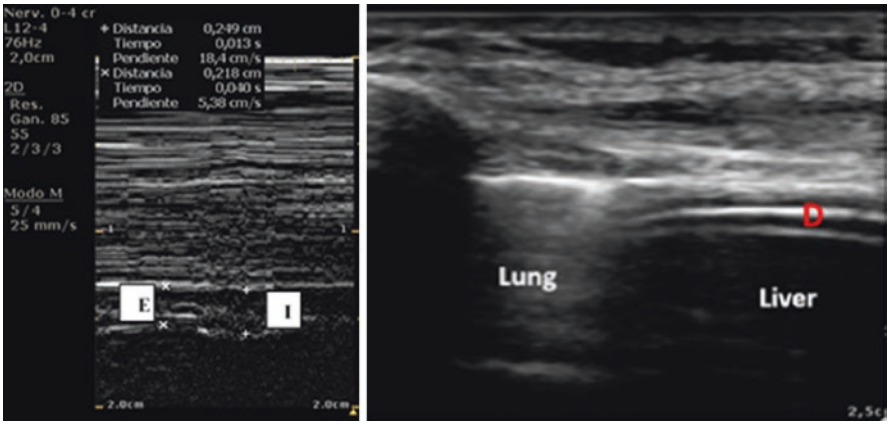

Fig. 23.3 Diaphragmatic ultrasound. M-mode (left): diaphragm thickness in inspiration (I) and expiration (E). We can observe a TI of 14% (diaphragmatic failure). B-mode (right): lung, liver and diaphragm (D)

patient a TI of 14% was calculated (Fig. 23.3), indicating diaphragmatic dysfunction. We observed improvement of diaphragmatic ultrasound parameters after several days of treatment (DE and TI). Therefore, diaphragmatic ultrasound can help us to observe the recovery of diaphragmatic function in the patient ongoing NIMV.

The patient was alert, cooperative and maintaining his own airway with NIMV. Although tracheal intubation had been considered on more than one occasion, this intervention was successfully avoided thanks to the use of NIMV. Regular neurological assessment confirmed the improvement motor and bulbar's function at the same time that improvement in the diaphragmatic indices (DE and TI) was observed. After 1 week in ICU, the patient was discharged to the neurology ward asymptomatic without NIMV.

Key Teaching Points

- LUS are useful to monitoring patients ongoing NIMV [5]. It allows estimate alveolar reaeration during NIMV and diagnose common lung diseases, such as pneumothorax, lung consolidation, pleural effusion and interstitial alveolar syndrome [6].
- LUS allowed to monitoring the improvement of ventilation in our patient, with a consolidation pattern (pneumonia) thanks to the antibiotic treatment and the use of NIMV. It also helped us rule out complications due to NIMV.
- Diaphragmatic ultrasound has been developed to assess diaphragmatic function. Parameters measured by diaphragmatic ultrasound are diaphragm movement or excursion (DE) during the respiratory cycle, and diaphragm thickening or thickening fraction (TI) [7, 8].
- Diaphragmatic ultrasound allowed us to diagnose and follow up multiple diseases that can cause diaphragmatic dysfunction, as is the case of myasthenic crisis.

Questions and Answers

1. What's the pattern that can be observed in patients with pneumonia ongoing NIMV?

   (a) Lung consolidation pattern
   (b) Dynamic air bronchogram
   (c) Hyperechoic punctiform images like a tissue-echotexture
   (d) All of the above.

   Answer: (d) All of the above
2. What is true in diaphragm ultrasound?

   (a) To measure diaphragmatic excursion (DE) we used a lineal probe that we will place below the right costal margin (hepatic window).
   (b) To measure DE in M mode we observed the diaphragmatic movement like a hyperechoic sinusoidal wave that ascended in the expiration and descended in the inspiration.
   (c) ED greater than 20 mm indicates diaphragmatic dysfunction.
   (d) All answers are false.

   Answer: (d) All answers are false.
3. How is diaphragmatic ultrasound performed to measure diaphragmatic thickening?

   (a) With a line probe that we placed in the right hemidiaphragm, in the zone of apposition of the diaphragm, on the midaxillary line between the eighth and tenth intercostal spaces.
   (b) A TI lower than 60% is related to diaphragmatic failure.
   (c) Diaphragmatic ultrasound can't help us to observe the recovery of diaphragmatic function in the patient ongoing NIMV
   (d) None of the above

   Answer: (a) With a line probe that we placed in the right hemidiaphragm, in the zone of apposition of the diaphragm, on the midaxillary line between the eighth and tenth intercostal spaces
4. What is the usefulness of lung ultrasound in patients ongoing NIMV?
   (a) To rule out complications due to NIMV.
   (b) To diagnose pneumothorax, lung consolidation, pleural effusion and interstitial alveolar syndrome.
   (c) LUS allows monitoring the improvement or worsening of respiratory ventilation.
   (d) All of the above

   Answer: (d) All of the above

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Chapter 24
Non Invasive Mechanical Ventilation and Bronchoscopy

Carmine D. Votta, Margherita Tozzi, and Giovanni Landoni

Abbreviations

FOB Fiberoptic bronchoscopy
NIV Non-invasive ventilation

24.1 Introduction

Since its introduction in 1968 by Ikeda [1], fiberoptic bronchoscopy (FOB) has progressively evolved and improved. Nowadays FOB is an essential and widespread tool for diagnostic and therapeutic purposes in several clinical settings. FOB's usefulness in the management of pulmonary diseases is well established and the main clinical indications are summarized in Table 24.1.

Although it is considered a safe procedure, FOB may hide some pitfalls, especially in patients with respiratory failure and in spontaneous breathing [2]. A decrease of 10–20 mmHg in arterial oxygen partial pressure usually occurs after uncomplicated bronchoscopies [3]. Furthermore, to make FOB's performance easier and to minimize patient's discomfort during the procedure, sedatives are often

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Table 24.1 Main indications to fiberoptic bronchoscopy in critically ill patients (Modified by Ref. [2])

Indication to fiberoptic bronchoscopy in critically ill patients
Airway aspiration
Airway bleeding
Airway assessment (e.g. acute inhalation injury, burns, trauma, tracheoesophageal fistula)
Airway management (e.g. difficult tracheal intubation, percutaneous tracheostomy, tracheal tube/double-lumen tube correct positioning evaluation, bronchial blocker insertion)
Airway stenosis
Atelectasis
Infections

administered [4]. Thus, in patients with limited respiratory function, performing FOB may be hazardous. Nevertheless, if such procedure is deemed indicated for the management of the patient, the clinician must balance risks and benefits of performing bronchoscopy. One promising strategy to enhance safety is performing FOB during non-invasive ventilation [5, 6].

This chapter will show, through a clinical case, the feasibility of awake fiberoptic-guided tracheal intubation during non-invasive ventilation.

Clinical Case

A 66-year-old woman, with a history of smoking, mild chronic obstructive pulmonary disease and obstructive sleep apnea treated with nocturnal continuous positive airway pressure presented to the emergency department because of fever, cough and increasing dyspnea in the last week.

At hospital admission she was awake, collaborative, tachypneic (respiratory rate was 28 breaths per minute) and clearly dyspneic. Blood pressure was 150/80 mmHg, heart rate 105 bpm, SpO_2 83% in room air, reaching 85% with oxygen in reservoir mask. Body temperature was 38.3 °C. At physical examination of the chest, crackles were present in the left basal and right mid-basal portions. Chest radiography showed a consolidation in the right lower lung lobe with mild pleural effusion which was confirmed with lung ultrasound.

At arterial blood gas analysis, pH was 7.32, pO_2 58 mmHg, pCO_2 48 mmHg, HCO_3^- 26 mmol/L, base excess −0.9, lactate 1.8.

The patient was first treated with non-invasive ventilation. After 30 min of non-invasive ventilation (NIV) the patient was still tachi-dyspneic (respiratory rate was 26 breaths per minute), SpO_2 was 90% and arterial blood gas analysis showed pH 7.33, pO_2 65 mmHg, pCO_2 47 mmHg, HCO_3^- 26 mmol/L, base excess −0.8, lactate 1.9.

Because of the limited patient's improvement, awake fiberoptic-guided tracheal intubation and invasive mechanical ventilation was considered the appropriate strategy as the patient was known to have a history of difficult intubation. Moreover, being the patient hypoxemic, interrupting NIV during the procedure could have been harmful. Thus, awake tracheal intubation was performed during non-invasive ventilation thanks to a particular mask for NIV, called Janus (Biomedical, Florence,

Fig. 24.1 Fiberoptic-guided tracheal intubation during non-invasive ventilation

Italy). The Janus mask is a full-face mask made-up with two halves joined together by a hinge and with a hole in the middle that allows the insertion of any kind of probe for procedures like bronchoscopy into patients' mouth or nose (Fig. 24.1) [7].

Before proceeding with intubation, a continuous infusion of low-dose remifentanil (0.05 mcg/kg/min) was started to achieve minimal sedation. The fiberscope with the tracheal tube embedded was inserted through the Janus hole and advanced into patient's airways till the trachea was reached. The tracheal tube was then left in place, the fiberscope removed and the patient deeply sedated and mechanically ventilated. During the procedure the patient remained stable with no hypotension nor desaturation observed.

24.2 Conclusions

There are several clinical scenarios in which the possibility to perform procedures like transesophageal echocardiography, upper gastrointestinal endoscopy or fiberoptic bronchoscopy during NIV would be desirable. This is particularly true in patients with acute respiratory distress and indication to NIV in whom endoscopy is deemed necessary for diagnostic or therapeutic purposes.

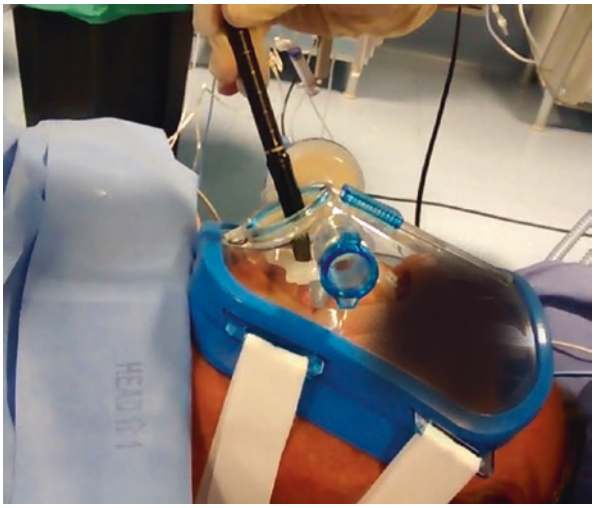

Fig. 24.2 Transesophageal echocardiography during non-invasive ventilation

Nowadays new available interfaces for NIV, like the Janus mask used in the clinical case described above in this chapter, allow simultaneously NIV and upper endoscopic procedures (Fig. 24.2) [8]. This may reduce respiratory complications.

Key Teaching Points

- Upper endoscopic procedures like bronchoscopy, gastrointestinal endoscopy or transesophageal echocardiography might be hazardous in patients with acute respiratory failure without advanced airway management
- The possibility to perform upper endoscopy during non-invasive ventilation might reduce procedure-related respiratory complications
- It is now possible to perform upper endoscopic procedures during NIV thanks to novel interfaces like the Janus mask

Questions and Answers

1. After an uncomplicated bronchoscopy, arterial oxygen partial pressure normally:

   (a) Does not change from its pre-procedural value
   (b) Increases 20–30% above baseline
   (c) Decreases by approximately 10–20 mmHg below baseline

   Answer: (c) Decreases by approximately 10–20 mmHg below baseline

2. In which of the following scenarios would you not perform bronchoscopy?

   (a) $PaO_2 < 90$ mmHg
   (b) $PaO_2 < 85$ mmHg
   (c) $PaO_2 < 75$ mmHg

   Answer: (c) $PaO_2 < 75$ mmHg

3. Which of the following statements is not correct?

   (a) Bronchoscopy may be performed in patients receiving non-invasive ventilation, without interrupting the ventilatory support
   (b) Non-invasive ventilation may not be applied to a patient who is already undergoing bronchoscopy, without interrupting the procedure
   (c) Fiberoptic-guided tracheal intubation may be performed during non-invasive ventilation, without interrupting the ventilatory support

   Answer: (b) Non-invasive ventilation may not be applied to a patient who is already undergoing bronchoscopy, without interrupting the procedure
4. While performing bronchoalveolar lavage in a ventilated patient, how much is the loss of tidal volume during each suctioning period?
   (a) 200–300 mL
   (b) 10–20 mL
   (c) 50–100 mL

   Answer: (a) 200–300 mL

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Chapter 25
Clinical Cases in Noninvasive Ventilation: NIV in Procedures Applications. Bronchoscopy

Szymon Skoczyński and Łukasz Minarowski

Abbreviations

ABG	Arterial blood gas analysis
AVAPS	Average volume assured pressure support
Bf	Bronchofiberoscopy
CF	Cystic Fibrosis
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
ECG	Electrocardiography
EPAP	Expiratory positive airway pressure
FiO_2	Fraction of inspired oxygen
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
NIV	Noninvasive positive pressure
NIV-BF	Noninvasive positive pressure facilitated bronchofiberoscopy
S/T mode	Spontaneous over timed mode
SaO_2	Oxygen saturation

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TB	Tuberculosis
$TcCO_2$	transcutaneous carbon dioxide
TV	Tidal volume
WBC	White blood cell count

Clinical Case 1: Noninvasive Positive Pressure Facilitated Bronchofiberoscopy Used in Continuation of a Weaning Trial

A 54-year-old, cachectic female with probable, but never confirmed by spirometry COPD was admitted to the pulmonary department from local ICU, where she was treated due to severe pneumonia and secondary acute respiratory failure. The ICU stay lasted for 21 days. After weaning the patient was treated with noninvasive mechanical ventilation in the ICU; however, due to persistent mild hypercapnia and a need to facilitate pulmonary diagnosis, she was admitted to the pulmonary department. During the ICU stay, the patient was suspected of having tuberculosis; however, at the time of direct transfer staining and BACTEC cultures after 25 incubation days, were negative. During the ICU stay, while still intubated, the patient required numerous bronchoscopies performed to clear the airways. Obtained at the ICU bronchial cultures contained multidrug-resistant pathogens including *Acinetobacter baumanii* and *Pseudomonas aeruginosa*. At the time of admission to the pulmonary department, the patient was still weary weak, have had evident respiratory effort and significant accessory respiratory muscles involvement. On entry, the patient was treated with colistin. However, the markers of inflammation were elevated (CRP 40 mg/L and WBC 13.9 × 10^3/μL). Arterial blood gases analysis revealed uncompensated respiratory acidosis (Table 25.1). It was assumed, that the respiratory failure was multifactorial, with hypercapnia caused by overlapping of severe cachexia and respiratory muscle wasting, exacerbated by prolonged hospitalization and invasive mechanical ventilation in the ICU. Airways narrowing and an excessive amount of sputum, in a patient with ineffective cough strength, caused observed hypoventilation. Observed hypoxemia was caused by ventilation to profusion mismatch in areas of infiltration and local atelectasis witnessed on an chest X-ray (Fig. 25.1).

Table 25.1 Blood gases in the course of treatment

	Arterial blood gases od admission	Arterial blood gases directly after the procedure	Arterialized blood gases 2 h after BF (patient still on NIV)	Arterialized blood gases 2 days after BF (NIV discontinued)
pH	7.3	7.27	7.4	7.44
pCO_2 [mmHg]	80.2	84.8	57.7	47.2
pO_2 [mmHg]	35	74	55.4	57.1
HCO_3^- [mmol/L]	38.6	37.8	34.7	31.6
SaO_2 [%]	62	92	89	91

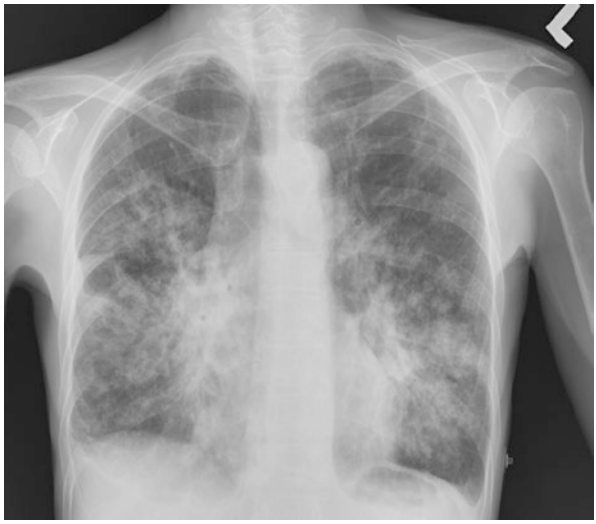

Fig. 25.1 Chest X-ray showing bilateral opacities localized predominantly mainly in lower lobes, general emphysema more evident on the left side and bilateral shallowing of costodiaphragmatic recesses

Based on this assumption and a need, to exclude potential postintubation trachea narrowing it was decided to perform NIV supported bronchoscopy. The indications were both diagnostic and therapeutic; however, considering previous weaning problems and intubation risk in a patient still with severe respiratory failure, NIV support was required.

NIV-Bf was performed according to previously described methods [1]. Sedation was performed with the use of midazolam and fentanyl intravenous administration, whereas xylocaine was used for local anesthesia. ResMed ASTRAL 150 and Philips Respironics PerforMax mask with bronchoscopy elbow were used during the procedure, which lasted for 22 min of total ventilation. The bronchoscopy lasted for 10 min. The machine was set in the S/T mode with following parameters: IPAP 20–27 [cmH_2O], EPAP 6–9 [cmH_2O], Inspiration time 0.8–1.0 [s], Rise time 100 [ms], Respiratory rate 18 [x/minute], Trigger low, and cycle settled on 15%, the supplementary oxygen flow was settled on 8 [L/minute] administered and blended in the machine which resulted in a median FiO_2 32 (29–35) [%]. The ventilatory parameters were adjusted based on patients SaO_2, heart and respiratory rate, observed on a cardio monitor and additional assessment of TV, minute ventilation, and leakage observed on the ventilator. During bronchoscopy, excessive amounts of bronchial secretions were removed and secured for bacteriological and TB cultures, no airway narrowing was observed. Directly after procedure arterial blood gases were collected. In the department, the patient was ventilated for an additional 2 h, after which the arterialized blood gas sample was collected. The blood gas results from bronchoscopy, as well as from the follow-up, are presented in Table 25.1. The procedure was safe and uncomplicated. Obtained bacteriological sampling revealed that the airway infection was caused by ESBL positive *Klebsiella pneumoniae*. Based on obtained cultures, antibiotic treatment was changed from Colistin into Meropenem. Within a few days, the patient clinical condition improved.

Clinical Case Example: Noninvasive Positive Pressure Facilitated Bronchofiberoscopy Used in Cystic Fibrosis Lung Disease Exacerbation

A 21-year old male with CF was admitted to the department due to exacerbation of CF-related lung disease. The symptoms were increasing gradually over 2 weeks before admission: loss of weight −4 kg, weak cough with expectorating small amounts of thick, purulent mucus, loss of appetite, fever up to 40 °C 2 days before hospitalization. The patient was chronically colonized with *MRSA* and *Pseudomonas aeruginosa*. Patients' clinical condition was severe, SpO_2 72%, HR 140 beats/min, temperature 37.9 °C. Multiple rhonchi and wheezing were audible in midscapular are with the diminishing of alveolar sound in suprascapular areas in both lungs. Lab results revealed WBC 15.2 × 10^3/μL, CRP 190 mg/L and hyperglycaemia 216 mg/dL. In arterial blood gas analysis, uncompensated respiratory acidosis was observed (Table 25.2). At the time of admission to the pulmonary department, the patient was weak, have had evident respiratory effort, significant accessory respiratory muscles involvement and he described constant pain in both hypochondriac regions suggesting diaphragm weakness. Initial therapy involved oxygen supplementation (2 L/min), chest physiotherapy (active breathing cycle and postural drainage), mucolytics both in inhalation and intravenous admission, mucoactive and secretive agents, intensive insulin therapy, empirical antibiotic therapy (ceftazidime+amikacine) in doses recommended for CF. Last available spirometry (before hospitalization) show FEV1 = 1.23 L (23%). NIV was introduced on the admission in S/T with AVAPS mode (Phillips Respironics Trilogy 100 with ResMed F20 face mask) with following parameters: IPAP 13–15 [cmH_2O], EPAP 8 [cmH_2O], Inspiration time 1.0 [s], Rise time 150 [ms], Respiratory rate 20 [x/minute], Trigger low, and cycle settled on 20%, the supplementary oxygen flow was settled on 5 [L/minute] administered and blended in the machine which resulted in a median FiO_2 32 [%]. Although initial therapy was successful in lowering of inflammatory status (CRP 51.5 mg/L), hypercapnia, difficulties with expectorating large amounts of hydrated mucus and marked dyspnea have persisted. To prevent a further decline in ABG the NIV-Bf was performed. Philips Respironics Trilogy 100 with Respironics PerforMax mask with bronchoscopy elbow were used during the procedure. The bronchoscopy time 4 min 30 s. The NIV machine was set in the S/T with AVAPS mode with following

Table 25.2 Blood gases in the course of treatment

	Arterial blood gases od admission	Arterial blood gases directly before the procedure	Arterialized blood gases 2 days after BF (NIV continued)
pH	7.323	7.323	7.427
pCO_2 [mmHg]	72.6	64.6	55.1
pO_2 [mmHg]	53.3	51.5	52.4
HCO_3^- [mmol/L]	31.1	28.1	32.6
SaO_2 [%]	83.7	82.6	87.3

parameters: IPAP 15–18 [cmH_2O], EPAP 8–10 [cmH_2O], Inspiration time 0.8–1.0 [s], Rise time 100 [ms], Respiratory rate 20 [x/minute], Trigger low, and cycle settled on 15%, the supplementary oxygen flow was settled on 8 [L/minute] administered and blended in the machine which resulted in a median FiO_2 32 (29–35) [%]. The total amount of 45 mL of thick purulent sputum was removed. The procedure was safe and uncomplicated. Obtained bacteriological sampling revealed that the airway infection was caused by *Pseudomonas aeruginosa*. Within 12 days, the patient clinical condition improved, and exacerbation symptoms have resolved. NIV was discontinued in ten the fifth day of the hospital stay. Control Bf performed on the seventh day of hospitalization showed improvement in mucosa condition and much lower sputum content in airways.

25.1 Discussion

Although looking into PubMed NIV-Bf may be considered as a new research area in clinical practice, it is increasingly used, especially in patients with respiratory failure.

Based on the pathophysiological rationale, NIV can be considered a useful instrument, facilitating BF in patients with respiratory failure. Using NIV enables to perform Bf in patients who before introducing this method would require intubation to facilitate procedure performance. In patients with respiratory failure bronchoscopy causes airway narrowing, increases airway resistance promoting SaO_2 drop; however, this may be limited by NIV support [1–3].

In patients with type two respiratory failure, especially with reduced respiratory muscle strength, BF, might exacerbate existing respiratory acidosis or even cause respiratory arrest.

It is especially crucial during weaning trials, where everything should be done to avoid the need for intubation, which was addressed in the current ERS/ATS clinical practice guidelines on noninvasive ventilation for acute respiratory failure, where it was stated that NIV should be introduced as soon as possible in extubated high-risk patients with respiratory distress [4]. NIV has a strong pathophysiologic rationale in patients with respiratory failure and a need to perform Bf which constrains the patient's airways because it increases minute ventilation, facilitates gas exchange together with downloading patients respiratory muscles effort.

Fortunately, the risk of all these complications may be diminished by the use of NIV, preferably when an S/T or hybrid mode with a secured backup rate is used. It is crucial, especially in patients with hypoxemic respiratory drive and a need to administered higher FiO_2 such as in the case of Bf. To avoid further pO_2 decrease, we have combined EPAP on a level of 6–9 [cmH_2O] with oxygen supplementation of 8 L/min. A slight pH drop was noted, but we are sure that increasing pO_2 from 35 to 74 mmHg without NIV support would end up with respiratory arrest (Table 25.1). This may be easily seen in our example where the use of a backup rate of 18 guaranteed stable minute ventilation in our patients with respiratory drive decreased by

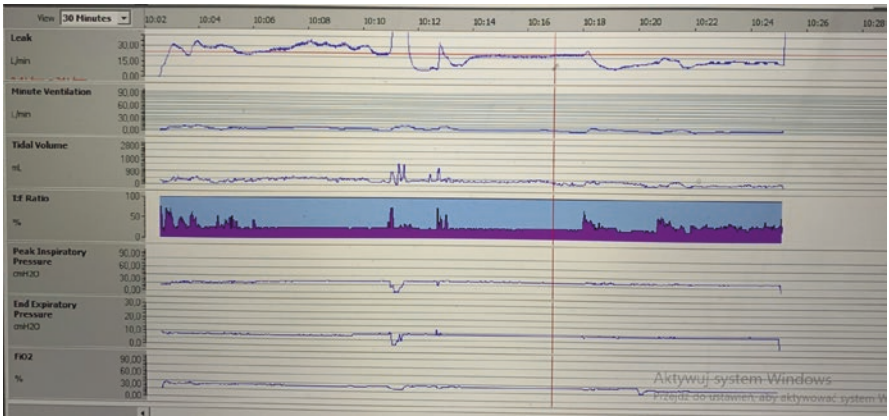

Fig. 25.2 Detail graphs obtained from ASTRAL 150 during NIV facilitated Bf. Derived parameters are seen during all procedure time, including sedation, bronchoscopy performance, and patients weakening

combination increased FiO_2 with the additional influence of fentanyl with midazolam analgosedation (Fig. 25.2).

It has to be underlined that up till now, no specific guidelines are describing NIV settings during BF. Therefore, in our example EPAP, IPAP is given as a range showing that during the procedure, there may be a need to adjust ventilator settings. In our patient operating pressures needed to be corrected, however, the ventilation parameters were stable throughout the procedure, showing only slight variations at the time of initiation and termination, but those were caused by a partial increase in the leakage amount. Fortunately, this was not related to a decrease in minute ventilation or SaO_2 (Fig. 25.2). During Bf, we have used an oxygen supplementation of 5–8 L/min to decrease initial hypoxemia and to reduce the acidosis risk during the Bf (Table 25.1).

We are aware that a chapter in the clinical book, represents a useful example, based on which it is difficult to formulate clinical pathway. However, we are sure that it has an educational value convincing that it is reasonable to introduce NIV-Bf in patients with respiratory failure, which require Bf performance.

Key Teaching Points

- NIV supported bronchoscopy should be considered as a safe diagnostic and therapeutic procedure even in patients with severe respiratory failure.
- NIV assisted bronchoscopy may be regarded as a secure method which may enable bronchoscopy performance in patients which would otherwise require intubation.
- NIV supported bronchoscopy may be useful in patients with impaired respiratory muscle strength and secondary cough malfunction.

- NIV supported bronchoscopy should be probably supported by additional measurements of pre-procedure blood gas analysis, and constant blood pressure, ECG, respiratory rate, SaO_2, and $TcCO_2$ measurement.
- NIV supported bronchoscopy needs further studies to indicate the patients who will benefit using NIV-Bf approach in the therapy.

Questions and Answers

1. What is the main reason to use NIV to support bronchoscopy performance?

   (a) To keep alveoli open
   (b) To reduce the risk bronchoscopy related risk of respiratory failure exacerbation in patients with pre-existing respiratory failure
   (c) To avoid the risk of atelectasis appearance
   (d) To avoid air trapping
   (e) To reduce the risk of foreign body aspiration

   Answer: (b) To reduce the risk bronchoscopy related risk of respiratory failure exacerbation in patients with pre-existing respiratory failure
2. What is the most important NIV-FOB contraindication?

   (a) Duodenal occlusion with concomitant gastric distension
   (b) Presence pre-existing hypoxemia
   (c) Pre-existing type two respiratory failure
   (d) Tachypnoea
   (e) None of the above

   Answer: (a) Duodenal occlusion with concomitant gastric distension
3. What is the recommended the NIV-FOB ventilation mode?

   (a) Bi-level (BiPaP) with leak circuit?
   (b) Hybrid mode (volume assured pressure support)
   (c) Continuous positive airway pressure (CPAP)
   (d) SIMV
   (e) Currently there are no precise recommendations on ventilation mode for NIV-FOB.

   Answer: (e) Currently there are no precise recommendations on ventilation mode for NIV-FOB
4. NIV-FOB is mostly recommended in patients with:
   (a) Lung mas in the lung hilum
   (b) Chronic asthma
   (c) Chronic obstructive pulmonary disease exacerbation
   (d) Cystic fibrosis exacerbation and impaired mucous clearance
   (e) Pulmonary embolism

   Answer: (d) Cystic fibrosis exacerbation and impaired mucous clearance

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Part VI
Clinical Conditions: Acute Hypoxemic Respiratory Failure

Chapter 26
Noninvasive Ventilation in Hematology-Oncology Patients with Acute Respiratory Failure

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Case Study

A 58 year-old male with past medical history of hypertension, gastro-esophageal reflux disease and acute myeloid leukemia (AML) on chemotherapy presents to the Emergency Department with 3-days of dry cough, dyspnea, and low grade fever. He was recovering from an upper respiratory infection a week earlier and had just begun returning to baseline when his symptoms started. He also reported nausea and poor oral intake. Home medications include: Aspirin 81 mg daily, Lisinopril 20 mg daily and Omeprazole 20 mg daily. He has no known allergies.

Initial evaluation showed patient's vital signs to be: low grade fever at 38 °C, tachycardia at 110 beats/min, hypotension at 98/60 mmHg, respiratory rate of 24 breaths/min. His oxygen saturation was 92% on room air, 96% on 2 L nasal cannula. Physical exam was positive for reduced breath sounds in right lower zone with crackles. The rest of the physical exam is unremarkable. Lab work showed a white cell count of 0.6 K/μL. Hemoglobin was 8.5 g/dL and platelet counts 17,000/mm^3. The renal & liver functions were normal. A chest radiograph showed a right middle lobe infiltrate concerning for pneumonia.

Patient was admitted, a septic workup including urine analysis, urine microscopy, two sets of blood cultures, sputum culture, respiratory viral PCR, urine legionella & streptococcal pneumonia antigens were done. He is started on intravenous fluids, and given azithromycin, cefopime and vancomycin for a presumed community acquired pneumonia. Over the next 2 days patient's condition worsened; he

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remained febrile with temperatures maximum of 38.5 °C, his respiratory rate remained elevated between 25–30 breaths/min. His hypoxia worsened; his oxygen saturation dropped to 85% on 6 L nasal cannula and his cough became productive. A CT thorax with contrast done to rule out pulmonary emboli was negative but showed right middle and lower lobe infiltrates consistent with likely pneumonia. His blood cultures came back positive for methicillin resistant staph-aureus (MRSA). The arterial blood gas showed pH 7.42, $PaCO_2$ 35 mmHg, PaO_2 55 mmHg. He was transferred to ICU where he was placed on high flow nasal cannula FiO_2 60% and 40 L of flow. Six hours later he was having more respiratory distress with labored breathing. A repeat ABG showed pH 7.20, $PaCO_2$ 65 mmHg, PaO_2 68 mmHg. The ICU team wanted to intubate the patient, however the wife asked if they could do anything else to avoid intubation. So he was put on noninvasive ventilation with iPAP 18 cmH_2O and ePAP 8 cmH_2O FiO_2 70%. After 3 h, he was not improving with obtundation, so after discussion with the wife, the patient was intubated and started on invasive mechanical ventilation. The patient's condition gradually improved in the following 3 days and he was successfully extubated. He was discharged home on the tenth day of hospitalization.

26.1 Introduction

Over the past two decades, the survival of cancer patients had significantly increased. This is due to advances in cancer detection and management [1]. This patient population is at high-risk for a number of life-threatening complications, and as a result more of them are seen in the intensive care unit (ICU). Acute respiratory failure (ARF) is the leading cause of admission to the ICU, followed by shock, and neurologic complications [2]. Overall 15% of patients with hematologic malignancies and up to 50% of patients with prolonged neutropenia have pulmonary complications [3].

ARF can be defined as a triad of clinical signs, radiographic findings, and gas exchange abnormalities. Symptoms usually develop or worsen over a period of 7-days [4]. The aims of the initial oxygenation and ventilation strategies are to restore adequate oxygenation, reduce the respiratory rate, alleviate respiratory distress and dyspnea, and improve patient comfort. Observational studies have shown that amongst hematological malignancies; lymphoproliferative disorders, prolonged neutropenia, and autologous or allogeneic stem cell transplant recipients had the highest incidents of respiratory events. Solid tumors are reported to have lower rates of ARF when compared to hematological malignancies with the highest rates reported in lung cancer patients [4].

The main causes of ARF in cancer patients can be divided into two groups: infectious; caused by bacteria, viruses, and fungi, and noninfectious; including tumor involvement, diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, pulmonary drug toxicity, and transfusion related lung injury [5] (Table S1).

Mortality rates from ARF are down trending, currently reported as ranging between 55% and 83% from >90% previously [6]. This improvement is believed to

be secondary to the development of more effective and targeted treatments; advances in the supportive care of patients with malignancy; continuous improvements in managing cardiovascular, renal, and pulmonary dysfunctions in ICU setting; and the optimization of triage criteria for admitting cancer and immunocompromised patients to the ICU [7]. While there is an overall downtrend in mortality numbers, they remain significantly elevated. Underlying etiologies affecting mortality can be grouped into five categories; (1) Factors affecting the severity of acute respiratory failure and the associated organ dysfunctions, (2) Factors related to delayed ICU admission, (3) Factors related to the underlying disease and comorbid conditions, (4) Factors related to the initial oxygenation and ventilation strategies, and (5) Factors related to the cause of respiratory failure itself [4].

In this chapter, we will be focusing on the role of noninvasive ventilation (NIV) in the management of hypoxemic ARF in the cancer patient. We will provide a comparison to other therapeutic modalities such as high-flow oxygen therapy (HFOT), and invasive mechanical ventilation (IMV).

26.2 Noninvasive Ventilation

It is well known that in cancer patients the need for intubation and mechanical ventilation is associated with higher mortality rates [2]. Thus efforts were made to avoid IMV when possible. This was done through the utilization of oxygen therapy and NIV. NIV allows for lung recruitment with proper use of positive end expiratory pressure (PEEP), improvement in hypoxia and dyspnea, and relief of respiratory muscle fatigue [8]. Guidelines from the European Respiratory Society and the American Thoracic Society advocate the use of NIV in cancer patients with ARF [9]. This was mainly based on the results of a study published in 2001 by Hilbert et al. [10] where 52 immunocompromised patients at a single center admitted to the ICU in early stages of ARF were randomized to receive either NIV or oxygen via standard therapy (Venturi mask). Each group had 26 patients with 15 of them having hematologic malignancies & neutropenia. Results showed that fewer patients in the NIV group required endotracheal intubation (12 vs. 20, $p = 0.03$), had serious complications (13 vs. 21, $p = 0.02$), died in the ICU (10 vs. 18, $p = 0.03$), or died at the hospital (13 vs. 21, $p = 0.02$). 81% mortality was reported in the group assigned to standard oxygen. Another trial in solid organ transplant recipients published by Depuydt et al. in 2004 also documented NIV benefits [11].

NIV as such gained popularity as first line respiratory support therapy that reduces the need for intubation and IMV. Thus, avoiding the need for heavy sedation, and intubation complications that come with IMV such as ventilator associated pneumonia, upper airway injury, and tracheomalacia. This overall lead to better clinical outcomes [10, 11]. However, this recommendation for NIV remained debatable given that Hilbert's study was small sized and conducted between 1989–1999. Especially with controversial results from subsequent studies that followed it; namely studies by Lemiale et al. [12], Schnell et al. [13], Gristina et al. [14], and

Azoulay et al. [15] published in 2015, 2014, 2011, and 2012 respectively. Current data show that patients who fail NIV and ultimately require intubation suffer from worse outcomes including; multiorgan failure, need for vasopressor support, development of acute respiratory distress syndrome (ARDS) and eventually not surviving their hospitalization [16]. In fact, Frat et al. published a post-hoc analysis of randomized trial in 2016 [17] that performed a subgroup analysis in a subset of cancer patients with non-hypercapnic ARF from a multicenter randomized control trial from 23 centers in France & Belgium where patients were randomly assigned to receive either standard oxygen, HFNT alone, or NIV interspaced with HFNT. Findings from 82 patients; 30 in the standard oxygen therapy group, 26 in the HFNT alone group, and 26 in the NIMV interspaced with HFNT group were reviewed. Eight (31%) of 26 patients treated with HFNT alone, 13 (43%) of 30 patients treated with standard oxygen, and 17 (65%) of 26 patients treated with NIV required intubation at 28 days ($p = 0.04$). After a multivariable logistic regression, the two factors independently associated with endotracheal intubation and mortality were age and use of NIV. The study concluded that NIV should be used cautiously in cancer patients.

In a systemic review and meta-analysis comparing NIV vs. IMV for ARF in immunocompromised patients published by Wang et al. in 2016, 13 observational studies with a total of 2552 patients were included. Compared to IMV, NIV was shown to significantly reduce in-hospital mortality and 30-day mortality. Subgroup analysis showed that NIV had greater advantage in less severe ARDS, BMT and hematological malignancies patients. They concluded that NIV has more benefit and causes less harm in this subgroup of patients [18].

Another systemic review and meta analysis published in 2017 by Huang et al. [19] reviewed five randomized controlled trials with 592 patients found that early NIV significantly reduced short-term mortality (RR 0.62, 95% CI 0.40–0.97, $p = 0.04$) and intubation rate (RR 0.52, 95% CI 0.32–0.85, $p = 0.01$) when compared with oxygen therapy alone, with significant heterogeneity in these two outcomes between the pooled studies. In addition, early NIV was associated with a shorter length of ICU stay (MD −1.71 days, 95% CI −2.98 to 1.44, $p = 0.008$) but not long-term mortality (RR 0.92, 95% CI 0.74–1.15, $p = 0.46$). It concluded that the limited evidence available indicates that early use of NIV could reduce short-term mortality in selected cancer patients with ARF.

It is worth mentioning here the study done Wermke et al. [20] on ARF in patients post hematopoietic stem cell transplant (HSCT) as it is the only randomized trial on early NIV in this particular group that has been published to date. Eighty-six (16%) of 526 patients that had undergone HSCT developed ARF. They were randomized into either treatment arm A; oxygen supply only, or treatment arm B; oxygen plus intermittent NIV. Although early ARF treatment with NIV was associated with decreased rate of failure to achieve sufficient oxygenation (39% in arm A vs. 24% in arm B, $p = 0.17$), neither ICU admission rate, nor need for intubation or survival parameters were affected by the treatment strategy. Early NIV was not associated with improved prognosis in this particular patient population.

Further studies are needed to identify in which selected patients NIV would be more beneficial. It is worth noting that above studies were focused on hypoxemic

ARF, NIV remains first line therapy hypercapnic ARF that is related or not related to underlying cancer in addition to cardiogenic pulmonary edema [18]. A Cochrane review had recently concluded that NIV decreased mortality by 46% when compared to standard oxygen with number needed to treat being 1264 patients in with COPD and hypercapnic ARF [21]. This is in concordance with latest published guidelines from the European Respiratory Society (ERS) and American Thoracic Society (ATS) in 2017 [9]. And continues to be the recommendation as per more recently published review by Thille and Frat in 2018 [22].

26.3 High Flow Oxygen Therapy

HFOT is a newer modality of oxygen delivery that allows heated and humidified gas up to 60 L/min to delivered to patients via a wide-bore nasal cannula. It reduces ventilation requirements by washing out the dead space in the upper airway and meeting patients' inspiratory demands with high FiO_2 [23]. It improves oxygenation, lowers respiratory rate, work of breathing, and minute ventilation at a constant $PaCO_2$. It also increases end-expiratory lung volume and dynamic compliance [24].

Several studies evaluated the feasibility and safety of HFOT in cancer patients with ARF [25–29]. One of which done on 45 patients with hematological malignancies [25] had shown that the hospital mortality rate was 13.3% when HFOT was successful and 86.7% when it failed. Failure of HFOT was reported at 15% in a single center study with 183 solid tumor patients [26]. But, was 80% in a study on 56 hematology patients [28]. No results from trials specifically assessing HFOT in cancer patients with hypoxia and ARF are available, but there are several studies that compared HFOT with other oxygenation and ventilation strategies. In a retrospective cohort published by Harada et al. [30] 178 patients with cancer and acute respiratory failure; 76 (43%) patients received NIV plus HFOT, 74 (42%) NIV plus standard oxygen, 20 (11%) HFOT alone, and 8 (4%) standard oxygen therapy alone. The combination of NIV and HFOT was associated with lower mortality rates; 37% vs. 52% in other groups with $p = 0.04$. It was also independently associated with higher 28-day survival. In 2018, Huang et al. [31] conducted a systemic review and meta-analysis looking into HFOT use in immunocompromised patients with ARF. Seven studies involving 667 patients were included. The authors concluded that the use of HFOT was significantly associated with a reduction in short-term mortality (RR 0.66; 95% CI 0.52–0.84, $p = 0.0007$) and intubation rate (RR 0.76, 95% CI 0.64–0.90; $p = 0.002$). In addition, HFOT did not significant increase length of stay in ICU (MD 0.15 days; 95% CI −2.08 to 2.39; $p = 0.89$).

In another publication by Cortegiani et al. [32] the role of HFOT compared to conventional oxygen therapy was evaluated via systemic review and meta analysis that included four randomized controlled trials for the main analysis. They found no significant difference in short-term mortality comparing HFOT vs. conventional oxygen therapy in ICU: $n = 872$ patients, odds ratio (OR) = 0.80 [0.44, 1.45], $p = 0.46$, $I^2 = 30\%$, $p = 0.24$; and at 28-day: $n = 996$ patients, OR = 0.79 [0.45, 1.38],

p = 0.40, I^2 = 52%, p = 0.12. They also found a reduction of intubation rate in the HFOT group (n = 1052 patients, OR = 0.74 [0.55, 0.98], p = 0.03, I^2 = 7%, p = 0.36). They concluded no benefit of HFOT over conventional oxygen therapy on mortality in cancer patients with ARF. However, HFOT was associated with a lower intubation rate warranting further research. Recently, Dumas et al. [33] looked at the risk of intubation in cancer patients with ARF based on oxygen vs. NIV initial management strategy. They looked at data from 847 patients with ARF to estimate the probability of intubation at day +1 within the first 3 days of ICU admission according to oxygen management. First, they compared NIV to oxygen therapy whatever the administration devise; second, standard oxygen was compared to HFOT alone, NIV alone, or NIV + HFOT. To take into account the oxygenation regimens over time and to handle confounders, propensity score weighing models were used. While in the original sample the probability of intubation at day +1 was higher in the NIV group vs. oxygen 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 HFOT group compared to standard oxygen (OR = 2.85, 95 CI 1.37–5.67). All these differences disappeared by handling confounding-by-indication in the weighted samples as well as in the pooled model. The authors concluded that these oxygenation/ventilation strategies had no impact on the probability of next day intubation. Current work is being done by Azoulay et al. in a multicenter, open label, randomized control superiority trial seeking to demonstrate the survival benefits of HFOT; the HIGH trial [34].

26.4 Conclusion

We can conclude from the above studies that there is no single best answer when it comes to NIV vs. HFOT as initial choice for therapy in ARF in cancer patients. Current evidence does not support either strategy being associated with survival benefit. Assessing patients response to selected therapy within the first 1–4 h is the best approach to evaluate improvement from continued respiratory distress that can guide decision for early intubation and IMV, which provides the benefit of lung protective ventilation. We propose Fig. S1 as a suggested initial approach to respiratory support for cancer patients presenting with acute respiratory failure.

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Chapter 27
Treatment of Acute Respiratory Failure in Patient with Congestive Heart Failure and Pneumonia

Biljana Joves

Abbreviations

CAP	Community acquired pneumonia
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CURB-65	Confusion–urea–respiratory rate–blood pressure–65 years of age
EPAP	Expiratory positive airway pressure
FiO_2	Fraction of inspired oxygen
IPAP	Inspiratory positive airway pressure
NIV	Noninvasive ventilation
PEEP	Positive end expiratory pressure
PSV	Pressure support ventilation
SPN-CPAP/PS	Spontaneous–Continuous positive airway pressure or Pressure support ventilation
Ti	Inspiratory time
Vt	Tidal volume

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27.1 Introduction

Noninvasive ventilation (NIV) of patients with pneumonia remains controversial. It is deemed that the patients with respiratory failure due to community acquired pneumonia (CAP) and cardiac or pulmonary comorbidity do better on NIV that the patients with "de novo" acute respiratory failure. The cited success of NIV in patients with CAP and no cardiopulmonary comorbidities ranges from 20% to 76% [1]**.** Although it has been proven that patients with pneumonia and preexisting COPD or heart failure who receive NIV have shorter hospital stay and lower mortality rates compared to patients on invasive mechanical ventilation, there are a few studies that found pneumonia to be an independent risk factor for NIV failure in patients with acute exacerbation of COPD [2]. Very strong arguments for NIV versus intubation extend to immunocompromised patients with hypoxemic respiratory failure and pulmonary infiltrates. However, as concisely stated in BTS guidelines—"neither NIV nor CPAP (continuous positive airway pressure) support is routinely indicated in the management of patients with respiratory failure due to CAP, and if a trial of non-invasive support is considered indicated in CAP, it must only be conducted in a critical care area where immediate expertise is available to enable a rapid transition to invasive ventilation" [3]**.**

Case Presentation

The patient was a 56 year old man with congestive heart failure who was initially referred to his cardiologist with the signs of cardiac decompensation. Previous medical reports showed he received intensive diuretic treatment 3 days before admission, with decreasing diuretic response. However, the cardiologist reevaluated the patient and referred him further to pulmonologist due to high inflammation markers, fever and cough.

Upon admission, he was awake and oriented but had fever, tachycardia, hypotension, dyspnea and oliguria. Pneumonia was confirmed based on a new pulmonary infiltrate on his chest radiograph upon admission, along with the high markers of inflammation and the symptoms of respiratory tract infection. Arterial blood gases showed severe hypoxemia with calculated PaO_2/FiO_2 ratio of 240 on 40% oxygen therapy. Chest radiograph demonstrated confluent patchy air space opacities of lower and middle right lung field with the presence of air bronchogram consistent with bronchopneumonia, but also an enlarged heart silhouette and incipient interstitial oedema (Fig. 27.1). Urinary test for Streptococcus pneumonia and Legionella pneumophila were performed, along with the blood cultures. Since the microbiology tests did not yield positive results, antimicrobial therapy remained empirical–dual combination antibiotics comprising a β-lactamase stable β-lactam and a macrolide for 7 days, as per BTS and NICE guidelines [2]. Laboratory values showed elevated leucocytes, CRP and procalcitonin, along with elevated blood urea nitrogen, creatinine, and pro-BNP. He was immediately given intravenous rehydration in attempt to reverse pre-renal acute renal insufficiency triggered by the mentioned overuse of diuretics, and the above listed parenteral antibiotics were immediately started. Severity of community acquired pneumonia as judged by CURB-65 score was 4 points.

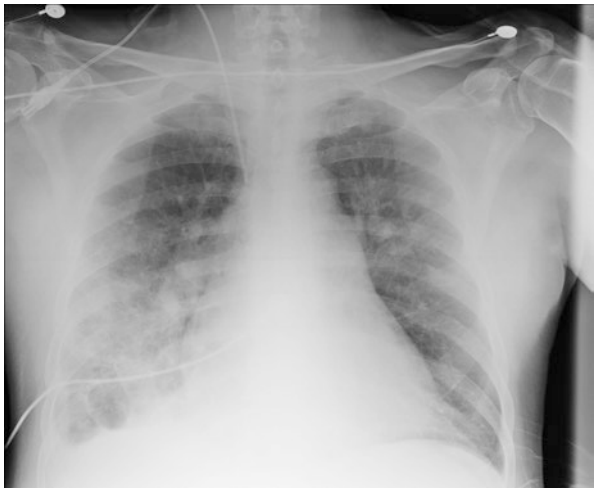

Fig. 27.1 Chest radiograph showing confluent patchy air space opacities of lower and middle right lung field with the presence of air bronchogram consistent with bronchopneumonia, an enlarged heart silhouette and incipient interstitial oedema

He had all the criteria for NIV use: severe dyspnea with respiratory rate of 32 breaths/min, apparent use of accessory respiratory muscles and severe hypoxemia. The choice of NIV location has been a moot topic and it largely depends on the internal resources of a hospital [4]. In our Institute, NIV is no longer undertaken on general wards, only in the dedicated respiratory unit, so the patient was transferred to our High Dependency Unit. The choice between a dedicated noninvasive and an ICU ventilator was made according to the plan to intubate the patient if NIV fails—so, the ICU ventilator was chosen. The choice of interface between oronasal and total face mask was made according to the patient's facial shape and preference and total face mask was used, but it is important to make sure the mask is right for the chosen ventilator. When using single limb circuit ventilators, exhalation/leak port must be incorporated either in the mask itself or in the circuit near the patient. This means that masks with exhalation port are used with a single limb circuit NIV ventilators and mask without exhalation port are used with ICU ventilators, since they have a dual limb circuit.

The next step was to explain the method to the patient. It is of great importance to adequately prepare the patient for NIV by explaining what will ensue and reassure them in order to provide maximum compliance. The staff explained the procedure and its benefits into detail and the patient accepted to undergo NIV. Noninvasive ventilation was performed in pressure support ventilation mode (SPN-CPAP/PS; Draegerwerk AG & Co.; Lubeck, Germany). On the initial screen, NIV option was first selected (as opposed to "Tube" option), in order to provide maximum leak compensation. Then the pressure support mode was selected. In patients who are hypoxic and not hypercapnic, and exhibit signs of incipient pulmonary edema, CPAP could be a legitimate option to use to improve oxygenation by decreasing preload and afterload as well as intrapulmonary shunt. CPAP value equals the value of PEEP (positive end expiratory pressure), that is EPAP (expiratory positive airway pressure), and the same level of positive pressure is maintained the whole time—thus the name "continuous positive airway pressure" [5]. However, the patient also

had pneumonia and that is why pressure support ventilation was needed—with additional application of inspiratory positive airway pressure (IPAP) creating the pressure support (difference between IPAP and EPAP) that enables reduction in the work of breathing and augmentation of tidal volume [1]. Also, care must be taken in order to distinguish between the delta PS value, which is pressure above PEEP/EPAP, and IPAP value, which is the total value of inspiratory pressure calculated by adding the delta PS value to PEEP value.

The patient was elevated in a semi-sitting position with the head of the bed elevated 30–45°. Ventilator was switched on first and then the mask was held over the patient's face by hand until he adapted. The mask was fixed afterwards with head straps at the minimum tightness that still prevented excessive air leak. He was ventilated initially with a low inspiratory positive airway pressure in order to reduce discomfort and to acclimate. EPAP/PEEP was set initially at 4 cmH_2O and the level was raised by 1 cmH_2O to achieve SpO_2 of >90%. Delta PS was increased starting from 4 cmH_2O, in increments of 2 cmH_2O to obtain a tidal volume (Vt) of 6 ml/kg and a respiratory rate <30 breaths/min.

Success of noninvasive ventilation depends also on the achieved synchrony between the patient and the ventilator. That is why it is important to observe the patient and follow the flow/volume curves in order to recognize the signs of asynchrony and then take steps to mend them by readjusting the settings. In our case, we found the situation on the ventilator monitor that looked similar to the graphic shown in Fig. 27.2. The image shown indicates the double-triggering meaning two mechanical insufflations are happening with only one neural inspiration. More

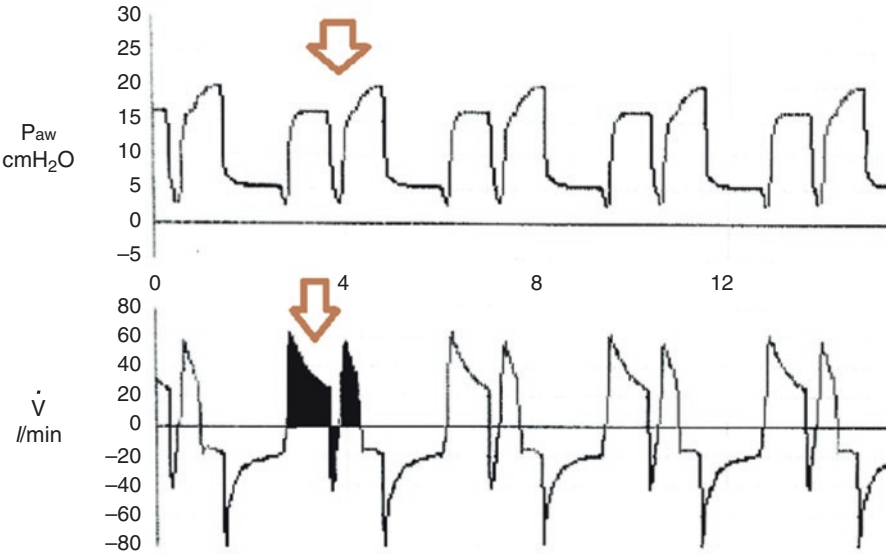

Fig. 27.2 Double triggering: notice two ventilator insufflations separated by a very short expiratory time within a single inspiratory effort of a patient

precisely, the patient is still trying to breathe in while the ventilator has already cycled off to expiration, which translates to neural inspiratory time being longer than mechanical inspiratory time. Inspiratory effort of the patient yet continues, and double triggering occurs. This may be connected with inadequate level of pressure support so the continued inspiratory effort retriggers the ventilator after it discontinued pressurization. So, in order to correct this type of asynchrony, we increased the level of pressure support. Also, one option to prolong inspiratory time is to delay the transition to expirium, by reducing the cycling threshold—in our case to 20%, in order to avoid premature termination of inspirium and cycling off to expirium. In one study, community-acquired pneumonia was more prevalent in patients in whom premature cycling was present [6].

Since the patient was a candidate for endotracheal intubation should NIV fail, he was closely monitored for signs of NIV failure: mental status change, increasing respiratory or heart rate, persisting accessory respiratory muscle use and hemodynamic instability. When it comes to identifying factors associated with NIV failure in patients with pneumonia, the following have been suggested: radiographic worsening after 24 h, higher heart rate and lower PaO_2/FiO_2, along with higher disease severity [4, 7].

Delayed intubation is a concern due to potentially higher mortality in this subgroup of patients, so it is crucial to make this decision early on, which dictates the location where NIV will be used, that is in the close proximity to the ICU [4]. First ABG control was performed after 1 h and the calculated PaO_2/FiO_2 increased to 270, while tachypnea decreased to 28 breaths/min. Desired targets were achieved with EPAP of 7 cmH_2O and IPAP of 15 cmH_2O, with FiO_2 0.6.

The patient preserved hemodynamic stability the whole time, and the consciousness was preserved. After initial rehydration, urine output increased and control lactate after 6 h started to decrease. Diuretics were reintroduced, along with careful rehydration. One of the biggest obstacles to NIV success in patients with pneumonia is clearance of secretions. One way to overcome this is early chest physiotherapy and nasotracheal suctioning before NIV application and during the breaks from NIV. Even though current evidence does not support routine airway clearance techniques, the risk of harm is low, and potential benefits are valuable [8]. Also, inability to clear secretions is a relative contraindication for NIV, so all measures should be taken to facilitate secretions clearance.

Chest radiograph on the following day showed initial improvement, and clinical response was good, so the NIV was continued until day 3. The weaning meant incremental decrease in parameters and successively longer breaks from NIV until final cessation. Remembering that NIV is just supportive until the underlying cause of respiratory failure is corrected translates to postponing the weaning until the underlying pneumonia starts resolving. That also brings into question the distinction between NIV failure and antibiotic failure. In our case, serial inflammation markers decreased and creatinine levels normalized. The patient was transferred to general ward on day 4 and discharged from hospital on day 11.

Key Teaching Points

- Appropriate patient selection is the key to success of NIV in patients with CAP.
- NIV is not routinely recommended to treat respiratory failure in patients with CAP without cardiopulmonary comorbidities.
- Inadequate secretion clearance may jeopardize success of NIV in patients with CAP.
- Adequate monitoring facilitates recognition of early predictors of NIV failure.
- Implementing NIV in the critical care setting enables quick transition to invasive mechanical ventilation.

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Chapter 28
Neurally Adjusted Ventilator (NAVA) Mode

Martin Scharffenberg and Jakob Wittenstein

Abbreviations

ARDS	Acute respiratory distress syndrome
AUC	Area under the curve
CODP	Chronic obstructive pulmonary disease
EADi/Edi	Electrical activity of the diaphragm
ECG	Electrocardiogram
FiO_2	Fraction of inspired oxygen
I:E	Ratio of inspiratory and expiratory time
ICU	Intensive care unit
NAVA	Neurally adjusted ventilatory assist
NEX	Distance of nose tip, earlobe and processus xyphoideus
NIV	Non-invasive ventilation
P/I Index	Ratio of EADi peak value and EADi inspiratory AUC
$PaCO_2$	Arterial partial pressure of carbon dioxide
PEEP	Positive end-expiratory pressure
SpO_2	Peripheral oxygen saturation
SVA	Subject ventilator asynchrony
VIDD	Ventilator-induced diaphragmatic dysfunction
WOB	Work of breathing

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28.1 Introduction

Neurally Adjusted Ventilatory Assist (NAVA) is a relatively new mode of mechanical ventilation [1]. In contrast to conventional pressure support modes, breaths are primarily triggered by the electrical activity of the diaphragm (EADi or Edi). This requires the placement of a special gastric tube, which is equipped with a certain number of electrodes at its distal end. After complex processing, the EADi signal is transferred to the ventilator to trigger a respiratory cycle. The corresponding respiratory assistance, e.g. the pressure support, is proportional to each processed EADi signal, using a proportionality factor called NAVA Gain or NAVA Level. Due to this so-called neural triggering, the timing, as well as the inspiratory pressure and consecutive tidal volume, are patient-controlled. According to the usually high variability of spontaneous breathing, NAVA exhibits intrinsic variable breathing patterns. The close coupling of respiratory effort and mechanical support is the main feature of Neurally Adjusted Ventilatory Assist. NAVA is implemented in the *Maquet SERVO-i* respirator (*Maquet Critical Care*, Solna, Sweden) and can be performed as both non-invasive and invasive mechanical ventilation for children and adults.

In this standard teaching clinical case, we describe a 56-year-old female patient who is admitted to the emergency department due to respiratory distress. Her physical examination reveals dyspnea, tachypnea, utilization of the accessory muscles, and tachycardia and the medical history includes a Chronic Obstructive Pulmonary Disease (COPD) as well as a common cold within the last 5 days.

28.2 Clinical Course

After a brief physical examination and administration of oxygen via nasal probes, the patient is admitted to the Intensive Care Unit (ICU). A five-lead electrocardiogram reveals no pathologies and the initial peripheral saturation (SpO_2) is 86% under nasal oxygen administration. An initial arterial blood gas analysis shows an elevated partial pressure of carbon dioxide, decreased oxygen partial pressure and signs of respiratory acidosis. The attending physician decides to start non-invasive ventilation (NIV) using Continuous Positive Airway Pressure (CPAP) via a face mask. Close monitoring and examination reveals only minor improvements within the first 45 min. However, respiratory distress continues and pressure support is added to the CPAP. The patient shows agitation as well as signs of discomfort. Due to the combined need for respiratory support and improvement of subject ventilator interaction, the attending physician decides to administer light sedation and try NIV-NAVA.

28.2.1 Indications and Contraindications of NAVA

NAVA is applicable to a wide range of patients and clinical scenarios. As NIV-NAVA, it can be combined with virtually every available patient-ventilator interface, e.g. nasopharyngeal tubes, nasal masks, face masks or helmets. This is due to the independence from pneumatic triggering and effective air leak compensation [2, 3]. Given the presence of a stable respiratory drive, NAVA can be applied in situations of respiratory distress of different causes. In general, NIV may reduce the intubation or re-intubation rates in acute or chronic respiratory failure, as long as a necessary escalation to invasive mechanical ventilation is not delayed. NIV-failure has to be identified early and treated appropriately. Other possible indications for NIV-NAVA include the need for respiratory support in the early post-extubation period, in the recovery phase of an acute respiratory distress syndrome (ARDS), in chronic respiratory failure, in bridge-to-transplant situations as well as weaning from mechanical ventilation. The contraindications for NIV-NAVA include situations and conditions, which prevent the introduction of a nasogastric or orogastric tube. Patients requiring deep sedation or with haemodynamic instability may be inappropriate for NIV-NAVA. Furthermore, impaired neural respiratory feedback mechanisms, instability or absence of spontaneous respiratory drive, severe neuromuscular disorders, pathologies of the phrenic nerve and diaphragmatic paralyses are contraindications for NAVA. Furthermore, the NAVA-Catheter is not approved for magnetic resonance imaging and should be removed prior to MRI examinations.

In the meanwhile, the attending physician has checked indications and contraindications and is now ready to place the patient interface and the NAVA-Catheter.

28.2.2 Patient Interfaces

In contrast to other modes of pressure support ventilation, the triggering and cycling-off are independent of pneumatic triggering, e.g. pressures and airflows, in the presence of stable EADi signals. While air leaks may cause major problems during conventional pressure support ventilation, the neural triggering in NAVA is usually not influenced by these disruptive factors, e.g. air leaks. This allows the application of many different, even non-sealing patient-ventilator interfaces. However, this is only true for correctly EADi-triggered breaths. If no adequate EADi signal is detected, breaths will be triggered pneumatically. Of note, there is a pressure controlled backup ventilation in case of absent neural or pneumatic triggers, which may be very ineffective if a non-sealing patient interface is applied. In general, well-fitting face masks and helmets can be used. The selection may depend on local standards and availabilities, patient's preferences and individual anatomical characteristics.

28.2.3 Placement of the NAVA-Catheter

The NAVA-Catheter is a special gastric feeding tube made of medical polyurethane designed for single use. At its distal end, ten bipolar electrodes are integrated. It is provided in different lengths (49–125 cm) and diameters (6–16 Fr) for neonates, children and adults by *Maquet* (*Maquet Critical Care*, Solna, Sweden). Depending on the size, it is equipped with one or two lumens. The manufacturer's instructions help to find the correct size according to the patient's height and/or weight. The catheter is detectable in X-ray films.

The correct placement is essential for an adequate signal and successful application of NAVA. For proper EADi detection and triggering, the electrode-equipped area of the catheter needs to reach a transdiaphragmatic position. Therefore, the EADi-Catheter will be introduced through the nose or mouth into the oesophagus, until the tip reaches the stomach, following the standard guidelines for the placement of a common nasogastric feeding tube. The exact insertion distance should be calculated using the so-called *NEX* measurement, where *N* stands for nose, *E* stands for earlobe and *X* stands for the Xyphiod processus. This prediction of catheter length is derived from early anatomical studies [4]. The *NEX* value is the sum of the distances between these three landmarks (Nose–Earlobe–Xyphiod, *N-E-X*) and can be converted into the introduction distance by multiplying the *NEX* value with a factor of 0.9 for nasal and 0.8 for oral placement and adding a size-dependent correction value [5]. Please see the manufacturer's instructions in the catheter packaging. After wetting the catheter and connecting it with the corresponding cable to the ventilator, the catheter can be introduced via nose or mouth.

Practical help for the catheter placement is provided by the *SERVO-i* ventilator by showing a series of unfiltered electrocardiogram (ECG) leads and the EADi curve throughout the placement procedure (positioning tool). During inserting the catheter, p-waves and QRS-complexes will appear in the top curves on the screen. These will decrease and disappear, as the catheter is advanced. The EADi catheter should be advanced or retracted until ECG complexes are highlighted in the center leads on the screen and p-waves disappear in the lower leads together with a stable EADi signal. Additionally, an expiratory hold may confirm a correct EADi signal when an increase of the signal coincides with a drop in the airway pressure at the onset of inspiratory effort.

The well-fitting facemask is already applied at our patient from the first NIV trial. It is kept for NIV-NAVA and connected to the ventilator circuit of the Maquet ventilator, which is now ventilating the patient using a standard pressure support mode. In our case, the patient's height is 165 cm. According to the manufacturer's instructions, the attending physician decides to introduce a wetted 8 Fr. Catheter with a total length of 125 cm. The NEX measurement reveals a total N-E-X value of 52 cm and therewith, the 8 Fr/125 cm catheter is introduced through the nose to a depth of 65 cm while the positioning tool of the ventilator confirms a proper placement. The catheter is fixated and the insertion depth is marked and noted in the records. An expiratory hold maneuver shows an increase in EADi while the airway pressure decreases simultaneously. NIV-NAVA is ready to start.

28.2.4 Initiation of NAVA

With the ventilator in standby mode, the patient category, e.g. children or adults, as well as the invasiveness (NIV-NAVA vs. NAVA) can be selected. The ventilator may be started manually but will also start automatically if any trigger is detected. Usually, one would initially ventilate the patient with common pressure support/CPAP mode and switch to NAVA in the presence of a stable EADi signal. After starting the NIV-NAVA mode, an adequate level of support, i.e. the proportion of work of breathing (WOB) performed by the ventilator, has to be selected using the NAVA Level (0–15 $cmH_2O/\mu V$). Accordingly, the corresponding pressure support over positive end-expiratory pressure (PEEP) equals the EADi signal [μV] times the NAVA Level [$cmH_2O/\mu V$]. With increasing NAVA Levels, the WOB will be increasingly transferred from the patient to the ventilator. Practically, one may start with a NAVA Level of 0.5 $cmH_2O/\mu V$ in children or 1 $cmH_2O/\mu V$ in adults, respectively. If necessary, this may be followed by a stepwise increase, e.g. up to 2–2.5 $cmH_2O/\mu V$ [6]. Furthermore, the NAVA Preview tool allows for estimating the resulting pressure support for a given NAVA Level. Therewith, the initial NAVA Level can be selected to achieve similar pressure support as under the previous common pressure support ventilation. This tool can be found by selecting "Neural Access" on the screen.

The other primary parameters to set in NIV-NAVA are PEEP (2–20 cmH_2O), the fraction of inspired oxygen (FiO_2; 21–100%) and the EADi trigger (0–2 μV). The EADi trigger represents the trigger threshold over the minimal EADi value. Adjustable parameters of the backup ventilation are pressure control over PEEP (5–80 cmH_2O), respiratory rate (4–150/min) and the ratio of inspiratory and expiratory time (I:E; 1:10–4:1). Different alarm limits can be adjusted and should be adapted cautiously depending on the patient's status.

The patient is connected to the Maquet ventilator and is first ventilated using conventional pressure support ventilation with CPAP. With the face mask and the catheter in place, as well as a stable EADi signal present, the ventilator is switched to NIV-NAVA. The attending physician selects the following initial settings: NAVA Level 1.5 $cmH_2O/\mu V$, PEEP 7 cmH_2O, FiO_2 60%, and an EADi trigger of 1 μV.

28.2.5 Ventilator Settings: Adjusting and Maintaining NIV-NAVA

Especially within the initial phase, a close monitoring and cautious adjustment of ventilator settings are necessary. This includes the selection of an adequate NAVA Level. It can be titrated to achieve the same level of pressure support from the time prior to starting NAVA (as within the NAVA Preview tool) or according to a decreasing EADi signal, representing optimal diaphragmatic unloading. Given intact neural feedback mechanisms, the tidal volume and respiratory rate will remain fairly

constant while the EADi amplitude may decrease [6], which are signs of improvement of neuro-muscular coupling. In contrast, over-assistance can be assumed if the EADi signal decreases and finally disappears for a given NAVA Level. An increasing EADi signal may represent insufficient respiratory support. Caution, both very low and very high NAVA Levels may disturb the respiratory control, impair the NAVA performance, and promote severe respiratory discomfort. Similarly, the PEEP can be selected according to the amplitude of the EADi signal. By titrating the PEEP to achieve the lowest possible EADi signal, optimization of work of breathing can be assumed. In contrast, an increasing EADi during PEEP titration may indicate pulmonary hyperinflation and too high PEEP levels. Nevertheless, the PEEP level may depend on the oxygenation of the patient.

The EADi trigger should be adjusted to low values to ensure sensitive triggering. However, very low values may promote auto-triggering.

Furthermore, the FiO_2 should be selected according to the patient's needs as high as necessary and as low as possible to ensure adequate oxygenation. Different safety limits and alarms for a number of respiratory parameters, e.g. airway pressure, apnoea time, respiratory rate etc., should be chosen with caution. As apnoeic phases may occur, especially in newborns, the backup ventilation parameters have to be chosen cautiously (pressure control over PEEP, respiratory rate, and I:E ratio). Despite safety mechanisms, the patient on NAVA has to be monitored closely. A dysregulation of respiratory drive and deterioration or loss of the EADi signal should be diagnosed immediately and treated appropriately. The insertion depth and position of the NAVA-Catheter should be checked regularly, as dislocation may impair the EADi signal and neural triggering. The catheter may be used up to days and has to be exchanged thereafter.

28.2.6 Alternative Ways of Setting NIV-NAVA

In a small physiological clinical trial in patients after extubation, a new, unconventional way of setting NIV-NAVA delivered via face mask was tested and compared to conventional pressure support ventilation as well as common NAVA settings [7]. Prior to initiation of NIV-NAVA, a short trial with pressure support ventilation (pressure support $\geq$8 cmH_2O to achieve a desired tidal volume of 6–8 ml/kg ideal body weight) was performed. Afterwards, the ventilator was switched to NAVA with the following settings: Instead of slowly and stepwise increasing the NAVA Level, it was set at its maximum of 15 $cmH_2O/\mu V$, airway pressure limit was set to achieve a similar airway pressure as during the initial pressure support trial, EADi trigger was 0.5 μV, and cycling-off was 70% of EADi peak by default. The FiO_2 and PEEP were selected according to adequate peripheral oxygen saturation and the decision of the attending physician, respectively [7]. These alternative NAVA settings increased the patient comfort, reduced the time to peak inspiratory flow after the onset of the inspiratory effort, improved the pressurization and triggering performance compared to conventional NAVA and conventional pressure support

ventilation. The analyses of SVA revealed asynchrony indexes of <10% with both the conventional and the new setting of NAVA. No differences were found regarding the respiratory drive, gas exchange and respiratory rate. In a similar small trial, the same alternative way of setting NAVA was studied in patients receiving NIV-NAVA via two different helmets after extubation [8]. Herein, the following settings were applied: NAVA Level 15 $cmH_2O/\mu V$, airway pressure limit 25 cmH_2O, PEEP 10 cmH_2O, and FiO_2 according to adequate peripheral oxygen saturation. This study revealed improved comfort and reduced respiratory drive compared to standard NAVA settings and conventional pressure support ventilation. Furthermore, both the new and standard NAVA settings improved the triggering and pressurization performances as well as rates of SVA, without showing differences between each other, irrespectively of the two different helmets used. Gas exchange and respiratory rate were similar between all three modes of ventilation. Despite these promising findings, further evidence is needed to analyse if this alternative way of setting NAVA will be beneficial for other patients and conditions.

After the initial setting, the attending physician increases the NAVA Level to 1.9 $cmH_2O/\mu V$ to assure adequate respiratory support. In the following 2 h, the patient already improves regarding respiratory distress, blood gas analyses and breathing comfort. Later on, the physician is able to reduce the NAVA Level to 0.9, and PEEP to optimal unloading indicated by lower EADi amplitudes, and reduces the FiO_2 to 40%. Despite less sedation, there is more comfort and fewer signs of subject ventilator asynchrony.

28.2.7 Subject Ventilator Asynchrony

Especially during mechanical ventilation or partial respiratory support with assisted spontaneous breathing, SVA occurs frequently, although modern ventilators with sensitive triggering already improved the incidences of SVA. Asynchrony can be described as the mismatch of inspiratory- and expiratory times between the patient and the ventilator and/or the missing or unintended application of respiratory support. SVA impairs breathing comfort and increases the WOB. Severe asynchrony, e.g. an asynchrony index of >10%, was shown to be associated with increased intensive care unit (ICU) mortality as well as longer length of ICU and hospital stay. However, due to the neural triggering, both NIV-NAVA and invasive NAVA significantly improved patient-ventilator synchrony compared to conventional pressure support ventilation in different studies [3, 9]. In fact, neural triggering in NAVA initiates the pressure support without delay and cycling-off depends on the neural inspiratory drive (cycling-off at 70% of the EADi peak value). Therefore, trigger delay and the risk of double triggering may be reduced in comparison to pneumatically triggered breaths in other assisted ventilation modes. However, some studies revealed SVA events during NAVA although the manufacturer claims that NAVA ideally exhibits no SVA. Of note, the incidences were significantly lower in NAVA than in other assisted ventilation modes. Both the secondary pneumatic trigger and

the backup ventilation may explain a certain number of asynchronous breaths during NAVA.

While being on NIV-NAVA, our patient undergoes close monitoring. This includes the essential vital signs, blood gas analyses, physical examinations and studying the curves on the ventilator's screen, where important information can be gained.

28.2.8 The Diagnostic Value of the EADi Signal

The EADi signal is not only the primary trigger but also referred to as the "vital sign of the respiration" by some authors because it can represent a valuable diagnostic tool. Besides during the application of NAVA, the EADi curve and its corresponding value can be displayed during other ventilation modes and even during standby. The presence of an EADi signal confirms spontaneous inspiratory efforts and diaphragmatic activity, and its absence may indicate central apnoeic phases and/or a diaphragmatic paralysis. Its amplitude provides information about the respiratory drive, the diaphragmatic loading or unloading, as well as the effects of ventilator settings and sedation. The peak value was shown to be a good surrogate parameter of the central respiratory drive in both healthy and respiratory failure subjects [6, 9]. In healthy subjects, a low EADi amplitude reflects a good efficiency of the diaphragm. In contrast, a very high EADi signal represents a high respiratory drive, which can be due to agitation, impairment of lung function, high oxygen consumption, hypoxemia or hypercapnia, and therefore may indicate worsening of the patient's condition. In turn, a decreasing EADi signal due to adjustments of respiratory parameters may represent an improvement of the patient's status. In conclusion, observing the effects of ventilator adjustments on the EADi signal is a helpful tool for titrating respiratory support, level of sedation, and respiratory drive. Accordingly, an optimum PEEP level may be achieved by titrating the PEEP to the lowest possible EADi value, as a decreasing value indicates decreasing WOB. Caution, a very low, flat or disappeared EADi signal may be due to excessive sedation, over-assistance and/or low partial pressure of carbon dioxide ($PaCO_2$).

There is a linear relationship between the EADi signal and the diaphragm's ability to recruit muscle fibres. The amplitude (EADi peak) and its slope depend on the rate of action potentials at the motor unit and the inspiratory part of the EADi signal's area under the curve (AUC); this reflects the maintenance of muscle force over time. The ratio of peak value and inspiratory AUC (P/I Index) has been proposed as a measure for the balance between respiratory drive and inspiratory effort maintenance. High index values were associated with short inspiratory times and weaning failure in a small physiological study. Furthermore, the P/I index was shown to better predict weaning failure than the rapid shallow breathing index [10]. Thus, the EADi signal provides information on muscle contraction efficiency and may also help to diagnose and monitor the ventilator-induced diaphragmatic dysfunction (VIDD), which is associated with prolonged mechanical ventilation and difficult weaning. In summary, NAVA can help to identify and quantify spontaneous

breathing efforts, respiratory muscle efficiency, monitoring patient-ventilator interaction and help to guide escalation, e.g. intubation, or de-escalation, e.g. weaning and discontinuation, of the respiratory therapy.

In combination with airway or oesophageal pressure curves, SVA can be detected. An EADi peak without an appropriate increase in airway pressure and airway flow represents an ineffective effort, where the patient's respiratory effort has not been answered by the ventilator. In contrast, a given breath without EADi amplitude was auto-triggered. Is the neural inspiratory time, e.g. the duration of elevated EADi value above baseline, longer than the inspiratory phase of the ventilator, double triggering may occur. The latter is unlikely in EADi-triggered breaths because cycling-off depends on the EADi peak value. However, this phenomenon is possible during pneumatically triggered breaths.

After initial stabilization, the patient further improves. With a further reduced NAVA Level, PEEP, and FiO_2, the EADi signal indicate effective diaphragmatic contractions and the blood gas analyses revealeno clinically significant values. Weaning from NIV-NAVA is started and the NAVA Level is further decreased accordingly. After total time on NIV-NAVA of 2 days, the respiratory support is discontinued and the patient is discharged from ICU.

28.2.9 Weaning with and from NAVA

Successful liberation from mechanical ventilation requires effective neuro-respiratory coupling and effective muscle contractions. While prolonged mechanical ventilation induces respiratory muscle atrophy, assisted spontaneous breathing activity prevents VIDD.

Numerous studies revealed important physiological advantages of NAVA, which may be beneficial during the liberation from both non-invasive and invasive ventilation. In the majority of trials, weaning with NAVA from invasive ventilation was studied but in general, there is very limited evidence that (NIV-)NAVA could reduce the time on the ventilator in comparison to other modes of mechanical ventilation. However, weaning success or failure may be predicted by analysing the EADi signal. In a physiologic study, the EADi area under the curve (AUC) was significantly lower and the ratio of the EADi peak value and the inspiratory AUC was higher in patients who failed ventilation liberation trials [10]. Further potential advantages of NAVA during weaning from ventilation are the possibility of monitoring the muscular efficiency and activity as well as the effects of changing respiratory parameters on the ventilator, the possibility to keep the same ventilator unit and just exchanging different patient interfaces during the consecutive steps of weaning. By keeping the NAVA-Catheter in place, even re-escalation of respiratory therapy is easy to perform. While all the aforementioned theoretical advantages suggest that NAVA may promote weaning, comparative trials evaluating the weaning efficiency are needed to prove this assumption.

Practically, one may reduce the NAVA Level as well as FiO_2 and PEEP during the weaning process and observe the effects on the EADi signal and other respiratory variables, as well as the vital signs. If the patient's condition is stable, stop ventilation and continue monitoring for a certain amount of time.

Key Teaching Points

- NAVA is a physiological-based mode of ventilation where breaths are neurally triggered by the electrical activity of the diaphragm, while the inspiratory pressure is applied in proportion to the detected myography signal
- NAVA can be used for non-invasive and invasive ventilation with different patient interfaces
- Proper placement of the NAVA-Catheter, close monitoring, as well as adjustments of ventilator settings and alarm limits, are essential for the success of NIV-NAVA
- Neural triggering can improve patient-ventilator synchrony and resembles the variable breathing patterns of the patient
- The EADi signal provides valuable information about neuro-respiratory coupling, respiratory effort and integrity of the diaphragm while helping to titrate the respiratory support and monitor the resulting effects

Conflict of Interest None.

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Chapter 29
Non-invasive Mechanical Ventilation in Pneumonia

Maria Joana Pereira

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
FEV1	Forced expiratory volume in the first second
FiO_2	Inspiratory fraction of oxygen
FVC	Forced vital capacity
IPAP	Inspiratory positive airway pressure
NI	Non-invasive ventilation
PEEP	Positive end-expiratory pressure
VC	Vital capacity

29.1 Introduction

Positive studies on hypoxemic, nonhypercapnic respiratory failure, mainly caused by community- or hospital-acquired pneumonia, have enrolled carefully selected patients who are cooperative with no associated major organ dysfunction, cardiac

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ischemia or arrhythmias, and with no limitations in clearing secretions, which may explain the benefits seen. The main risk of NIV for the indication of "de novo" acute respiratory failure (ARF) is to delay the need of intubation. Early predictors of NIV failure include higher severity score, older age, acute respiratory distress syndrome (ARDS) or pneumonia as the etiology for respiratory failure, or a failure to improve after 1 h of treatment [1].

Clinical Case

A 32-years-old male patient came to the emergency department with shortness of breath and fever. His medical history included severe obesity (index mass body of 45 kg/m^2), he was a never smoker and he had no past medication.

The patient described 1 week of increasing shortness of breath and dyspnea on exertion and fever for 4 days. He reported cough with sputum and denied hemoptysis, chest pain, or lower extremity edema. He presented at emergency department with fever, tachypnea, tachycardia and his arterial blood gases revealed a hypoxemic acute respiratory failure with respiratory alkalosis (pH 7.53, pCO_2 30 mmHg, pO_2 49 mmHg, HCO_3^- 24 mEq/L, PaO_2/FiO_2 233). The thoracic X-ray revealed an image of pulmonary consolidation in the left lower lobe, compatible with pneumonia. It was identified a positive pneumococcal urinary antigen test and the patient started amoxicillin/clavulanic acid and azithromycin.

In order to correct acute respiratory failure and decrease respiratory effort, the patient started NIV at the emergency department with cardio-respiratory monitoring. He was treated with bilevel positive pressure NIV (Philips Respironics V60) through facial mask, spontaneous/time mode with IPAP 16 cmH_2O, EPAP 8 cmH_2O, respiratory rate 16, inspiratory time 1.0 s, inspiratory fraction of oxygen (FiO_2) 80% with controlled leaks and total volume of 550 mL. The clinical case was also discussed with the intensive care team to consider invasive ventilation if there were signals of NIV failure.

The patient was admitted to the Pulmonology ward to maintain cardio-respiratory monitoring and to proceed with medical care. With the intention to correct hypoxemia, the patient alternated NIV with high concentration oxygen mask. Despite the initial severe hypoxemia, the patient had a good response to antibiotics with rapid recover of pneumonia and correction of hypoxia. The NIV weaning was performed by reducing the number of hours and reducing the pressure support and FiO_2.

During hospitalization we asked the patient symptoms compatible with obstructive sleep apnea. He reported that had morning headache, daytime hypersolence, nocturia and insomnia. The patient was discharged without oxygen and was referred for sleep disorders consultation. He was submitted to a type 3 polysomnography on an outpatient basis, which revealed obstructive sleep apnea with apnea-hypopnea index (AHI) of 30. His lung function test revealed a mild restrictive syndrome (Fig. 29.1 and Table 29.1). The patient started auto CPAP 6–14 cmH_2O and at follow-up visit, it was found that the patient was on CPAP every night (about 6–8 h), with AHI less than 5 and reported significant improvement in his symptoms.

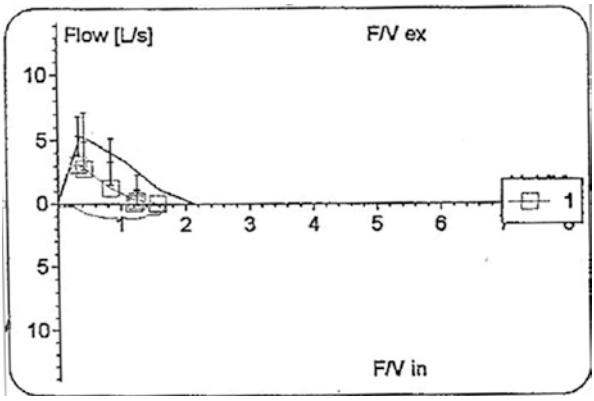

Fig. 29.1 Flow-volume curve (see Table 29.1)

Table 29.1 Ventilatory parameters

	Unit	Theoretical value	Actual value	%Act./Th.
VC MAX	[L]	2.22	1.65	74.5
VC IN	[L]	2.22	1.65	74.5
FVC	[L]	2.13	1.56	73.2
FEV1	[L]	1.75	1.20	68.5
FEV1 % FVC	[%]	–	–	77.15

VC vital capacity, *FVC* forced vital capacity, *FEV1* forced expiratory volume in the first second

29.2 Discussion

NIV has been used for patients with respiratory failure since the 1940s. Initially, NIV aimed to support ventilatory respiratory failure, e.g. during exacerbations of COPD. Later, the benefit of NIV was confirmed for cardiogenic pulmonary oedema. Nevertheless, the application of NIV in hypoxaemic respiratory failure is still controversial. The indications and contra-indications of starting NIV in acute care are described in Table 29.2 [1].

In acute hypoxaemic respiratory failure (mostly patients with ARDS), the pathogenesis and physiological alterations are substantially different from those of cardiogenic pulmonary oedema. The alveolar damage, including injury of pulmonary capillary vessels, occurs in almost the entire lung, leading to fluid leakage into pulmonary tissues and marked inflammation. Although invasive mechanical ventilation is a standard treatment as a protective strategy in these patients, NIV can also play a role in acute hypoxemic respiratory failure. Improvement of oxygenation during NIV has been observed in ARF patients. This is caused by several mechanisms: modern NIV machines can provide a high concentration of oxygen, which is adjustable, as with the invasive mechanical ventilator; the applied CPAP can work as PEEP in order to recruit and keep open the collapsed alveoli; the CPAP decreases

Table 29.2 Indications and contra-indications of NIV in acute respiratory failure

Indications
Increased dyspnea moderate to severe
Tachypnoea (>24 breaths/min in obstructive, >30/min in restrictive)
Signs of increased work of breathing, accessory muscle use, and abdominal paradox
Acute $PaCO_2$ >45 mmHg, pH <7.35
Hypoxaemia (use with caution), PaO_2/FiO_2 ratio <200
Absolute contra-indications
Respiratory arrest
Unable to fit mask
Relative contra-indications
Agitated, uncooperative
Unable to protect airway
Swallowing impairment
Excessive secretions
Multiple organ failure
Hypotensive shock
Uncontrolled cardiac ischaemia or arrhythmia
Upper gastrointestinal bleeding

the gradient pressure across pulmonary capillaries, probably resulting in decreased extravascular lung water. In terms of inflammation, application of bilevel positive airway pressure ventilation can reduce the concentrations of inflammatory cytokines such as interleukin-8 measured in serum and bronchoalveolar lavage fluid [2].

In highly selected cooperative patients with isolated respiratory failure, NIV has been shown in experienced hands to prevent intubation. The overall effect in the studies is positive on this end-point, but not for other end-points such as mortality [1].

The application of NIV in patients with so called de novo acute hypoxemic respiratory failure related to pneumonia or acute respiratory distress syndrome (ARDS) has long been known to be more challenging than in more favourable diagnoses like COPD or acute cardiogenic pulmonary edema, with NIV failure rates for pneumonia/ARDS exceeding 60% in some studies [3].

NIV could be considered for acute hypoxemic respiratory failure due to respiratory infections especially in immunosuppressed patients, for palliation, acute exacerbation of interstitial lung disease [1]. However, may be contraindicated in a patient with pneumonia caused by gram positive bacteria due to high amount of secretions

[2]. During application of NIV, the most important issue is to have the patient under cardio-respiratory monitoring. If goals such as decreasing FiO_2 levels are reached, it may be continued. Nevertheless, if the patient response is not sufficient, invasive ventilation should be instituted without delay [2].

The settings for NIV in acute hypoxemic respiratory failure patients may be started with IPAP of 10 cmH_2O and EPAP of 10 cmH_2O. However, final settings should be adjusted according to patient comfort and oxygenation. The target of gas exchange is to keep PaO_2 above 60 mmHg (8.0 kPa) and to optimise ventilation. In case of hypotension or shock, NIV should be avoided, especially in severe community acquired pneumonia.

Reasons for the poor track record of NIV for patients with pneumonia/ARDS include the need for higher levels of positive end-expiratory pressure (PEEP) to treat the hypoxemia and higher levels of pressure support to counter the increased stiffness of lungs to alleviate work of breathing and dyspnea. These higher pressures necessitate greater strap tension to control mask leaks, contributing to mask discomfort. In addition, the air leaks, in combination with the high respiratory rates and minute volumes seen in patients with pneumonia/ARDS make it difficult for ventilators to achieve good synchrony, contributing further to patient intolerance [1, 2].

Recently, high-flow nasal cannula therapy has been shown to offer several advantages compared with NIV, including better tolerance and dead space reduction [1]. Therefore, high-flow nasal therapy can be other option than NIV for hypoxia in pneumonia but there is a need for further studies [4]. On the other hand, Patel and colleagues favours the idea that the interface makes a big difference when NIV is used and that the helmet may lead to an even greater reduction in need for intubation than high-flow nasal therapy when compared to face mask NIV [4]. This can be explained by the fact that, differently from face masks, helmets permit longer-term treatments and allow the setting of higher levels of PEEP without causing air leaks or important patient-ventilator asynchrony; this aspect may be crucial when treating severely hypoxemic patients with acute respiratory failure and the acute respiratory distress syndrome [5]. As a general rule, more severe patients are more recruitable and most benefit from higher PEEP that can be assured through the helmet during NIV with minimal leaks.

In this clinical case, hypoxemia could be corrected using NIV with high levels of EPAP and FiO_2. The patient was young, collaborative, and had few secretions these, we believe, were the reasons why NIV was a success, avoiding the complications inherent to intubation and invasive mechanical ventilation. Furthermore there was no registration of ventilator asynchronies (see Fig. 29.2).

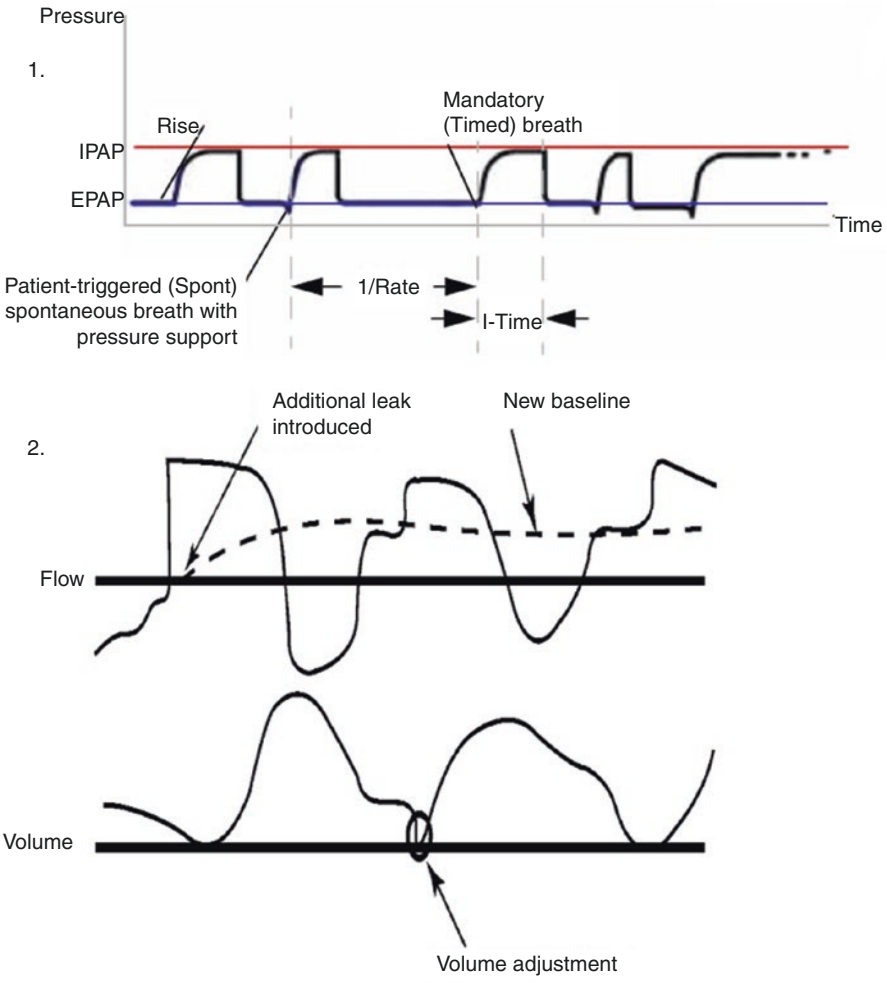

Fig. 29.2 (1) Mode spontaneous/time bilevel non-invasive ventilation (Philips Respironics V60). (2) Tidal volume adjustment. Every breath, the ventilator compares the inspiratory and expiratory tidal volumes. Any difference is assumed to be due to an unintentional circuit leak. The ventilator adjusts the baseline to reduce this tidal volume difference for the next breath (Philips Respironics V60)

Key Teaching Points

- Noninvasive ventilation may be used in the initial period of supportive treatment in acute hypoxic respiratory failure.
- NIV can be used in immunosuppressed patients with pneumonia.
- NIV may be contraindicated in a patient with pneumonia with high amount of secretions.
- It is mandatory to avoid delaying intubation in patients who do not respond to NIV.

Questions and Answers

1. About Neuromuscular Disease, what is the correct statement?

   (a) Long-term NIV should be considered in patients with severely compromised bulbar function.
   (b) Severe bulbar involvement is a controversial indication for noninvasive respiratory care.
   (c) Noninvasive mechanical ventilation does not provide rest to the respiratory muscles because the disease is neuromuscular.
   (d) Symptoms of alveolar hypoventilation are irrelevant in patients with hypercapnia.
   (e) All of above.

   Answer: (b) Severe bulbar involvement is a controversial indication for noninvasive respiratory care.

2. The introduction of NIV in neuromuscular patients is predicted in which of the following situations?

   (a) Hypoxemia of 64 mmHg, without hypercapnia.
   (b) Vital capacity of 75% with 5% loss in dorsal decubitus.
   (c) Nocturnal oximetry demonstrating ≤88% for 5 consecutive minutes.
   (d) Maximal Inspiratory Pressure above 60 cmH_2O.
   (e) All of above.

   Answer: (c) Nocturnal oximetry demonstrating ≤88% for 5 consecutive minutes.

3. From the following statements, choose the true

   (a) For patients with nocturnal NIV, pressure ventilation is preferable because it is more comfortable and allows leakage compensation.
   (b) In neuromuscular disease, NIV should only be introduced when there is hypercapnia.

(c) The choice of ventilation mode does not depend on the degree of ventilatory dependence.
(d) NIV has not been shown to increase the quality of life of neuromuscular patients.
(e) None of the previous.

Answer: (a) For patients with nocturnal NIV, pressure ventilation is preferable because it is more comfortable and allows leakage compensation.

4. In the assessment of respiratory failure in neuromuscular patients:

(a) The residual volume may be increased
(b) Maximum inspiratory pressure decreases earlier than vital capacity
(c) Transcutaneous CO_2 night recording is useful to detect nocturnal hypoventilation
(d) The reduction in vital capacity in the supine position suggests diaphragmatic dysfunction.
(e) All points are correct.

Answer: (e) All points are correct.

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Chapter 30
Non Invasive Ventilation in High Risk Infections

Maria Joana Pereira and Sónia André

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CV	Vital capacity
EPAP	Expiratory positive airway pressure
FEV1	Forced expiratory volume in the first second
FiO_2	Inspiratory fraction of oxygen
FVC	Forced vital capacity
IC	Inspiratory capacity
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
NIV	Non-invasive ventilation
PEEP	Positive end-expiratory pressure
PPE	Personal protective equipment
RCT	Randomized clinical trial
TB	Tuberculosis

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30.1 Introduction

Acute respiratory failure (ARF) is the main indication for Intensive Care Unit (ICU) admission in immunocompromised patients. Currently available literature supports the use of NIV as a first-line approach for managing mild to moderate ARF in selected patients with immunosuppression of various aetiologies [1]. Several studies have reported clinical benefits of NIV, although strict monitoring in the ICU and prompt availability of invasive mechanical ventilation are mandatory [1]. From the first descriptions of HIV, the lung has been the site most frequently affected by the disease. Bacterial pneumonia is currently the most frequent cause of pulmonary infections in HIV-infected patients, followed by Pneumocystosis and tuberculosis [2]. The use of NIV in the setting of acute hypoxemic respiratory failure reduces the rate of endotracheal intubation, ICU length of stay, and ICU mortality in HIV patients with pulmonary infections [1].

In this chapter, the authors present a case report of an HIV patient with a severe hypoxic acute respiratory failure due to a pulmonary infection that was submitted to NIV.

Clinical Case

A 67-years-old male patient infected with HIV came to the emergency department with shortness of breath and fever. His medical history included also hypertension, obesity (index mass body of 32 kg/m^2) and he was a never smoker. From the last follow-up he had CD4+ above 400 and had no viral charge. The last respiratory function test was normal (Fig. 30.1 and Table 30.1). He was previously medicated with losartan and antiretroviral therapy.

The patient described 1 week of increasing shortness of breath and dyspnea on exertion. He noted a decreased exercise tolerance, as he previously was able to walk long distances without limitation, but at the time of presentation could walk only a few steps before becoming short of breath. He report cough with sparse sputum and had fever for 2 days. The patient denied hemoptysis, chest pain, or lower extremity edema. He presented with tachypnea, tachycardia and his arterial blood gases

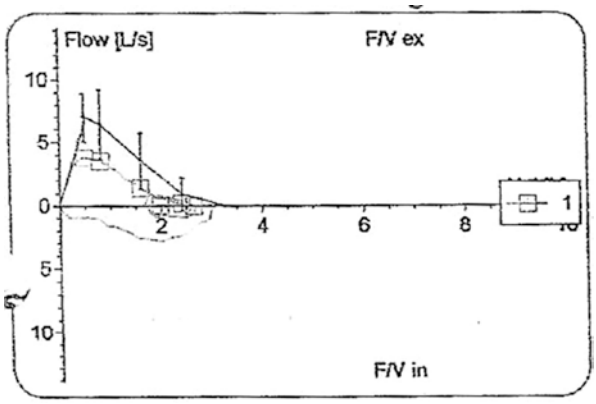

Fig. 30.1 Flow-volume curve (see Table 30.1)

Table 30.1 Ventilatory parameters

	Unit	Theoretical value	Actual value	%Act./Th.
VC MAX	[L]	3.31	3.19	96.6
VC IN	[L]	3.31	3.19	96.6
FVC	[L]	3.21	2.63	82.0
FEV1	[L]	2.34	1.97	84.2
FEV1 % FVC	[%]	–	–	74.84

VC vital capacity, *FVC* forced vital capacity, *FEV1* forced expiratory volume in the first second

revealed a hypoxemic acute respiratory failure with respiratory alkalosis (pH 7.53, pCO_2 30 mmHg, pO_2 47 mmHg, HCO_3^- 24 mEq/L, PaO_2/FiO_2 224). There was no major alteration at thoracic X-ray or echocardiogram. The bacterial sputum culture and the Ziehl-Neesel staining were negative, however it was identified syncytial respiratory virus. In order to decrease respiratory effort, the patient was treated with bilevel positive pressure NIV (Philips Respironics V60) through facial mask, spontaneous/time mode with IPAP 18 cmH_2O, EPAP 8 cmH_2O, respiratory rate 16, inspiratory time 1.2 s, inspiratory fraction of oxygen (FiO_2) 95% with controlled leaks and total volume of 700 mL (Fig. 30.2). The patient was admitted to an intermediate unit care for cardio-respiratory monitoring and to proceed with medical care. With the intention to correct hypoxemia, the patient was treated with NIV and alternated with high concentration oxygen mask. Despite the therapy instituted, the patient remained with severe hypoxemia. In addition to the bi-level NIV strategy, the patient also alternated with CPAP at 8 cmH_2O pressure and 100% FiO_2 (Fig. 30.2), which proved to be as effective as bi-level positive pressure therapy. The patient underwent chest CT that showed a pattern of dispersed ground glass. In order to try to identify another opportunistic agent, bronchofibroscopy with bronchoalveolar lavage collection was performed and it was sent to microbiology for identification of fungi, cytomegalovirus, Ebstein-Barr virus, herpes simplex, *Pneumocystis jiroveci* and *Mycobacterium tuberculosis*. From the microbiological study, the culture test was positive for *Mycobacterium tuberculosis*. Therefore, the patient was admitted to a negative-pressure isolation room and started anti-bacillary therapy. Tuberculosis screening was also performed for family members, health professionals and other patients.

After the institution of antibacillary therapy, there was a progressive improvement in respiratory insufficiency and weaning of NIV was possible, leaving the patient with oxygen therapy only at 2 L/min.

30.2 Discussion

Acute respiratory failure is the most common cause for ICU admission in HIV patients. It is the presenting symptom in 25–50% of HIV cases, being pneumonia the most common ICU admission diagnosis [2]. Currently, the most frequent

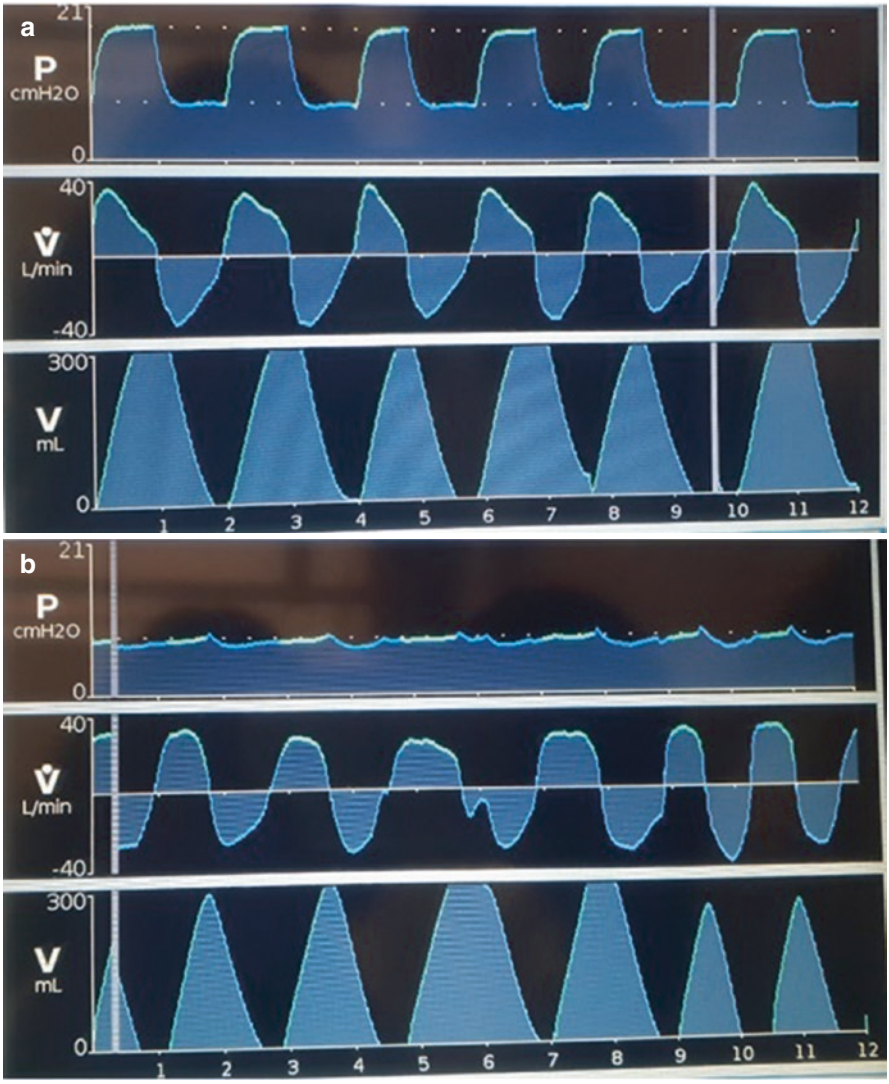

Fig. 30.2 (**a**) Waveforms of pressure (cmH_2O), flow (L/min) and volume (mL) in the patient under NIV (Philips Respironics V60) through facial mask, spontaneous/time mode with IPAP 18 cmH_2O, EPAP 8 cmH_2O, respiratory rate 16, inspiratory time 1.2 s, inspiratory fraction of oxygen (FiO_2) 95% with controlled leaks and total volume of 700 mL. (**b**) Waveforms of pressure (cmH_2O), flow (L/min) and volume (mL) in the patient under CPAP 8 cmH_2O pressure and 100% FiO_2, with controlled mask leaks. (Courtesy of Dr Sónia André from Intensive Care Unit of Hospital Centre of Porto University)

diagnosis in HIV patients from developed countries is bacterial pneumonia, especially pneumococcal pneumonia, the second most frequent cause is Pneumocystis pneumonia and the third is tuberculosis [2]. Moreover, respiratory viruses also

contribute to pulmonary complications in HIV-infected patients and might be a cause of ARF.

In order to identify the microbiologic agent, spontaneously expectorated sputum sample can be an option. However, because of its high yield and low complication rate, fibreoptic bronchoscopy remains the procedure of choice for diagnosing many pulmonary diseases in HIV-infected patients and it can be performed under NIV.

Concerning to the treatment of ARF in immunocompromised patients, the outcomes of applying NIV in this group of patients have been shown in RCTs. Antonelli et al. (2000) administered NIV to solid organ transplantation patients, and compared it with standard oxygen therapy in a total of 40 randomised patients. Approximately 40% of patients had ARDS and 10% had pneumonia. The NIV group showed higher improvement of PaO_2/FiO_2 than the standard oxygen therapy group. Four (20%) patients on NIV required intubation. Among these, three patients had ARDS and one patient had pneumonia. The failure rate was significantly higher in the standard oxygen therapy group [3]. Another RCT by Hilbert et al. (2001) included diverse immunocompromised patients: some with haematological malignancy, and some with other diseases requiring immunosuppressive agents and/or organ transplantation. A total of 52 patients were randomly assigned to receive NIV or standard oxygen therapy. Failure occurred in 12 (46%) patients in the NIV group, significantly fewer than in the standard oxygen therapy group. Most of the failure patients had haematological malignancies. The mortality rate was found to be significantly lower in the NIV group than in the standard oxygen therapy group [4].

NIV showed to contribute for lung recruitment with proper use of PEEP and it was associated with improvement in hypoxia, dyspnea, and relief of respiratory muscle fatigue [5]. In addition, applying NIV in immunocompromised patients can avoid side effects directly related to endotracheal intubation and invasive mechanical ventilation, such as ventilator-associated pneumonia, excessive sedation, upper-airway injuries and tracheomalacia, thus it can lead to a better clinical outcome [5]. Similarly, early CPAP has been reported as a practical, simple and inexpensive method to prevent deterioration of respiratory function and complications in such patients. The recommendation is inclusive both of bilevel NIV and early CPAP as the current evidence demonstrates the benefit of both interventions compared with standard care. Furthermore, the use of high-flow nasal cannula oxygen therapy to correct severe hypoxia might be a good choice; however more studies are required to determine whether this modality has advantages over NIV [1]. It is also important to understand that, although NIV should be used in immunocompromised patients to treat ARF, when the patient has severe respiratory failure with acute respiratory distress syndrome (ARDS), NIV should not be considered as a first-line therapy [1].

In regard to high risk infections, NIV can be a solution not only for the provision of long-term and domiciliary-assisted ventilation in patients with sequelae of pulmonary tuberculosis (TB), but also for acute exacerbations of pulmonary TB (Table 30.2) and may be helpful in early cases of acute respiratory infection (e.g. influenza) to avoid the need for intubation and invasive ventilation [5]. The concern with the use of NIV in such acute situations is linked with the potential risk of the transmission of TB or other contagious pathogen.

Table 30.2 *ARF-TB* acute respiratory failure associated with TB pulmonary infection, *HCW* healthcare workers, *MV* mechanical ventilation, *AEPTS* acute exacerbations of pulmonary TB sequelae, *ARDS* acute respiratory distress syndrome

First author	Year	Country	Study design	Type of ARF-TB	Interface	NIV failure	Transmission among HCW[a]	Mortality	Home MV after AEPTS
Tsuboi	1996	Japan	Prospective cohort (n = 17)	AEPTS in mixed groups	Nasal mask	0	No	0	Yes
Machida	1998	Japan	Retrospective survey (n = 58)	AEPTS	Nasal mask	0	No	0	Yes
Prats Soro	1999	Spain	Case report (n = 1)	AEPTS	Nasal mask	0	No	0	Yes
Schulz	1999	Germany	Prospective cohort (n = 26)	AEPTS	Nasal mask	0	No	0	Yes
Agarwal	2005	India	Cases series cohort (n = 3)	ARDS and *Mycobacterium tuberculosis* AEPTS	Face mask	0	No	0	No
Utsugi	2006	Japan	Case report (n = 1)	ARF, miliary TB and AEPTS	Face mask	0	No	0	No
Aso	2010	Japan	Prospective cohort (n = 58)	AEPTS	Face mask	13.8%	No	1.7%	No

Adapted from Ref. [6]

[a]Instances of transmission of *Mycobacterium tuberculosis* among HCW

Whether or not NIV should be considered a high-risk procedure in infectious diseases like TB continues to be a controversial issue. Therefore, it is crucial that reasonable and adequate precautionary steps are followed in order to protect healthcare workers from an infectious spread, as well as other patients and family members [6]. When considering the choice of ventilators, physicians should give preference to machines equipped with a dual-limb circuit without an unfiltered expiratory port (i.e. plateau exhalation valve, anti-rebreathing valve, etc.) [7]. Such technology avoids the dispersion of expired air contaminated by infected particles through a circuit leak. Moreover, those leaks are caused by bias flow necessary to prevent rebreathing in single-limb circuits and are magnified by the high positive end-expiratory pressure levels that are often required in the treatment of acute hypoxemic respiratory failure [8].

Initial low pressures (e.g. IPAP 10 cmH_2O and EPAP 4 cmH_2O) should be employed to reduce the risk of barotrauma, with further titration to relieve respiratory distress, and correct SpO_2 and arterial blood gas tensions. CPAP (e.g. 5–10 cmH_2O) may be sufficient in previously fit patients but in those with a high work of breathing, hypercapnia, or comorbidities such as obesity hypoventilation syndrome, neuromuscular disease or COPD, NIV is the intervention of choice.

Regarding interface selection, full face or total face masks might be preferred to nasal masks in order to theoretically prevent the potential spread of contaminated exhaled air particles from unintended air leaks through the mouth [6]. Therefore, choosing the brand and size of mask that best fits the anatomy of the patient's facial contours and, at the same time, allows delivery of adequate pressure levels which is crucial to minimise unintended air leaks around the interface [8]. Recently, a helmet interface has become available for delivering NIV and, in the majority of patients, a helmet is better tolerated than a face mask and may decrease the dispersion of infected respiratory droplets [6]. Furthermore, education in infection control is essential, including the aspects of personal protected equipment (PPE). All staff applying NIV should be experienced in its use. Handwashing facilities and PPE should be fully available. Moreover, negative-pressure rooms should be used if available but dissemination may be largely by large droplets and direct contact. Therefore, there should be a minimum distance of 1 m between beds in cohort-managed areas.

Key Teaching Points

- It is recommended to use bilevel NIV or early CPAP to correct acute respiratory failure in immunocompromised patients.
- The majority of HIV patients who received NIV avoided intubation and had better outcome compared to patients under invasive mechanical ventilation.
- NIV remains an option for ventilatory support in both acute and chronic respiratory failure secondary to pulmonary TB.
- The use of a helmet interface for NIV together with negative pressure rooms equipped with high-efficiency particulate air filters, may decrease the dispersion of infected respiratory droplets.

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Chapter 31
Clinical Conditions—Acute Hypoxemic Respiratory Failure: Non Invasive Ventilation in Pneumonia

Christos Triantafyllou and Pavlos M. Myrianthefs

Abbreviations

AHRF	Acute hypoxemic respiratory failure
APACHE	Acute physiology and chronic health evaluation system II
APE	Acute pulmonary edema
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
CAP	Community acquired pneumonia
CI	Confidence interval
CMO	Comfort-measures-only
COPD	Chronic obstructive pulmonary disease
CXR	Chest X-ray
DNI	Do-not-intubate
ED	Emergency department
EPAP	Expiratory positive airways pressure

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FiO_2	Fraction of oxygen in inspired air
HAP	Hospital-acquired pneumonia
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
IPAP	Inspiratory positive airways pressure
LoS	Length of stay
NIV	Non-invasive ventilation
OR	Odds ratio
PaO_2	Arterial partial pressure of oxygen
PEEP	Positive end-expiratory pressure
RCT	Randomized controlled trial
RF	Respiratory failure
RR	Relative risk
SaO_2	Oxygen saturation
VS	Versus
Vt	Tidal volume

31.1 Introduction

In the United States, Acute Respiratory Failure (ARF) is the leading cause of Emergency Department (ED) admissions and is associated with high mortality rate (≈20%) and annual costs (≈54 billion USD) [1]. ARF is classified as hypercapnic or hypoxemic. In Acute Hypoxemic Respiratory Failure (AHRF) the arterial partial pressure of oxygen (PaO_2) is less than 55 mmHg when the fraction of oxygen in inspired air (FiO_2) is 0.60 (60%) or greater. Intrapulmonary shunting is the main cause of hypoxemia (low blood oxygen saturation) in conditions such as pneumonia in which the lungs become consolidated.

Concerning pneumonia, it is defined as inflammation of the substance of the lungs and can be caused by bacteria, viruses and fungi. Clinically, it usually presents as an acute illness with cough, purulent sputum, breathlessness and fever, together with physical signs on auscultation or radiological changes compatible with consolidation of the lung. Nevertheless, it can present with more subtle symptoms, particularly in the elderly. Pneumonia is usually classified by the setting in which the person has contracted their infection.

- **In the community setting**: community-acquired pneumonia (CAP) in a person without underlying immunosuppression or malignancy (immunocompetent).
- **In a hospital or other institution such as a nursing home**: hospital-acquired pneumonia (HAP) or nosocomial pneumonia (NP).
- In a patient whose **immune system is compromised**, through either a genetic defect, immunosuppressive medication or acquired immunodeficiency such as human immunodeficiency virus (HIV) infection.

The management of AHRF **along with the administration of anti-infective agents and other supportive measures** may require an "escalation therapeutic strategy" based on the application of a wide range of ventilatory and non-ventilatory interventions. Non-invasive ventilation (NIV) refers to the provision of ventilatory support through the patient's upper airway using a mask or similar device [2]. This technique is distinguished from those which bypass the upper airway with a tracheal tube, laryngeal mask, or tracheostomy which are considered invasive [2].

Benefits of NIV in AHRF etiologies, such as pneumonia, acute respiratory distress syndrome (ARDS) and immunosuppression, have not been clarified since results from studies remain conflicting [1]. Therefore; the aim of this chapter is to determine the efficacy of the use of NIV in patients with pneumonia **according to current literature**.

31.2 Acute Hypoxemic Respiratory Failure Due to Pneumonia and Non-invasive Ventilation

Currently, randomized controlled trials (RCTs) describing whether NIV is beneficial in pneumonia and AHRF are still scarce and uncommon incorporating heterogeneous patient population with varying causes of ARF including a small percentage of pneumonia patients.

A recent meta-analysis [1] evaluated current recommendation for the use of NIV in AHRF, excluding chronic obstructive pulmonary disease (COPD). NIV showed a significant protective effect for intubation in immunosuppressed patients (cancer and transplants) and in patients with acute pulmonary edema (APE)/CAP. The pooled relative risk (RR) (95% Confidence interval-CI) for intubation in patients with APE/CAP and in immunosuppressed patients (cancer and transplants) were 0.61 (0.39–0.84) and 0.77 (0.60–0.93), respectively (Fig. 31.1). For Intensive Care Units (ICU) mortality, the RR (95% CI) in patients with APE/CAP was 0.51 (0.22–0.79).

Moreover, in this meta-analysis, two studies that analyzed patients with CAP were included [3, 4]. The first one was an RCT involving patients admitted to the ICU with AHRF to determine whether high-flow oxygen therapy or NIV therapy, as compared with standard oxygen therapy alone, could reduce the rate of endotracheal intubation [3]. It was found that the intubation rate was 38% (40 of 106 patients) in the high-flow–oxygen group, 47% (44 of 94) in the standard group, and 50% (55 of 110) in the NIV group ($P_{value} = 0.18$ for all comparisons) and the number of ventilator-free days at day 28 was significantly higher in the high-flow oxygen group (24 ± 8 days, vs. 22 ± 10 in the standard oxygen group and 19 ± 12 in the NIV group; $P_{value} = 0.02$ for all comparisons). The other study compared standard treatment plus NIV delivered through a face mask to standard treatment alone in patients with severe CAP and ARF [4]. The results showed that the use of NIV was well

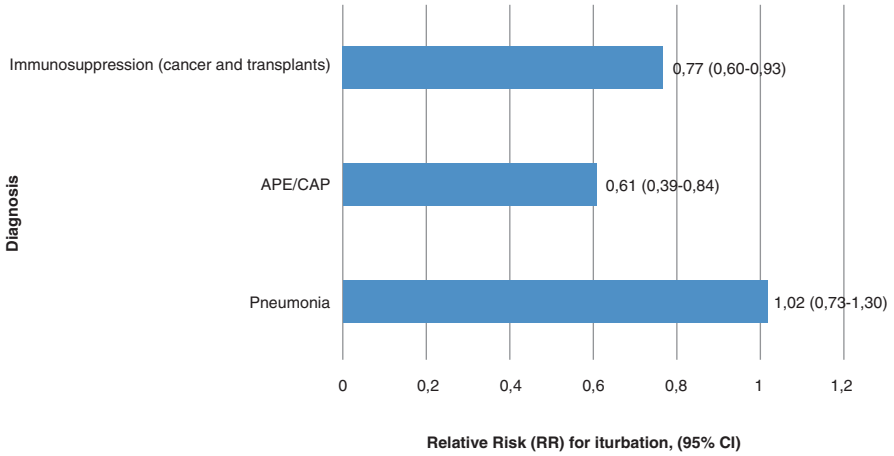

Fig. 31.1 Pooled relative risk (RR) for intubation in immunosuppression, acute pulmonary edema/community acquired pneumonia and pneumonia. *APE/CAP* acute pulmonary edema/community acquired pneumonia, *CI* confidence interval

tolerated, safe, and associated with a significant reduction in respiratory rate, need for endotracheal intubation (21% vs. 50%; $P_{value} = 0.03$) and duration of ICU stay (1.8 ± 0.7 days vs. 6 ± 1.8 days; $P_{value} = 0.04$). In the meta-analysis, the pooled RR of these two studies [3, 4], did not show that the NIV has a protective effect for intubation (1.02; 95% CI: 0.73, 130) (Fig. 31.1), with no heterogeneity ($I^2 = 0.0\%$; $P_{value} = 0.497$).

In 2018, a meta-analysis was published [5], assessing the effectiveness of NIV in patients with ARF and do-not-intubate (DNI) or comfort-measures-only (CMO) orders. The primary outcome in patients with DNI orders was survival (hospital and long term) and the secondary outcomes in survivors were quality of life, psychological symptoms, cognitive function, functional status, return home, as well as tolerance of NIV and adverse effects. In this meta-analysis, seven studies that analyzed patients with pneumonia were included. It was found that the pooled hospital survival was less in patients with ARF due to pneumonia (41%; 95% CI: 24–59%) than in patients with COPD (68%) and pulmonary edema (68%), with no statistical significant heterogeneity between the 7 studies ($I^2 = 59.84\%$; $P_{value} = 0.03$). The authors concluded that the provision of noninvasive ventilation in a well-equipped hospital ward may be a viable alternative to the ICU for selected patients.

A retrospective cohort study [6] was conducted among consecutive patients with CAP requiring ventilator support who received NIV as first line ventilatory therapy in the ED in order to describe the use and to analyze the predictors of NIV failure. The primary outcome was NIV failure defined as the need for rescue—emergency intubation and mechanical ventilation after at least 1 h of NIV and the secondary outcomes were acute hospital mortality and hospital length of stay (LoS). Of the 301 patients that initially included in the study, 218 were taken into account in the final analysis of whom, 163 (75%) were not intubated and initially treated with NIV

whereas 55 patients (25%) were intubated and mechanically ventilated. Of the 163 patients who received NIV as the first line therapy 50% failed and required endotracheal intubation. Crude acute hospital mortality rates were significantly higher in the NIV failure group (41.5% vs. 16.1%; $P_{value} < 0.001$) as were the median length of hospital stay (22.5 days vs. 10 days; $P_{value} < 0.001$). The authors suggested that the selection of the appropriate patient and monitoring of physiological parameters while on NIV is crucial to ensure successful treatment.

In 2017, a retrospective large cohort study was published [7], that aimed to determine the relationship between receipt of NIV and outcomes for patients, aged 65 years and older, with pneumonia in a real-world setting. The primary outcome was 30-day all-cause mortality measured from hospital admission and the secondary outcome was the evaluation of Medicare reimbursements for each patient that represent the real-world transaction of money paid by American taxpayers to compensate hospitals for the care provided to each patient. The final study sample included 65.747 patients admitted to 2.757 hospitals of whom, 53.267 (81.0%) received IMV first and 12.480 (19.0%) received NIV first. Moreover, of those who received NIV first, 2.485 (19.9%) subsequently received IMV and patients receiving NIV were more likely to be older, male, white, rural-dwelling, and have less comorbidities and acutely ill by organ failure scores than patients receiving IMV. This study concluded that in the instrumental variable analysis, which estimated the effect in the subset of marginal patients and controlled for patient and hospital characteristics, there was no significant difference in 30-day mortality between patients receiving NIV compared with patients receiving IMV (54.3% for NIV vs. 55.0% for IMV; $P_{value} = 0.92$) with an absolute difference in 30-day mortality of 0.7% points favoring NIV (95% CI of absolute difference: 13.8–12.4). However, this study has been criticized because of the significant difference in primary diagnosis (pneumonia) for "NIV first" group and "IMV first" group (35.2% vs. 16.9%, respectively) and the absence of clinical score does not allow for identification of subgroups at highest risk. Also, there was a significant difference in primary diagnosis (pneumonia) for "NIV first" group and "IMV first" group (35.2% vs. 16.9%, respectively).

Another historical cohort study tried to evaluate outcomes of the first ventilatory treatment applied, NIV or IMV and to identify predictors of NIV failure [8]. Of the 399 subjects with pneumonia that were admitted to the intensive care unit (ICU) during the study period, 159 were final included in the study: 113 (71%) were connected to IMV as initial ventilatory treatment and 46 (29%) received first-line NIV. Moreover, in 27 of the 46 subjects (59%) that received first-line NIV, the initial attempt failed, and they were ultimately intubated. The results of this study showed that there was no significant difference in hospital mortality between subjects with first-line IMV (35%) and subjects with first-line NIV (37%) or between subjects with first-line IMV and subjects with NIV failure (56%) (Fig. 31.2), however, the NIV failure group had higher hospital mortality than the first-line IMV group. Furthermore, compared with IMV, NIV failure delayed intubation ($P_{value} = 0.004$), and prolonged the length of IMV ($P_{value} = 0.007$), ICU LoS ($P_{value} = 0.001$) and was associated with need for vasoactive drugs (Odds Ratio-OR: 7.8; 95% CI: 1.8–33.2;

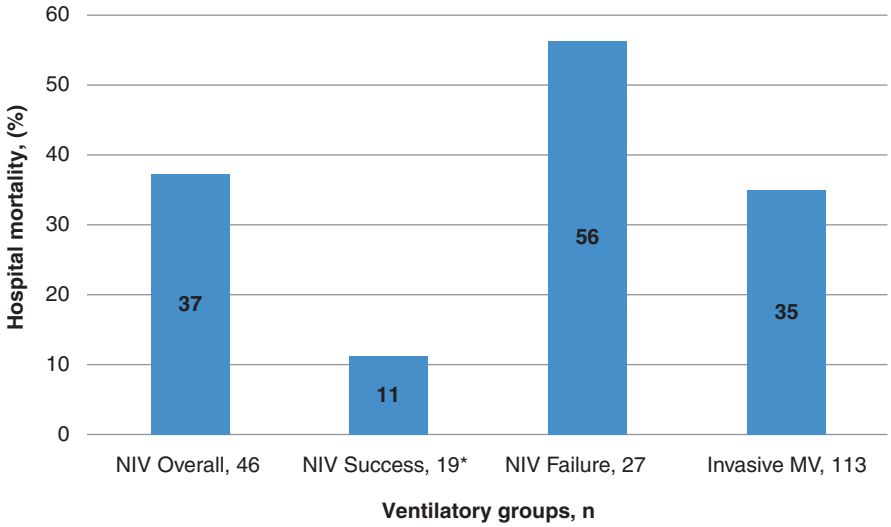

Fig. 31.2 Hospital mortality of the different ventilatory groups. *IMV* invasive mechanical ventilation, *NIV* non-invasive ventilation. $^{*}P_{value} < 0.01$

$P_{value} = 0.006$). This study suggested that in non-COPD subjects with pneumonia and need for ventilator support, those treated with first-line NIV did not have better outcome than subjects treated initially with invasive MV. Also, the authors found that NIV failure was associated with longer duration of MV and hospital stay, and with increased hospital mortality.

A large prospective study found that in pneumonia patients ≥65 years old, no or weak cough (cough strengths scale 0–2 vs. 3–5 moderate/strong coughs) is associated with NIV failure (odds ratio = 13.83, 95% CI: 6.01–31.81) and hospital death (odds ratio = 4.41, 95% CI: 2.49–7.81) [9]. Thus the authors concluded that NIV must be used only with caution in no/weak cough patients.

In a case report published in 2013 a 58-year-old man affected by severe bilateral pneumonia caused by *Legionella pneumophila* [10]. This man started a management protocol that is consisted of NIV as the main therapeutic intervention along with medication in a respiratory medicine department. Since the beginning of this treatment, patient showed a gradual improvement, with a progressive reduction of FiO_2 need and after 14 days since the hospitalization, his medical condition was improved and was discharged. In addition, authors concluded that the best location for NIV treatment is where there is a staff with training and expertise in NIV, available throughout 24 h period and with the opportunity of a rapid endotracheal intubation and an adequate monitoring in the case that the patient's condition is getting worse [10].

Carillo et al. emphasized that increased mortality risk was directly related to postponing intubation after an ineffective NIV trial or predictors of NIV failure. Increased duration of NIV before intubation for NIV failure was associated with increased in-hospital mortality [11]. Also, in patients without previous cardiac or pulmonary disease, defined "de novo," the use of NIV was associated with a high likelihood of NIV failure and consequently high intubation rates, whereas, in patients with cardiac or pulmonary diseases (i.e., chronic obstructive pulmonary disease), defined "comorbidities" group, NIV success was more frequent compared with those with "de novo" ARF (74% vs. 54%, respectively) [11].

Finally variables that independently predicts NIV failure in patients with pneumonia were found to be a higher Simplified Acute Physiology Score II (SAPS II), a worsening radiological infiltrate at 24 h after admission and a higher heart rate, lower PaO_2/FiO_2 ratio, and lower plasmatic level of bicarbonate after 1 h of NIV trial [11]. The authors concluded that patients with "de novo" ARF failed NIV more frequently than patients with previous cardiac or respiratory disease (47%, 46% versus 21%, 26%, P = 0.007) [11].

In a small trial from Italy it was patients who worsen or do not improve PaO_2/FiO_2 oxygenation index (OI) after 1-h NIV predicts NIV failure and endotracheal intubation should be an early alternative [12].

In another more recent study it was found that factors at baseline associated with NIV failure were to be associated with the absence of COPD, higher Acute Physiology and Chronic Health Evaluation II (APACHE II, per 1 point increase) score, the number of chest X-ray (CXR) quadrants involved and the need for hemodynamic support which is the strongest predictor of failure [6]. In that study it was also found that 2-h physiological parameters associated with NIV failure included higher respiratory rate, lower serum pH and the ongoing need of hemodynamic support [6]. The use of vasoactive drugs predicted NIV failure in another study and is a discouraging factor for NIV application [8]. All suggested factors predicting NIV failure in patients with pneumonia and AHRF are shown in Table 31.1.

In 2001, Hill in his historical editorial [13], concluded that there was no convincing evidence to support the routine use of NIV in non-COPD, non-immunocompromised patients with severe CAP and highlighted the need of conducting properly designed randomized controlled trials (RCTs) to prove the effects of NIV in these patients.

In conclusion further targeted, well designed randomized trials to evaluate the appropriate criteria and mode of ventilatory support for patients with pneumonia and AHRF are needed due to the lack of existing evidence to support such a critical clinical decision.

Table 31.1 Factor predicting non-invasive ventilation failure in patients with pneumonia and acute hypoxemic respiratory failure [6, 8–12]

1.	Absence of COPD
2.	Increasing APACHE II score (per 1 point increase)
3.	The number of CXR quadrants involved
4.	The need for hemodynamic support
5.	After 2-h of NIV trial physiological parameters: (a) Higher respiratory rate (b) Lower serum pH (c) Ongoing need of hemodynamic support [6]
6.	Use of vasoactive drugs [8]
7.	No or weak cough
8.	Absence of 24 h availability of trained and expertise staff in NIV [10]
9.	Increasing SAPS II score
10.	A worsening radiological infiltrate at 24 h after admission
11.	After 1 h of NIV trial: (a) A higher heart rate (b) Lower PaO_2/FiO_2 ratio (c) Lower plasmatic level of bicarbonate [11]
12	Worsen or not improve in PaO_2/FiO_2 (OI) after 1-h NIV [12]

COPD chronic obstructive pulmonary disease, *APACHE II* acute physiology and chronic health evaluation II, *CXR* chest X-ray, *NIV* non-invasive ventilation, *SAPS II* simplified acute physiology score II, *OI* oxygenation index

Key Teaching Points

- Benefits of NIV have not been clarified in AHRF etiologies, such as pneumonia, since results from studies remain conflicting and insufficient. Also, although the application of NIV for pneumonia increased significantly in recent years its role in pneumonia is controversial.
- The use of NIV to support patients presenting to the ED with AHRF and CAP is common and is associated with a significant failure rate.
- Characteristics which may indicate that NIV should be avoided as first-line therapy include higher severity of illness at admission, the need for hemodynamic support and the absence of COPD.
- The early recognition of patients with AHRF due to pneumonia that can be advantaged by the use of NIV and the correct management of the ventilation programme are fundamental to improve the AHRF treatment.
- The application of NIV to patients with pneumonia should be cautioned until enriched or well-powered randomized trials can be performed.
- NIV treatment requires a well trained and experienced staff available throughout 24 h period, an adequate patient clinical monitoring and availability of a rapid endotracheal intubation in case that the patient is getting worse.

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Chapter 32
Non Invasive Ventilation in Asthma Exacerbation

Burhan Sami Kalın

Abbreviations

%	Percent sign
bpm	Beats per minute
cmH_2O	Centimeter of water
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
ECG	Electrocardiogram
FiO_2	Fraction of inspired oxygen
HCO_3	Bicarbonate
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
L/min	Liter per minute
mg/h	Milligram per hour
μL	Microliter
mL/kg	Milliliters to kilograms
mmHg	Millimeter of mercury
mmol/L	Millimoles per liter
NC	Nasal cannula
NIV	Non-invasive ventilation
P/F	Partial pressure of arterial oxygen/fraction of inspired oxygen

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$PaCO_2$	Partial pressure of arterial carbon dioxide
PaO_2	Partial pressure of arterial oxygen
PEEP	Positive end expiratory pressure
pH	Potential of hydrogen
SpO_2	Peripheral capillary oxygen saturation
WBC	White blood cell

32.1 Introduction

Asthma is a significant public health threat, inflammatory chronic disorder of the airways affecting more than 300 million individuals globally. It is described by the respiratory symptoms such as chest tightness, dyspnea, shortness of breath, wheeze, bronchospasm, cough and often with variable expiratory airflow limitation can be displayed [1]. The severity of asthma changes both between individuals and within individuals over time. Some people may have intermittent asthma and others may experience severe, potentially life-threatening disease. An estimated 2 million patients visit emergency departments in America for asthma attacks each year. These patients can present severely hypercarbic, hypoxemic, and acidotic. Asthma attacks are typically treated with dense inhaled bronchodilators, inhaled and systemic corticosteroids, self-management education and oxygen. Adjunctive therapies used in severe or life-threatening exacerbations include epinephrine, methylxanthines, ketamine, intravenous magnesium, heliox, and invasive mechanical ventilation (IMV) and non-invasive ventilation (NIV) [2]. Guidelines for asthma management have recommended that assessment of disease severity is essential to initialize therapy and maintain treatment through a step-wise process [3]. Misclassification of the grade of severity may subscribe to the wrong using of anti-inflammatory medications, resulting in either poor asthma control or adverse side effects. Actually, NIV is commonly used for hypercapnic respiratory failure secondary to acute exacerbation of chronic obstructive pulmonary disease (COPD) in an effort to refrain IMV, congestive heart failure, acute pulmonary oedema and pulmonary infiltrates in immunocompromised patients, but there is recent interest in the use of NIV as an alternative to intubation in select patients with severe acute asthma. Endotracheal intubation requires the risk of ongoing sedatives and/or paralytics, and this procedure itself carries risk and is associated with its own relative difficulties. In spite of the lack of supporting evidence, NIV is usually used in patients with severe asthma attack for obviating the need for intubation and mechanical ventilation and its negative effects. We applied NIV to an acute asthma patient to provide the required ventilatory assistance without exposing the patient to the risks of endotracheal intubation. The aim of the case report was to describe the experience of NIV utilization in the setting of acute a severe asthma patient who does not respond to oxygen therapy.

Case Examination

A 55-year-old female with a history of asthma, with no history of smoking and no prior intubations for exacerbations had shortness of breath that was not relieved by her salbutamol inhaler (ventolin®, Glaxo Wellcome Production, France) and she activated emergency medical services for an asthma exacerbation. She had purulent sputum but neither fever. She had been diagnosed with asthma many years ago, but was treated only with a salbutamol inhaler, which she used rarely. On arrival, emergency medical services found the patient with shortness of breath and bronchospasm. She were treated with three standard doses of salbutamol nebulizer (ventolin®, GlaxoSmithKline, Australia), ipratropium bromide nebulizer (atrovent®, Boehringer Ingelheim, France) and oxygen; and transported her to *intensive care unit* (*ICU*) for an acute severe asthma exacerbation in a hour. During admission to intensive care, she was able to complete sentences, her respiratory rate was 34 breaths/min. She was using her accessory muscles to aid respiration. She was not able to lie down and remained in an orthopneic position. Her heart rate was 120 bpm, a temperature of 36.8 °C and she was normotensive (110/75 mmHg). Initial pulse oximetry was 91% with bag-mask assistance, with FiO_2 (fraction of inspired oxygen) 90%. Auscultation of the chest revealed a bilateral wheeze. Baseline a 12-lead electrocardiogram (ECG) at the time of admission showed sinus tachycardia. The remainder of the examination was normal. Medications included standard dose of intravenous magnesium (Magnesium Sulfate 40 mg/mL, WG Critical Care, LLC, Switzerland), subcutaneous epinephrine (Adrenalin® 1 mg/mL, JHP Pharmaceuticals, US) and albutamol nebulizer (ventolin®, GlaxoSmithKline, Australia) and also was given antibiotic prophylactically for potential community-acquired pneumonia (piperacillin tazobactam-Tazocin®, Wyeth Lederle S.r.L, Catania, Italy). Arterial blood gas analysis revealed acute respiratory acidosis with hypercapnia during bag-valve-mask assistance on 90% oxygen (pH 7.19, PaO_2 87 mmHg, SpO_2 92%, $PaCO_2$ 68 mmHg and HCO_3 30.2 mmol/L). Serum C-reactive protein (CRP) level was 4 mg/dL; white blood cell (WBC) count was 11,000 cells/μL. The chest X-ray revealed no infiltrate or pneumothorax, well aerated lung fields, and a hyperinflated chest. NIV (VIASYS Carefusion VELA® Comprehensive Ventilator) settings used were as follows: pressure support 10 cmH_2O, PEEP (Positive End Expiratory Pressure) 5 cmH_2O, FiO_2 50%, and noninvasive breath mode via an oronasal mask. The settings were titrated for targeted exhaled tidal volumes (6–8 mL/kg) and SpO_2 >92% and patient tolerance. The pressure support level was set at 14 cmH_2O and PEEP 5 cmH_2O to achieve targeted tidal volume values and adequate oxygenation. Pressure support was continued with close monitoring that included serial arterial blood gas analysis, and cardiac and neurological monitoring for signs of deterioration. The patient's arterial blood gas sample was normal at 3 h after ICU admission, with a pH of 7.32 and $PaCO_2$ 42 mmHg on NIV. The P/F ratio is improved and pressure support levels were weaned to maintain exhaled VT within target range in the ICU. After NIV mask removed re-exacerbation of hypercapnia, respiratory acidosis, wheezing, tachypnea, dyspnea and vital signs was not observed, and the

follow-up was continued with nasal cannula (NC) for oxygen therapy after 4 h (3–5 L/min). Eventually, oxygen therapy were withdrawn 18 h after being admitted to the emergency department. She was subsequently transferred to a general floor on day 2, discharged on day 4 post admission and prescribed budesonide and a formoterol fumarate dihydrate (SYMBICORT® TURBUHALER® 160/4.5 mcg dose) inhaler. After discharge, her asthma was well controlled, and she was followed up by a respiratory specialist.

Table 32.1 shows the timeline of arterial blood gas analysis and type of respiratory support and Fig. 32.1 shows changes in $PaCO_2$ and FiO_2 over time in the ICU and emergency department.

Table 32.1 Timeline of arterial blood gas analysis and type of respiratory support

Time	pH	$PaCO_2$, mmHg	PaO_2, mmHg	SpO_2, %	HCO_3, mmol/L	Respiratory support
Initial	7.19	68	87	92	30.2	NIV
Hour 1	7.24	58	91	92	29.2	NIV
Hour 3	7.32	42	92	96	27.1	NIV
Hour 4	7.41	42	93	95	24	NC
Hour 8	7.39	39	94	95	26	NC
Hour 12	7.38	42	90	93	25	NC

NIV non-invasive ventilation, *NC* nasal cannula

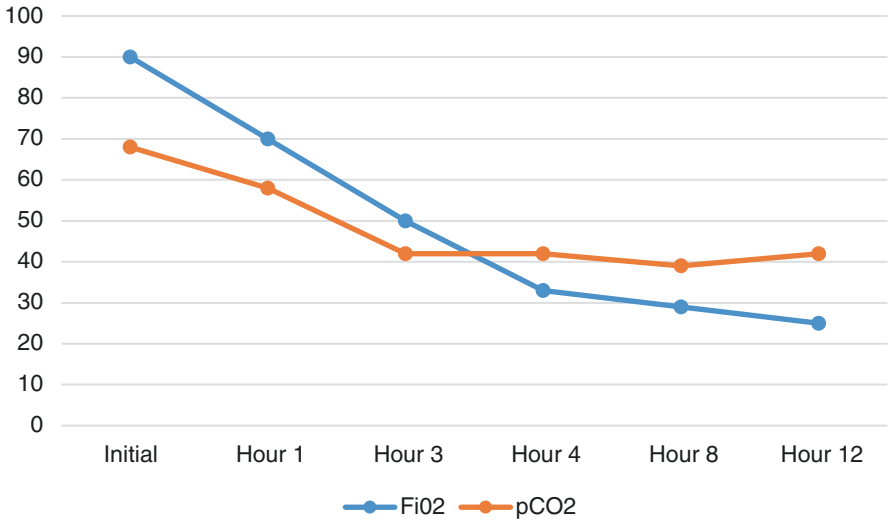

Fig. 32.1 Changes in partial pressure of arterial carbon dioxide ($PaCO_2$) and fraction of inspired oxygen (FiO_2) (at the time of initiation and at 1, 3, 4, 8 and 12 h after initiation of respiratory support)

32.2 Discussion

We present a case of asthmatic woman in whom symptom of severe dyspnea, hypoxemia and hypercarbia due to acute asthma exacerbation were alleviated following NIV in addition to standard therapy. Even though NPPV is a ventilatory support that is being increasingly used during asthma attack, a exact consensus is lacking in guidelines. Regarding the results of several previous reports, NIV for asthma attacks are observational and cohort research subjects, and only a small number of randomized controlled trials are on the scale of 10–20 patients [4, 5]. However, the effect of NIV on acute asthma attacks cannot be entirely negated. The effects of NIV on asthma are considered as follows; applying PEEP in the trachea may cause bronchodilation and reduce airway resistance [6], and respiratory muscle fatigued with tachypnea is assisted by inspiratory positive airway pressure [7]. Also, use of NIV may decrease the relative risks and complications associated with orotracheal intubation of a patient by optimizing oxygenation and ventilation. Fernández et al., performed a 7-year observational review and concluded that NIV appears to be an appropriate method to develop ventilation in a subgroup of asthmatic patients [8]. Gupta et al. reported that adding NIV for asthmatic attack may accelerate improvement in lung function, reduce bronchodilator requirement, and shorten ICU and hospital stay [9].

The optimal asthmatic patient for NIV is the one who is fully conscious and cooperative, and also the facility should have an appropriate system for emergency intubation within a critical care environment. This patient described in this report presented at the emergency department with hypoxemia, hypercarbia and severe dyspnea. Nevertheless, she was conscious and cooperative. Treatment with appropriate standard medications combined with NIV was initiated to reduce hypoxemia and dyspnea. Patient was informed about the need for intubation and invasive mechanical ventilation in case of respiratory failure. Patient were closely followed in terms of possible mechanical ventilation requirement. Rapid-sequence induction medications and intubation equipment were also kept readily at the bedside. However, the patient did not need IMV because of her successful response to NIV.

As a consequence, the benefit and safety of NIV therapy for severe acute asthma have not yet been established through randomized controlled trials. Use of NIV as a complement in asthma attack should be done only by experienced personnel and in a critical care setting with experienced support personnel and resources readily available.

Key Teaching Points

The role of non-invasive ventilation in acute asthma is not well described and there are concerns about its safety. Over a 10-year period, non-invasive ventilation was used without significant complications in patients with moderate acute asthma exacerbation. Successful results could be obtained with NIV for asthma attack in a critical care setting with experienced support personnel.

Questions and Answers

1. What is the disadvantage of NIV in asthma patients?

   (a) Increased risk of barotrauma
   (b) Dynamic hyperinflation
   (c) Incorrect patient selection may lead to delayed intubation
   (d) All of the above

   Answer: (d) All of the above

2. What is the advantage of NIV in asthma patients?

   (a) Improved V/Q mismatch and gas exchange
   (b) Decreased dead space
   (c) Direct bronchodilation
   (d) All of the above

   Answer: (d) All of the above

3. What is the criteria for switching from NIV to invasive ventilation?

   (a) Increasing lactate levels
   (b) Respiratory acidosis
   (c) The problem of hypoxemia that does not improve with NIV
   (d) All of the above

   Answer: (d) All of the above

4. What are the indications for NIV use in asthma patients?

   (a) Limiting drug side effects and improving rate of recovery
   (b) To avoid intubation
   (c) A post-extubation strategy for preventing reintubation
   (d) All of the above

   Answer: (d) All of the above

5. Which of the following criteria is suitable for NIV in an asthmatic patient?

   (a) Hypoxia with a P/F ratio <100
   (b) Decreased level of consciousness (while PCO_2 value is not high)
   (c) Significant haemodynamic instability
   (d) Hypercapnia with $PaCO_2$ <60 mmHg

   Answer: (d) Hypercapnia with $PaCO_2$ <60 mmHg

6. Which of the following values is not suitable for initial NIV values in asthma patient?
   (a) PEEP at 5 cmH_2O
   (b) IPAP at 10–15 cmH_2O
   (c) Low I:E ratio
   (d) Adjust to target RR >25/min

   Answer: (d) Adjust to target RR >25/min

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Chapter 33
Unusual Case of Acute Pulmonary Edema Treated by Non Invasive Ventilation: A 30 Years Ago "Cold Case"!

Corrado Mollica, Giovacchino Pedicelli, Savino Spadaro, and Massimo Pistolesi

Abbreviations

ABG	Arterial blood gas
ADH	Anti-diuretic hormone
AFC	Alveolar fluid clearance
AG	Anion gap
APACHE II	Acute physiology and chronic health evaluation
APE	Acute pulmonary edema
ARDS	Acute respiratory distress syndrome
CPAP	Continuous positive airway pressure
CRX	Chest radiograph
CVP	Central venous pressure
ED	Emergency department
EVLW	Extra-vascular lung water
FiO_2	Inspiratory oxygen fraction

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GCs	Glasgow Coma score
HR	Heart rate
ICU	Intensive care unit
MV	Mechanical ventilation
NIV	Noninvasive ventilation
O_2T	Oxygen therapy
P/F	PaO_2/FiO_2 ratio
$PaCO_2$	Carbon dioxide arterial pressure
PaO_2	Oxygen arterial pressure
PAWP	Pulmonary arterial wedge pressure
PEEP	Positive end-expiratory pressure
PSV	Pressure support ventilation
pts	Patient/s
RHDCU	Respiratory high-dependency care unit
RR	Respiratory rate
SB	Spontaneous breathing
SID	Strong ion difference
SpO_2	Trans-cutaneous pulse oximetry saturation
Va/Q	Ratio of ventilation to perfusion
VPW	Vascular pedicle width

33.1 Introduction

As shown by Bone and Balk 1988 [1], a non-invasive respiratory care unit is a cost-effective solution in acute respiratory failure treatment of patients whose primary need consists in monitoring or assistance with weaning, and are hemodynamically stable.

In Italy, respiratory high dependency care units (RHDCUs) provide an intermediate level of care between the intensive care unit (ICU) and the general ward for patients with single organ respiratory failure, who do not need ICU admission. Although Italian RHDCUs are mainly devoted to the monitoring and treatment of acute and chronic respiratory failure by non-invasive ventilation (NIV), they also help weaning from invasive mechanical ventilation. In 1984, an 8 beds RHDCU at the S. Camillo-Forlanini Hospital, Rome (Italy) was instituted. In this short paper, we report the arguments that were discussed by RHDCU's medical staff in 1990 and that allowed to recognize the kind of edema and to choose a proper treatment, in terms of both medical and ventilatory therapy.

Clinical Case

A 31-year-old female, coming from another Hospital, where she had been admitted for drug intoxication (benzodiazepines) that she had taken to commit suicide (Lorazepam 1 mg >20 tablets; Trihexyphenidyl Hydrochloride 2 mg >15 tablets); Bromperidol tablets (unspecified number), and treated with Flumazenil 1 mg/10 mL

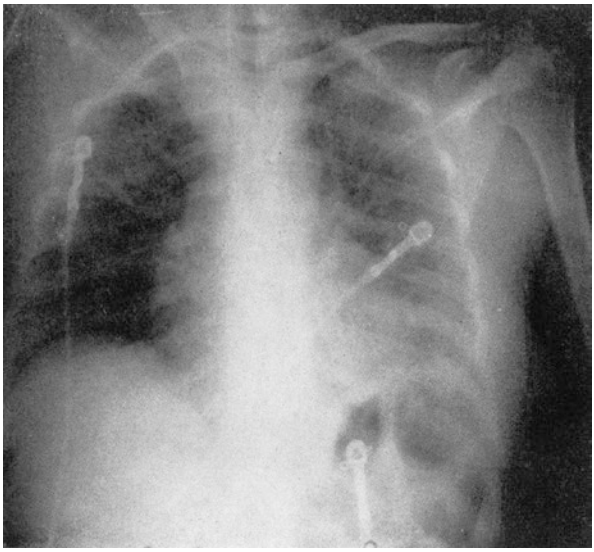

Fig. 33.1 CRX at hospital admittance

IV, diuretics, and fluid therapy (crystalloid), was admitted to the emergency department (ED) of our Hospital. ***At admittance*** she was afebrile and tachypneic—respiratory rate (RR) equal to 30 breaths/min—showing dyspnoea, light deterioration of mental status: Glasgow Coma score (GCs: 13). She was mydriatic with pupil poorly reacting to light and accommodation; moreover, auscultation of the lungs highlighted decreased breath sounds at the right base and diffuse crackling rales. No lower extremity edema. The electrocardiogram showed sinus rhythm rate 100 beats/min. Blood pressure was 130/90. A chest radiograph (CXR) revealed "*widespread ground-glass thickening of the lung parenchyma with relative sparing of the lower right half. The pleural sinuses appear free. The mediastinal image is morphologically normal with moderate widening of the vascular pedicle. CRX compatible with ARDS in early stage*" (Fig. 33.1). The arterial blood gas (ABG) showed hypoxemia (PaO_2: 59.2 mmHg; Standard PaO_2: 42 mmHg) at inspiratory oxygen fraction (FiO_2): 21%, (PaO_2/FiO_2 or P/F = 280 mmHg), hypocapnia with (acute) respiratory alkalosis ($PaCO_2$: 29.6 mmHg; pH: 7.50; HCO_3^-: 23.3 mmol/L).[1] Oxygen arterial saturation (SaO_2): 92.8%, with alveolar-arterial oxygen gradient (DA-aO_2): 54 mmHg (expected DA-aO_2 for age: 11.8 mmHg).[2] Electrolytes: hyponatraemia (Na^+: 129 mmol/L) with plasmatic hyposmolality (Osm: 255 mOsm/kg) (n.v. = 285–305 mOsm/kg), hypokalaemia (K^+: 3.1 mmol/L), Cl^-: 98 mmol/L. Other values: Urea: 90 mg/dL, Glicemia: 83 mg/dL, Red Blood Cells (RBC): 3,940,000/mm^3; White Blood Cells (WBC): 11,600/mm^3; Hb: 12.9 g%, Ht: 37%. Acute

[1] When pt was in spontaneous breathing (SB) all the ABG samples were measured in the air room (FiO_2: 21%) for at least 15 min after discontinuation of O_2T. PaO_2 Standard: $1.66 \times PaCO_2 + PaO_2 - 66.4 = 41.93$ mmHg (rounded up: 42 mmHg).

[2] Da-$aO_2 = PAO_2 - PaO_2$; $PAO_2 = (PB - PH_2O) \times FiO_2 - (1.25 \times PaCO_2)$.

Table 33.1 ABG values in spontaneous breathing (SB) on admission, 2° and 3° day (h 8 am); from the third day onwards in CPAP treatment at variable FiO_2 values (see text)

	In spontaneous breathing (SB) FiO_2: 21% [a](Standard PaO_2)			3° day MV (CPAP: PEEP 5, FiO_2: 30%)					4° day S.B. FiO_2: 35%
	Hospital admission no. 1	E.D. 24 h no. 2	RHDCU 48 h h 8 am	h 10 am 1 h	h 3 pm 5 h	h 5 pm 7 h	h 8 pm 10 h	h 10 pm 12 h	h 10 am
pH	7.50	7.42	7.28	7.33	7.41	7.43	7.42	7.40	7.38
PaO_2 (mmHg)	59.2 (42)[a]	46.7	30.4	49.2	51.8	57.5	85.7	95.6	82
$PaCO_2$ (mmHg)	29.6	36.6	56.4	50.6	48.3	43.3	41.1	47.5	46
SaO_2 (%)	92.8	83.4	55.1	72.7	84.7	90.6	96.5	97.3	88
P/F (mmHg)	282 (200)[a]	222	145	164	173	192	286	319	234
RR (breathing/ min)	30		9						
HR (beats/ min)	100		130						
GCs	13	12	11	12			15		
DA-aO_2 (11.8 mmHg)	54	57.55	49	101.5	102.1	102.3	76.8	58.9	108.2
Na^+ (mmol/L)	129	122	125						
K^+ (mmol/L)	3.1		2.9						
Cl^- (mmol/L)	98		101						
HCO_3^- (mmol/L)	23.3		22.9						
Hb (g/L)	12.9								
Osm (mOSm/ kg)	255	244	251						
APACHE II (score)	10		19						
SAPS 2 (score)	14		27						
HACOR (score, v.n ≤5)				5					

Physiology And Chronic Health Evaluation (APACHE) II score: 10 [2] (Table 33.1). The trans-cutaneous pulse oximetry saturation (SpO_2) on 100% oxygen delivered for 20 min by a non-rebreather mask was equal to 96% (Rossier test). Therapy was started with loop diuretics and fluid infusions. ***Twenty-four hours after***, the drowsiness worsened (GCs: 12); at chest, radiograph showed a dense right lower lobe consolidation. The lung examination showed inspiratory crackles, rhonchi and silence in lower (base) of the right lung. Worsening in ABG values (P/F = 222 mmHg), hyponatraemia (Na^+: 122 mmol/L) with plasmatic hyposmolality (244 mOsm/kg) and negative water balance (urine output: 1 L within the last 24 h), both furosemide

(Lasix®) 40 mg × 4/24 h, Albumine (Behring®) 200 g/L (20% 50 mL) and saline 0.9% NaCl (≈308 mOsm/L) in I.V. slow infusion were administered; the latter in order to counterbalance the hypotensive effect of diuretics. Aerosolized Ambroxol fl (Mucosolvan®) was added to antibiotics, corticosteroids, digoxin already on line. Oxygen therapy (O_2T) via Ventimask, with FiO_2 equal to 28% was set up. ***Forty-eight hours after admittance***, further worsening in neural status (GCs: 11), hemodynamics (HR: 130 b/min; PA: 90/60), increasing in WBC: 16,000/mm^3, and ABG values occurred: PaO_2: 30.4 mmHg, $PaCO_2$: 56.4 mmHg pH: 7.27 (FiO_2: 21%) (P/F = 145 mmHg) (APACHE II score: 19). CXR showed "*widespread lung parenchyma consolidation with confluent patches morphology and moderate asymmetric volumetric reduction of both lungs. Widened vascular peduncle. Pleural sinuses free from effusion. The finding is compatible with diagnosis of ARDS in the acute phase*" (Fig. 33.2).

It was necessary to start mechanical ventilation (MV) by NIV in RHDCU. NIV was performed by Bird 8.400 ST® (Bird Products Palm Springs, CA, USA) via face mask (Respironics® Murrysville, PA, USA) in continuous positive air pressure (CPAP) mode (ventilator) with positive end-expiratory pressure (PEEP) equal to 5 cmH_2O and an FiO_2 (30%) able to obtain a SaO_2 >90% and to reduce RR <25/m. In this kind of ventilator (in CPAP mode) neither backup respiratory rate, nor controlled air-leaks system was present (Table 33.1). During NIV, on-line measurements recorded included heart rate (HR) and SpO_2 (with a finger probe). At 10 h pm, after ABG measurement, the patient was disconnected and treated with a FiO_2 equal to 35%. In the following days a reduction in FiO_2 value was gradually done, thanks to an improvement in neural status and in chest infiltration (Fig. 33.4). Four days after, O_2T was definitively suspended, and patient was discharged and entrusted to a psychiatric institution.

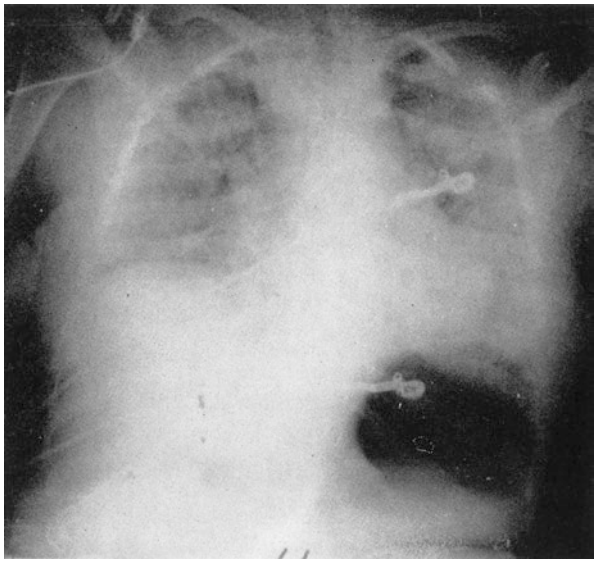

Fig. 33.2 CRX at RHDCU admittance

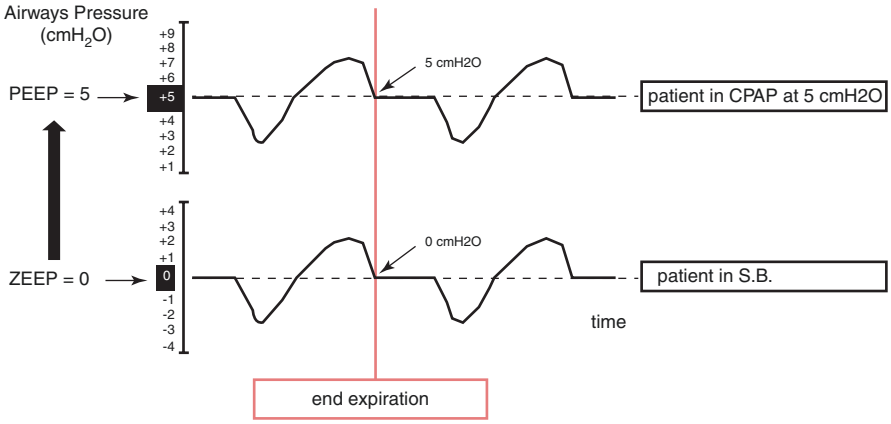

Fig. 33.3 Airways pressure (cmH_2O) and waveform in spontaneous breathing (S.B.) without PEEP (ZEEP) and in CPAP with PEEP at 5 cmH_2O. (From: Ventrella F. (2015) [46]; Courtesy of the author)

33.2 Discussion

33.2.1 Formation and Resolution of Edema

Acute pulmonary edema (APE) is caused by an excess of fluid in the lungs due to an elevated vascular pressure or to a more permeable membrane that is not matched by an adequate lymph clearance rate. It can be defined as the abnormal increase in the amount of extra-vascular lung water (EVLW). In an un-anesthetized sheep, Erdman et al. (1975) showed that EVLW content, measured post-mortem, does not change significantly until microvascular hydrostatic pressure is more than doubled, indicating a large safety factor that normally protects the lungs against fluid accumulation [3]. Nevertheless if the trans-capillary protein osmotic pressure decreases, along with lymphatic removal incapacity, pulmonary edema can develop at a lower than usual level of net filtration pressure [3]. Lung lymphatics remove edema fluid in either hydrostatic or increased permeability lung edema, but they cannot entirely compensate for an increase in intrans-vascular fluid flux or an impaired alveolar fluid clearance (AFC) [4]. The mechanism for the resolution of alveolar edema is provided by the active ion transport across the alveolar epithelium that creates an osmotic gradient that drives AFC [5]. Both type I and type II alveolar cells are involved in transepithelial ion transport. The primary driving force for alveolar fluid clearance is the active transport of sodium from the alveolar space to the interstitium by alveolar epithelial type II cells. The transport of sodium ions is the most important driver for the generation of the osmotic gradient [6]. The system of active ion-driven alveolar fluid reabsorption is the primary mechanism that removes alveolar edema fluid under both physiologic and pathological conditions, such as hypoxia [7]. If pulmonary hydrostatic pressures are elevated, the rate of AFC is also reduced.

'In vivo' studies conducted on animals, showed that net AFC was reduced under clinically relevant pathologic conditions [7]. Alveolar fluid clearance driven by active epithelial Na^+ and secondary Cl^- ions absorption counteracts edema formation in the intact lung. In left heart disease, lung edema was previously attributed to passive fluid filtration across an intact alveolo-capillary barrier. Conversely, it has been demonstrated that a major part of cardiogenic edema results from an active epithelial secretion of Cl^- and secondary fluid flux into the alveolar space [8]. As the inhibition of (Na^+)–(K^+)–(Cl^-)-cotransporters blocks alveolar fluid secretion, it has been identified as a unique therapeutic target in cardiogenic lung edema. "*This evolving concept may not be uniquely restricted to cardiogenic pulmonary edema, but it could also apply to other forms of hydrostatic lung edema*" [8].

33.2.2 Detection Methods

Criteria generally used to define hydrostatic pulmonary edema include central venous pressure (CVP) $\geq$14 mmHg, pulmonary arterial wedge pressure (PAWP) $\geq$18 mmHg, or a cardiac ejection fraction $\leq$45% by echocardiogram, radionuclide, or contrast ventriculography, and/or positive physical findings, including a third heart sound and jugular venous distension [9].

33.2.2.1 Radiological Aspects

Patients with pulmonary edema are likely to present many upholding causes (cardiogenic as opposed to non-cardiogenic). Different hemodynamic conditions and changes of the extravascular protein osmotic forces may be the main factors underlying the radiographic patterns in the various types of pulmonary edema. Conventional chest radiograph aspects can help orienting the diagnosis: as opposed to chronic cardiac failure, where the distribution of flow is usually "inverted" (base-to-apex redistribution), in overload edema, the distribution of pulmonary blood flow and pulmonary regional edema is "balanced" (homogeneous), along the horizontal axis (central), with increased pulmonary blood volume; heart size and vascular pedicle width (VPW) are enlarged;[3] lung volume is normal or increased; not commune are septal lines and air bronchogram, while peribronchial cuffs and pleural effusions are very commune findings [10].

[3] The vascular pedicle width (VPW) is the mediastinal silhouette of the great vessels. It is the distance between parallel lines drawn from the point at which the superior vena cava intersects the right main bronchus and a line drawn at the takeoff of the left subclavian artery from the aorta. It can provide a clue in the assessment of patients' intravascular volume status. Its value varies depending on the position; at the supine position the VPW can increase up to nearly 20%, compared to the upright position. Thus when the patient is supine, the "normal" VPW spans between 58 and 62 mm. A VPW value of 72 or higher is likely due to volume overload [10, 11].

As to the case in point, in the absence of echocardiogram, CVP, PAWP, or brain natriuretic peptide and troponin-T values, the only chest radiograph—using portable, supine CXR—did not offer an accurate evaluation for distinguishing causes of pulmonary edema.

There are explanations for the limited diagnostic accuracy of the chest radiograph.

Edema may not be visible until the amount of lung water increases by 30% [11]. Moreover, VPW, which could provide a clue in assessing patients' intravascular volume status, varies depending on the position; the supine position, as in our case, can increase the VPW by nearly 20% compared to the upright position [11].

Recognizing and differentiating acute hydrostatic pulmonary edema from acute respiratory distress syndrome (ARDS) is always a tricky task in the early stages. This is due to the fact that ARDS pts are not necessarily always affected by edema, as it happens, for instance, when low hydrostatic pressures in the lungs, or other factors in the Starling equation, alleviate the increased trans-vascular transport of fluid. Conversely, over-hydration by aggressive fluid therapy can affect the lungs, thus resulting in pulmonary edema but without increased permeability. This is the reason why over-hydration is hard to recognize at the bedside and hence to differentiate from ARDS. A case in point, which mirrors our present one, is that of pts infused with crystalloid fluids, in that over-hydration is likely to lower plasma colloid osmotic pressure. As a consequence of this—and even in the absence of increased permeability—we witness a lowering of the threshold value of hydrostatic pressure (i.e. pulmonary capillary wedge pressure) above which interstitial edema and thus the alveolar flooding develop [12]. Therefore, the distinction of hydrostatic from permeability pulmonary edema is difficult, especially when using portable, supine CXRs; nevertheless "*in supine, mechanically ventilated patients, measurements of high-resolution computed tomography and VPW correlate with pulmonary artery occlusion pressure*" [13]. Although the absence of clinical signs of congestive heart failure along with the hemodynamically stable situation could suggest to rule out an acute cardiogenic pulmonary edema, it is well known that APE caused by excessive infusions of blood, blood products and fluids is included among the cardiogenic types of edema, because the overload edema too, is caused by increased hydrostatic pressure [14]. As a result, the diagnosis of hydrostatic pulmonary edema usually relies on clinical information and response to treatment: if oxygenation and radiograph finding improve rapidly with diuresis, this favours hydrostatic edema [14]. As to the case in point, despite diuretic therapy, neither oxygenation nor radiograph improved in the first 24 h after admission. Quite the contrary, the clinical and functional status worsened considerably, in accordance with a CXR finding, also compatible with diagnosis of ARDS in the acute phase.

33.2.2.2 Acid Base Findings

Extravasation of fluid into the alveoli prevents oxygen from being absorbed into the bloodstream and neutralizes surfactant' s lubricating properties. The lungs become less compliant and the effort of breathing increases, causing dyspnea and CO_2

retention. The hypoxemia that occurs in alveolar flooding is more severe than in interstitial pulmonary edema—which causes ventilation-perfusion (Va/Q) mismatch—and is caused by right-to-left shunting of blood [14].

In our case, as opposed to radiological aspects of ARDS, neither aetiology (fluid overload) nor P/F value at admittance and in the first 24 h induced to a diagnosis of a (even mild) ARDS [15].

Chest radiogram, hyponatraemia with plasmatic hyposmolality and the presence of negative water balance, oriented towards over-hydration acute pulmonary edema; the history established that in 48 h before admission the patient was really resuscitated with an unspecified number of liters of crystalloid (Saline and Normosol M), the last one at hyperosmotic set up (Osm: 390 mOsm/L) that can cause interstitial fluid withdrawn into the bloodstream. Moreover, loop diuretics (and thiazides) were previously administered, which could be the cause of the electrolyte imbalance (hypokalaemia, hyponatraemia and hypochloraemic alkalosis) [16]. An "inappropriate" anti-diuretic hormone (ADH) syndrome (hyponatremia with hypervolemia) is described in situations in which ADH secretion may be increased as postoperative ADH release due to barbiturates or transient "idiopathic" hyponatremia (secondary to diuretics, especially thiazides) [16]. Furthermore it cannot be ruled out that the drowsiness was also caused by over-hydration of the central nervous system, that may occur in the presence of concentrations of plasma sodium equal to or below 120 mEq/L [16]. Hypocapnia (with respiratory alkalosis) is generally caused by hypoxemia; as to the case in point, fluid overload could be a contributing factor in leading to hypocapnia, via juxta-capillary receptors (J-receptors, or pulmonary C-fiber receptors) that are involved in events which cause a decrease in oxygenation, responding by an increase in respiration [17]. Hypocapnia in APE is often associated with the rise in serum lactate produced by a marked reduction of splanchnic and muscle blood flow associated with a high degree of hypoxemia [18, 19]. This compensatory hyperventilation is relatively slow and is not complete for 12–24 h [20]. In our case acute respiratory alkalosis ($PaCO_2$: 29.6 mmHg, pH: 7.50) at admission was not associated to metabolic acidosis[4] [21]. In the absence of serum lactate measure and despite anion gap (AG) value was normal (10.7 mEq/L; nv: 8–12 mEq/L) at admission, we cannot rule out the presence of hyperlactatemia in the continuation of the ED stay, since the AG may result from an insensitive screen for elevated lactate in critically ill patients[5] [22]. Moreover it has long been recognized that the infusion of large volumes of "normal" (0.9% NaCl) saline can cause acidosis [23]. This has been traditionally explained as a "dilutional' 'acidosis in which the serum bicarbonate is diluted by the fluid, resulting in lower serum bicarbonate and a metabolic acidosis. However, the Stuart approach offers an alternative

[4] This is a primary disorder: in (acute) respiratory alkalosis, the decrease in expected HCO_3^- is equal to 2 mmol/L for a decrease in $PaCO_2$ equal to 10 mmHg; thus for a decrease in $PaCO_2$ equal to [40 – 29.6] = 10.4 mmHg, the expected HCO_3^- is ≈23; OR (it is easier): for a decrease in $PaCO_2$ equal to 1 mmHg, the pH increase is equal to 0.01 U: thus, for a decrease in $PaCO_2$ equal to ≈10 (40 – 29.6) mmHg, the increase in pH is 0.1: that is 7.50, as in our case.

[5] Anion Gap (AG) = $[(Na^+ + K^+) - (Cl^- + HCO_3^-)] = [(129 + 3.1) - (98 + 23.3)] = 10.8$ mEq/L.

explanation [24]. Saline causes metabolic acidosis not by 'diluting' HCO_3^- but rather by its Cl^-content. The reason why this occurs with saline administration is that, although saline contains equal amounts of both Na^+ and Cl^-, plasma does not. When large amounts of salt are added, the Cl^- concentration increases much more than the sodium concentration [25]. Since normal saline has a strong ion difference (SID) of 0, its administration would tend to lower the serum SID resulting in a metabolic acidosis[6] [26]. A shift of free water from the intracellular volume to the extracellular volume in order to reach an osmolar equilibrium will result in additional dilution of the extracellular, and therefore an additional acidifying effect [27, 28]. That is why, in our case, neither hyponatraemia nor hyposmolarity were corrected with saline infusion; actually a marked mixed respiratory and metabolic acidosis on 48 h after hospital admission was highlighted (Table 33.1).[7]

33.2.3 Ventilatory Therapy

The appearance of respiratory acidosis could be ascribed to hypoventilation as a sign of pump failure, either owing to an increased load of the respiratory system, or strictly related to decreased compliance due to interstitial/alveolar flooding [29]. CPAP—also known as spontaneous PEEP—is a mode of ventilation in which the patient is in spontaneous breathing (SB) and is exposed to a continuous pressure from the ventilator (equal to 5 cmH_2O as in this case). This is the pressure in force at the end of expiration, that is named positive end-expiratory pressure (PEEP). The patient creates a negative pressure in inspiration and a positive pressure in expiration, thereby the circuit pressure varies throughout the cycle; but at the end of the expiration the pressure will return to the set PEEP value (5 cmH_2O) (Fig. 33.3). Thus, in preventing alveolar collapse at end-expiration and reducing intrapulmonary shunting of blood, CPAP redistributes excess lung water to sites where it interferes less with gas exchange, hence improving oxygenation (arterial PO_2 and lung compliance) [30]. According to Demling et al. (1975), PEEP cannot decrease EVLW, but increases the difference between pulmonary microvascular pressure and plasma colloid osmotic pressure (net intravascular filtration pressure), therefore impairing the venous return. In patients with volume overload, decreasing venous return will directly decrease the amount of pulmonary edema being generated, by decreasing right cardiac output [31].

It is noteworthy, in this regard, that the hypoxemia occurring in alveolar flooding is caused by right to-left shunting of blood that is reduced by PEEP (through a reduction in cardiac output) [32].

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[6] The difference between the sum of all strong cations [Na^+, K^+, Ca^{2+}, Mg^{2+}] and all strong anions (mainly Cl^-, Lactate and Albumine) is known as the strong ion difference (SID).

[7] This corresponds to a mixed disorder. In fact the expected HCO_3^- in acute respiratory acidosis: $[(PCO_2 - 40)/10] + 24$ should be 25.64 mmol/L instead of 22.9 mmol/L (actual value); thus there is an associated metabolic acidosis.

On the contrary, in interstitial pulmonary edema (as in ARDS), the hypoxemia is due to Va/Q mismatch—by the presence of shunt or units of very low Va/Q ratio; in these pts a fall of the cardiac output caused by PEEP leads to a decrease in the perfusion of unventilated lung and an increase in the ventilation of unperfused alveoli [32].

Moreover, when used in combination with furosemide, given intravenously, PEEP improves lung fluid resorption by increasing the plasma colloid osmotic pressure, as shown in experimental hydrostatic pulmonary edema [33].

"*In patients with hydrostatic pulmonary edema, mechanical ventilation could have either beneficial or detrimental effects on alveolar fluid clearance. Beneficial effects of positive pressure ventilation that might indirectly increase alveolar fluid clearance include decreased preload and afterload and decreased myocardial oxygen consumption due to decreased work of breathing. These factors could reduce the formation of pulmonary edema and thus promote net alveolar fluid clearance*" [34].

However, it is well established in medical literature that mechanical ventilation at high tidal volumes can promote lung injury [35]. Furthermore, high levels of PEEP may raise CVP, inhibiting lung lymphatic drainage from the interstitium and thereby limiting alveolar fluid clearance [34].

As we pointed out earlier, CPAP can reduce inspiratory work of breathing both by decreasing pulmonary resistance, related to an increase in functional residual capacity, and by increasing lung volume to a more favourable position on the pressure-volume curve [36]. Reducing the work from respiratory muscles also reduces the generation of CO_2 and lactate from these muscles, helping improve acidosis. At the same time, the decreased return may improve over-distension in the left ventricle, placing it at a more advantageous point in the Frank-Starling curve and possibly improving cardiac output [37]. Furthermore, inspiratory muscle unloaded reduce intrathoracic and left ventricular transmural pressures (and afterload), as seen in patients with congestive heart failure, thereby improving oxygenation [37]. Although CPAP decreases ventilation/min and respiratory rate, $PaCO_2$ value generally does not increase, thanks to the decrease in dead space ventilation [36]. As reported in Aliberti et al. (2010), in case of a mixed acidosis (as in ours), pH increased very fast during the first hours of CPAP treatment, possibly owing to beneficial effects on the heart and hemodynamics, as well as to tissue perfusion [29]. However, in our case, the slower decrease in $PaCO_2$ levels related to the lung decreased compliance ("stiff lung") forced to apply a low PEEP value (5 cmH_2O), given the risk of barotrauma. A light increase in $PaCO_2$ value at the 12th hour of CPAP can be explained by the fact that, unlike pressure support ventilation (PSV), CPAP does not provide inspiratory assistance to the rest of the muscles of respiration [38]. It is now established that the rise in intrathoracic pressure and not the modality of ventilation (CPAP vs PSV) seems to be important in acute cardiogenic pulmonary edema patients [39, 40].

33.2.4 Outcome

Thanks to medical therapy, the increasing in urine output dramatically reduced edema in few hours (Fig. 33.4) and CPAP reduced $PaCO_2$ within 7 h (Table 33.1).

A "post hoc" analysis according to the "risk scale score" named HACOR, at 1 h of NIV, on a value obtained by analysing five variables—i.e. heart rate (H), acidosis (pH), consciousness (GCs), oxygenation (P/F), and respiratory rate (R)—showed a low (5) prediction (NIV) failure [41].

33.3 Limits of the Present Contribution

A faster and more accurate diagnosis would have been certainly made, were hemodynamic factors (including pulmonary arterial wedge pressure and left ventricular ejection fraction) routinely measured, along with monitoring EVLW by single transpulmonary thermal dilution. Likewise, the availability of main electrolytes (Na^+, K^+, Cl^-, $Latt^-$) and serum osmolarity, together with ABG values in the same blood sample, would have allowed a more rapid assessment of the acid-base status. Most notably, a quasi-continuous monitoring of urinary pH and principal urinary electrolytes available by the applications of the K.IN.G® urinary analyzer would have helped "*to disentangle the great mosaic concerning acid-base chemistry*" [42]. It is also important to highlight that, hemodynamic factors being routinely monitored, some therapeutic errors, i.e. the administration of diuretics and of other infusion drugs, such as NaCl 9% saline (instead of an early conservative fluid

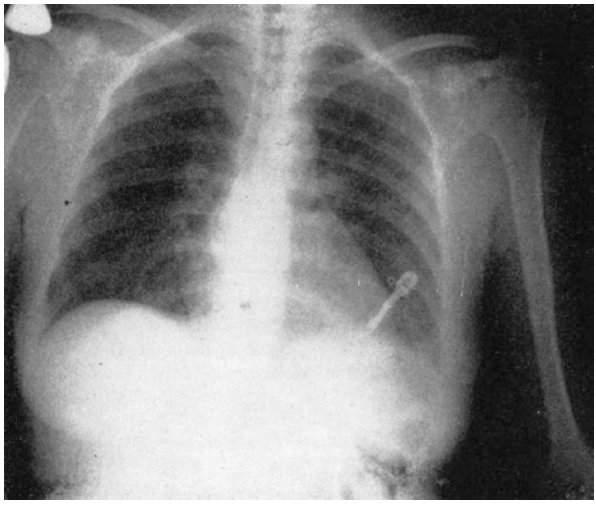

Fig. 33.4 CRX at RHDCU discharge

management strategy) which caused overload and the onset of "iatrogenic" metabolic acidosis, could have been successfully avoided. The availability of NIV-ventilators which can provide air-leaks compensation could have proved equally useful. Despite there are no significant differences in clinical outcomes when comparing CPAP vs BiPAP, would a Bi-level mode have been applied at the first occurrence of hypercapnia, the overall time of mechanical ventilation could have been perhaps reduced.

33.4 Conclusions

It has been shown that central active substances may cause pulmonary edema by increased permeability of the alveolar-capillary membrane [43–45].

The evolution of the chest radiographic findings in the present case are compatible with an initial acute increase of vascular permeability due to the intoxication. The increase in density in the peripheral regions of the lung is an indication of alveolar involvement. There are no findings compatible with an interstitial phase preceding the alveolar flooding as it happens in conditions of severe cardiogenic pulmonary edema. According to this interpretation, despite the presence of alveolar edema, there are no findings of septal lines, peribronchovascular cuffing, perihylar haze and pleural effusion that usually are hallmarks of cardiogenic pulmonary edema. From the pathophysiologic point of view this type of edema occurring after drug overdose can be considered as a normal pressure injury edema that could be reversible after the cessation of the pharmacologic injury [10]. The evolution of this case is conditioned by the presence of over-hydration with marked enlargement of the vascular pedicle and further involvement of the central regions of the lungs. Over-hydration could cause an increased hydrostatic pressure within the pulmonary capillaries favoring further development of edema. The quite rapid resolution of the radiographic findings could be related on the one hand to the removal of the toxic condition with consequent reduction of the injury component of pulmonary edema and on the other hand to the effect of CPAP facilitating the re-absorption of edema of hydrostatic origin. In summary, the radiographic aspect of this case can be speculatively defined as toxic injury edema (ARDS) with superimposed over-hydration hydrostatic edema [10].

Despite an occurrence of mild hypercapnia in the continuation of the treatment, CPAP appeared to be an effective treatment. Furthermore, the existence of a metabolic acidosis associated to the acute respiratory acidosis, also due to the high degree of hypoxemia, can affect its outcome. Careful interpretation of AB status is recommended.

Key Teaching Points

- In patients with acute pulmonary edema an initial acute increase of vascular permeability due to drug intoxication can lead to radiological finding of ARDS.
- The superimposed over-hydration can lead to hydrostatic pulmonary edema.
- The diagnosis of hydrostatic pulmonary edema usually relies on clinical information and a rapid improvement of oxygenation and of the radiograph findings after increased diuresis.
- In patients with hydrostatic pulmonary edema CPAP can reduce edema owing to beneficial effects on the heart and hemodynamics as well as on work of breathing and tissue perfusion which lead to a reduction in acidosis.
- High tidal volume ventilation and high levels of PEEP must be avoid to prevent the consequent lung injury and reduction of alveolar fluid clearance.
- Similarly, since inducing metabolic acidosis both I.V. rapidly infused saline (NaCl 0.9%) and loop diuretics (thiazides) must be avoided, or they should be administered very carefully.

Questions and Answers

1. During continuous positive airway pressure (CPAP) ventilation:

   (a) The pressure is delivered by the ventilator in the expiratory phase only and represents the positive end-expiratory pressure (PEEP)
   (b) The airways pressure has no different value both in inspiration and in expiration
   (c) The pressure delivered by the ventilator is the airways pressure at the end of expiration
   (d) None of them above

   Answer: (c) The pressure delivered by the ventilator is the airways pressure at the end of expiration

2. In Acute Hydrostatic Pulmonary Edema the occurrence of a Respiratory Alkalosis is due to:

   (a) Fluid overload involved in leading to hypocapnia
   (b) The rise in serum lactate produced by a marked reduction of splachnic and muscle blood flow, caused by hypoxemia
   (c) Can be managed with a conservative fluid strategy and oxygen therapy
   (d) All of them above

   Answer: (d) All of them above

3. In Acute Hydrostatic Pulmonary Edema the occurrence of a metabolic acidosis is due to:

   (a) Administration of diuretics (especially thiazides)
   (b) Infusion of a large volumes of fluids (NaCl 9% saline)
   (c) High degree of hypoxemia
   (d) All of them above

   Answer: (d) All of them above

4. In Acute Hydrostatic Pulmonary Edema the occurrence of a hyponatremia:

   (a) Can be transient or "idiopathic" (secondary to diuretics, especially thiazides)
   (b) Is described in situations where ADH secretion may be increased (as a post-operative ADH release due to barbiturates)
   (c) When equal to or below 120 mEq/L causes drowsiness owing to overhydration of the central nervous system
   (d) All of them above

   Answer: (d) All of them above

5. In Acute Hydrostatic Pulmonary Edema beneficial effects of CPAP that might indirectly increase alveolar fluid clearance are:
   (a) Decreased preload and afterload
   (b) Decreased work of breathing
   (c) Decreased myocardial oxygen consumption
   (d) All of them above

   Answer: (d) All of them above

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Chapter 34
Non Invasive Ventilation in Acute Cardiac Pulmonary Edema

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Abbreviations

ACPE	Acute cardiac pulmonary edema
BiPAP	Bilevel positive airway pressure
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
IPAP	Inspiratory positive airway pressure
NIMV	Non invasive mechanical ventilation
NIPSV	Non invasive pressure support ventilation
PEEP	Positive end expiratory pressure

Clinical Case

JM is a 56 years old man, active smoker of 20 cigarettes per day and alcohol consumption of three units of alcohol per day. No other relevant medical history. He consulted in the primary care because of 2 months of asthenia, malaise and loss of 10 kg of weight. He started 1 week before with fever and worsening of the general condition and he was derived to the emergency room of our hospital. He arrived with fever, low blood pressure, chest X-ray with bilateral pulmonary infiltrates.

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Initially oriented as septic shock of respiratory origin it was managed with fluid therapy, antibiotics and continuous infusion of norepinephrine. During the stay at the emergency department the patient started with agitation, profuse sweating, anxiety, tachypnea increase work of breathing and disorientation. He presented bilateral crackles at auscultation and a new chest X-ray revealed increase of bilateral pulmonary infiltrates, including Kerley B lines. Thoracic echography revealed B lines in both thoracic sides. An echocardiography revealed bicuspid aortic valve with severe insufficiency, images suggestive of vegetations on aortic valve and an aortic root aneurysm. He was managed with non-invasive ventilation for respiratory support with a pressure support ventilation of 10 cmH_2O and 6 cmH_2O of positive end expiratory pressure (PEEP) with a tidal volume of 6 mL/kg/expected body weight and the fraction of inspired oxygen of 70% for a oxygen saturation of 94%. They was also managed with intravenous diuretics and antibiotics. The ventilatory support was progressively weaned and latter on his hospitalisation valve surgery was performed without significant complications.

34.1 Introduction

Heart failure is one of the leading causes of hospital admission around the world. In this line, acute cardiac pulmonary edema (ACPE) is among the most frequent causes of acute respiratory failure. The main causes of ACPE are acute coronary disease, acute cardiomyopathy including myocarditis and Takotsubo syndrome, acute valvular dysfunction, tachyarrhythmia, hypertensive crisis, myocardial stunning, cardiac tamponade, between others. There are some diagnostic criteria for acute pulmonary edema. Clinical criteria include: (a) the presence of acute respiratory distress that is evaluated by an increase or the work of breathing, tachypnea (more than 25 breaths/min), the use of accessory muscles or respiration with thoracoabdominal dissociation; (b) a physical examination with crackles and or wheezes, the presence of third heart sound; (c) orthopnea; and (d) respiratory failure defined by oxygen saturation on room air of <90% by pulse oximetry or a PaO_2 less than 60 mmHg or a ratio of PaO_2: FiO_2 <300 mmHg; or values of PCO_2 above 45 mmHg. At least two of the diagnostic confirmatory test should be present: (a) signs of pulmonary congestion on chest radiography or computed tomography scan; (b) multiple B lines on lung ultrasound (more than 3 B lines in 2 chest zones on each hemithorax); (c) elevated pulmonary capillary pressure on catheterization with swan ganz catheter, increased total lung water on pulse contour and hemodilution analysis system, (d) signs of elevated filling pressures on echocardiography (E/E′ ratio more than 15); and (e) significant elevation of natriuretic peptides (proBNP more than 900 or more than 1800 in patients older than 75 years old).

One of the cornerstone treatment for ACPE is the respiratory support while the medical, interventional and/or surgical treatment is performed to treat the etiology of the acute heart failure. In general, oxygen, non invasive mechanical ventilation

(NIMV) and invasive mechanical ventilation are the main respiratory support tools. In this regard, there are many studies demonstrating that NIMV is a useful tool to prevent complications associated with orotracheal intubation and invasive mechanical ventilation, such as ventilator associated pneumonia, prolonged sedation, myopathy, between other, and thus decreasing the hospital stay and improvement of survival in selected patients. There are several modalities of non-invasive ventilation, including the continuous positive airway pressure (CPAP), the bilevel positive airway pressure (BiPAP) and non invasive pressure support ventilation (NIPSV). In some cases, a controlled non invasive mechanical ventilation can be used and some new strategies such as neurally adjusted ventilatory assist ventilation but they are out of the interest of this chapter. Here, we will review the physiopathology of ACPE and the main strategies of NIMV in this pathology.

34.2 Physiopathology of Pulmonary Edema of Cardiogenic Origin and Effects of Positive Airway Pressures

There is a fine layer of fluid in the alveoli in normal lung that allows gas exchange. According to starling forces, the fluid that passes through the vascular endothelium depends on two outward forces (the capillary pressure and the interstitial osmotic pressure) and two absorptive forces (the plasma oncotic pressure and the interstitial pressure). Then, the net movement of fluids and solutes are normally carried out of alveolar capillaries into the interstitium, and then the lymphatics remove the interstitial fluid to the circulation.

In general, acute pulmonary edema is due to a sudden increase in the filling pressure of the left ventricle that generates a backward rise in the pulmonary capillary pressure with a subsequent leak of fluid into the interstitial space. This, finally leads to an increase of fluid into the alveolar space with an imbalance of the alveolocapillary space (Fig. 34.1). This originates an increase of pulmonary resistance, decrease of lung compliance, decreased of lung residual capacity and alteration of the capillary alveolar gas exchange which is the main cause of hypoxemia and the increase in the work of breathing in patients with ACPE. The respiratory musculature needs to generate a higher negative pressure to introduce air into the thoracic cavity, whereas this increase in intrathoracic negative pressure generates hemodynamic consequences with an increase in pre- and post-load with a subsequent worsening of cardiac function.

The use of positive intrathoracic pressure either with or without pressure support in situations of interstitial or alveolar edema generates beneficial hemodynamic and ventilatory effects. The hemodynamical benefits are related with the increase of the intrathoracic pressure. There is an equal increase of right atrial pressure an the mean systemic filling pressure, that causes a decrease of systemic venous return with reduction of the preload of the right ventricle and the relaxation of the wall of the left ventricle. Also, it causes a decrease in the gradient of pressure between the left

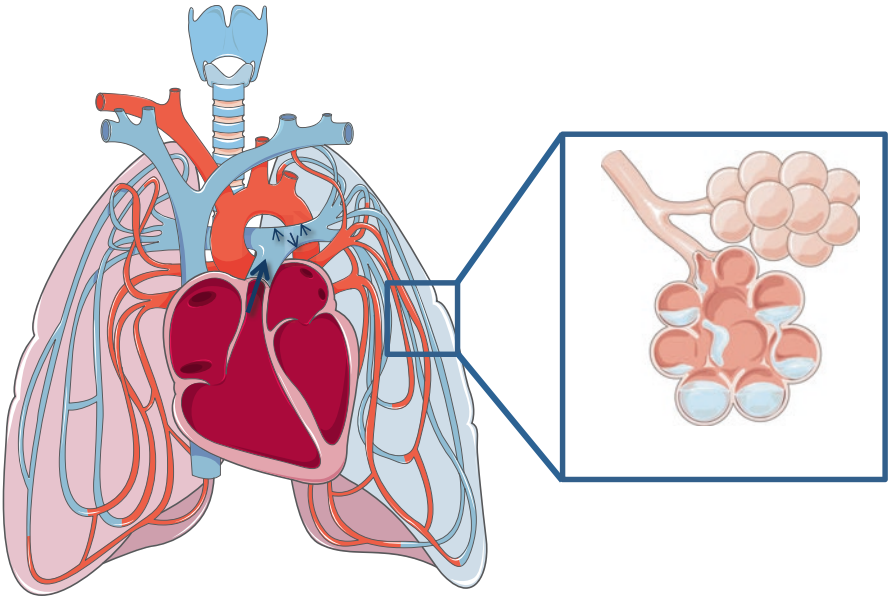

Fig. 34.1 Physiopathology of cardiac pulmonary edema. In acute cardiac pulmonary edema the imbalance of starling forces produces a backward increase in the hydrostatic pressure with a subsequent increase in pulmonary capillary pressure. The fluid, pass through the interstice to the alveolar space reducing the residual lung capacity, increasing the pulmonary resistance, with the concomitant alteration in the alveolar exchange which cases hypoxemia and increase of the work of breathing. (Courtesy of Servier Medical Art, reproduced with permission)

ventricle and the extrathoracic arteries with reduction of afterload, a decrease of pressure swings by the respiratory system, both producing an improvement in the cardiac output (see Fig. 34.2). Finally, in patients with diastolic dysfunction the use of CPAP produces a hemodynamic benefit by a decrease in left ventricular end diastolic volume following a venous return.

In some cases, mainly in more unstable patients, the application of intrathoracic pressure decreases the venous return and, consequently, decreases the cardiac output and pulmonary perfusion. This may be aggravated by the increase in right ventricular afterload, producing secondary dysfunction of the right ventricle with decreased systolic function. Both parameters can be monitored by echocardiography with the analysis of systolic displacement of the base of the free wall of the right ventricle (TAPSE) and the S′ wave by tissue doppler in the tricuspid annulus, that represents the speed the longitudinal fibers move in the tricuspid annulus of the free wall of the right ventricle. Also, the dilation of the right cavity and the increase in the right ventricle and left ventricle ratio can be assessed in an apical plane of four chambers evaluating the end-diastolic diameter of both ventricles. However, as we

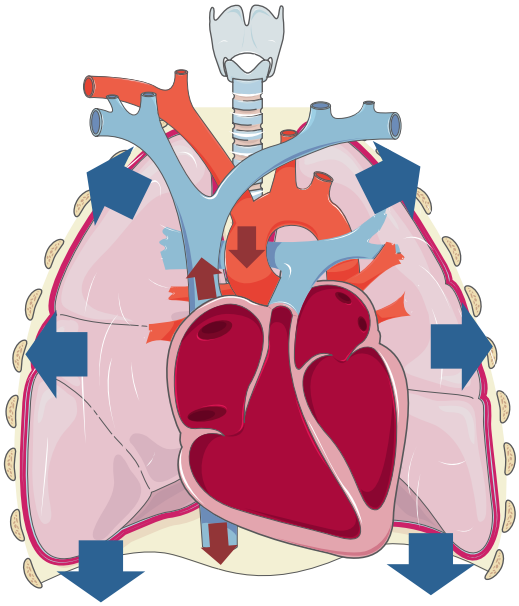

Fig. 34.2 Effects of positive pressure during NIMV in ACPE. The increase in positive intrathoracic pressure causes a decrease in the systemic venous return and therefore a reduction in the right ventricular preload, decreasing the trans-mural pressure of the left ventricle (red arrows). In addition, it produces a decrease in the pressure gradient between the left ventricle and extrathoracic arteries and reducing the afterload improving the cardiac output (red arrows). At the respiratory level, with the positive pressure (blue arrows), there is a progressive recruitment of alveoli occupied with an increase in the alveolar units available for the gas exchange, with an increase in functional residual capacity. (Courtesy of Servier Medical Art, reproduced with permission)

mentioned before, the increase in intrathoracic pressures may result in a better function of the left ventricle due to an effective reduction in left ventricular afterload. Therefore, in patients with left heart failure, elevated intrathoracic pressure can improve cardiac function, and elimination of intrathoracic pressure can result in weaning failure of NIMV.

The benefits in the respiratory system is produced by the positive pressure at alveolar level that causes a progressive recruitment of previously occupied or totally or partially collapsed alveoli, with an increase in the units available for alveolocapillary exchange, improvement in compliance, and an increase in functional residual capacity. This improves the right to left shunt, ameliorating the oxygenation, and lung mechanics. If we also add pressure support, there will be a discharge of the work of ventilatory musculature with an increase in dynamic volumes with the subsequent improving ventilation.

34.3 Respiratory Support in Acute Cardiac Pulmonary Edema

In 2008, a large multicenter trial demonstrated that non invasive mechanical support with CPAP or NIPSV were associated with earlier resolution of dyspnea, decrease the respiratory distress and metabolic alterations, but they did not improve survival in patients with respiratory failure due to cardiogenic pulmonary edema. Several studies were performed after this that are summarized in a recent systematic review and meta analysis by the Cochrane library. They included a total of 24 randomized clinical trials with 2664 participants. They showed that the use of non invasive mechanical ventilation for ACPE compared to standard medical care may reduce the hospital mortality and the needs of orotracheal intubation. Also, they did not observe any difference of NIMV compare with standard of care in terms of rates of acute myocardial infarction, systolic blood pressure, diastolic blood pressure, mean blood pressure after 1 h of therapy. In contrary, they observe improvement in respiratory rate and values of PaO_2 after 1 h of treatment. Finally, they do not observe an increase in hospital stay and adverse secondary events. In a subgroup analysis they did not observe differences between using CPAP or BiPAP, both forms reduce hospital mortality.

As mentioned previously, there are three main strategies for NIMV in ACPE. The CPAP does not provides assisted ventilation because of lack of inspiratory assistance, it exclusively provides a constant pressure produced by a constant flow throughout all the respiratory cycle. It is important to know that to set CPAP it is necessary that the patient has an effective respiratory drive and a correct alveolar ventilation.

The bilevel positive airway pressure (BiPAP) modality is programmed with two different levels of pressure, the expiratory positive airway pressure (EPAP) and the inspiratory positive airway pressure (IPAP). The EPAP is a continuous positive airway pressure at the end of expiratory effort whereas the IPAP corresponds to the sum of the pressure support plus the EPAP. The ventilation is produced by the difference of pressure (or delta pressure) between the IPAP and the EPAP.

The non invasive respiratory support can be performed with pressure support ventilation (PSV) and positive end-expiratory pressure (PEEP) in ICU respirators. The PSV is a pressure targeted flow-cycled mode of ventilation that apply an inspiratory pressure to assist spontaneous breathing. The inspiratory pressure is provided when the inspiratory effort of the patient exceed the sensitivity trigger set either by specific flow or by specific pressure. Once the reduction of the inspiratory flow until achieving the expiratory sensitivity (Esens) pre-set values, the respirator drives to cycle to expiration. In some cases a mandatory controlled or assisted-controlled mechanical ventilation can be used in patients with ACPE, when no or little patient effort is required.

Until now, all the studies have not shown significant differences comparing the types of non-invasive mechanical support strategies in ACPE. However, the CPAP is easy-to use, cheap and simple to set up technique that can be used in less equipped

areas, like pre hospital care and areas outside the intensive care unit. The NIPSV could be more indicated in patients with hypercapnia in whose alveolar ventilation are not highly effective.

There is a wide range of mechanical ventilators in the market, from the simplest in which only the pressure is a modifiable parameter, to the state-of the art high-tech respirators. Those ventilators are equipped with display monitoring, alarm setting, different triggers, cycling and flow and ramp control and one of the most important attribute for NIVM is the compensation of leaks by an increase in the air flow (up to 120–180 L/min). This compensation of leaks improve ventilation in patients with specific anatomical characteristics such as beard or patients with nasogastric tubes.

The main interfaces used in non-invasive ventilation are the oro-nasal mask, the total facemask, and the helmet. The nasal mask is a triangular device that includes a deep sealing flange to prevent skin damage mainly in the nose; it can be used in patients that feel claustrophobic with the facial or helmet devices. The most used interface is the total facial mask that eliminates the nasal bridge discomfort because it is supported by the perimeter of face covering the mouth and nose. It can be used when nasal mask has significant leaks or the mouth breathers due to the air hunger in the acute phase of ACPE. Finally, the helmet, a transparent hood covering the patient whole head, limits the air leaking. It contains two ports that acts as inlet and outlet of inspiratory and expiratory tubes of the circuit. The helmet can be used mainly for the continuous positive pressure mode in the respiratory tract, since it allows a greater autonomy of the patient and it is highly indicated when a prolonged NIMV is anticipated. Also, it is possible to deliver a higher PEEP or CPAP without increasing the air leaks, improving the oxygenation and ventilation.

In general, it is recommended the use of skin protectors, and humidification. Nebulizers can be safely used without the interruption of the NIMV. Finally different adaptors are available for other exploratory interventions such as bronchoscopy. In the acute phase, the use of sedative drugs such as morphine or recently the use of dexmedetomidine as an a2-adrenergic receptor agonist that causes less central respiratory depression alleviate dyspnea and helps an adequate adaptation to NIMV.

It is important to know the contraindications for the technique before initiation of support. The main contraindications for NIMV are: significant altered mental status or severe central nervous system disorders, inability to cooperate with fitting and wearing the interface, apnea, inability to protect the airway or clear respiratory secretions, the upper airway obstruction, severe upper gastrointestinal bleeding, severe hemodynamic or rhythm instability, recent facial surgery or significant facial trauma, burns or deformity (unless helmet is used), recent gastro-esophageal surgery, un-drained pneumothorax and vomiting. Also, it is important to know which patients with ACPE will require rapid intubation: patient intolerance of NIMV devices because of pain, discomfort or claustrophobia, inability to improve gas exchange with the NIMV, patients with signs of muscle fatigue, with severe or persistent hemodynamic instability or significant electrocardiogram abnormalities, severe neurological deterioration or inability to improve mental status within 30 min after application of NIMV in hypercapnic, lethargic patients or agitated hypoxemic patients and finally patients after cardiac or respiratory arrest.

The initial settings of the ventilator should ensure patient comfort and progressive tolerance of NIMV. Initial pressures of CPAP or EPAP of 3–5 cmH_2O and IPAP of 8–12 cmH_2O can be used. When using pressure support it can be started at 4–8 cmH_2O. All the parameter should be gradually increased to 5–12 cmH_2O of CPAP or EPAP and the IPAP or pressure support to deliver a tidal volume between 6 and 8 mL/kg/predicted body weight, to reduce dyspnea, improve respiratory rate without compromising the patient-ventilator interaction or promoting an increase of air leakage. Oxygen supplementation should be titrated to maintain a pulse oximetry between 92% and 98%, or between 88% and 92% in patients at high risk for hypercapnia.

To ensure the success of NIMV, close monitoring is necessary, including heart rate, blood pressure, and continuous electrocardiography. Also, it is important to assess the patient respiratory effort, chest wall motion, use of accessory muscles, continuous oxygen saturation, the blood gases including the pH, PaO_2, and $PaCO_2$, and the visualization of the flow and pressure curves in the ventilator. Monitoring neurological status and patient comfort is also needed. A general reassessment is recommended at 60, 90 and 120 min since the initiation of the respiratory support. In general, air leak of less than 0.4 L/s (less than 25 L/min) can be tolerated. However, air leakage, is often involved in cases of asynchrony, which can be reduced by one or more adjustments of the mask, shortening the inspiratory time, changing the pressure support in steps of 2 cmH_2O or moving the inspiratory and expiratory triggers (when available), and finally, giving sedation.

Like in invasive ventilation, during NIMV asynchronies can be present. These includes ineffective triggering, double triggering, auto-triggering, premature cycling and delayed cycling. Air leaks can cause that the expiratory flow do not achieve the pre set values of Esens that leads to prolonged inspiratory flow and asynchrony. In some ventilators you can reduce leaks by reducing the inspiratory pressure or by controlling the inspiratory time with the spontaneous inspiratory time limit in order to avoid asynchronies. In some cases the only method to prevent asynchronies because of leaks is by adjusting or changing the interface.

There are specific issues when the helmet is used. At the time the NIMV is initiated using helmet, most of the pressure that is administered is used to pressurize the interface. It is important to notice that when you will ventilate with helmet, the use of higher flows and higher pressures may improve the compliance of the helmet and also you can reduce asynchronies. One more consideration is the CO_2 rebreathing during helmet ventilation; when fresh gas flow more than 35–40 L/min makes this rebreathing insignificant.

Non-invasive ventilation usually is suspended when there is a satisfactory recovery or, on the contrary, if there are signs of failure of NIMV and then requiring invasive mechanical ventilation. It is important to know that here are some predictors of NIMV failure observed in hypoxemic patients with acute respiratory failure, that are listed as follows:

1. Previous initiation of ventilation:
   (a) High severity score [Simplified Acute Physiology Score (SAPS) II ≥35 (68)/SAPS II >34/higher SAPS II
   (b) Older age (>40 years)

(c) Presence of acute respiratory distress syndrome or community acquired pneumonia
(d) Extremely high respiratory rate and also
(e) Need for vasopressors
(f) Need for renal replacement therapy
(g) Altered mental status
(h) Copious secretions

Answer: (a) High severity score [Simplified Acute Physiology Score (SAPS) II ≥35 (68)/SAPS II >34/higher SAPS II

2. After initiation of ventilation:

(a) Inappropriate ventilator settings
(b) Non fitting interface
(c) Excessive air leakage
(d) Asynchrony with the ventilator
(e) Poor tolerance of NIMV
(f) Expired tidal volume above 9.5 mL/kg predicted body weight in patients with PaO_2/FiO_2 ≤200 mmHg

Answer: (f) Expired tidal volume above 9.5 mL/kg predicted body weight in patients with PaO_2/FiO_2 ≤200 mmHg

3. After 60–90 min of NIVM:

(a) Failure to improve oxygenation after 1 h of treatment [ratio of partial pressure arterial oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) ≤146 mmHg/PaO_2:FiO_2 ≤175 mmHg
(b) No reduction of respiratory rate or PCO_2
(c) No improvement in pH or oxygenation
(d) Signs of fatigue
(e) Neurological or underlying disease impairment
(f) Higher respiratory rate under NIMV

Answer: (a) Failure to improve oxygenation after 1 h of treatment [ratio of partial pressure arterial oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) ≤146 mmHg/PaO_2:FiO_2 ≤175 mmHg

The weaning of respiratory support should be progressive, reducing the oxygen delivery, the inspiratory pressure and finally the PEEP or EPAP until the support is not needed. NIMV is usually stopped when satisfactory recovery has been achieved that in ACPE can be around 2–5 h after initiation of support.

34.4 Concluding Remarks

Respiratory support in ACPE is essential to give time to interventions directed to treat the etiology of the cardiac failure. First of all, we should determine if a patient has one or more contraindications for apply NIMV or if the patient requires rapid orotracheal intubation. If there is not contraindication of NIMV, we should select the initial settings and the interface, according to the specific pathology and the characteristics of the patient in order to avoid asynchronies with the ventilator. We should have in mind the risk factors for failure of NIMV previous the initiation, when we initiate the ventilator support and finally, we should assess closely during the first 90 min. It is important not to delay intubation because this is associated with worst prognosis.

Non invasive ventilation has positive effects in the hemodynamic and ventilator parameters, due to the positive pressure applied in the intra-thoracic cavity leading to reducing the preload and the afterload of the cardiovascular system and recruiting the alveoli in the lungs. The use of NIMV has demonstrated that reduce the orotracheal intubation and hospital stay without increasing the secondary effects compared with the standard of care. Also, the benefit is independent of the modality of NIMV. In some circumstances the CPAP could be easy to apply in a non-highly equipped areas whereas NIPSV or BiPAP can be used in more experiences areas including the emergency room or intensive care.

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Chapter 35
Clinical Conditions Acute Hypoxemic Respiratory Failure: Non Invasive Ventilation in Thoracic Trauma

Fabrizio Bottino

Abbreviations

DEX	Dexmedetomidine
HDU	High Dependency Unit
ISS	Injury severity score
LUS-ReS	Lung ultrasound reaeration score
PCA	Patient control analgesia

Chest trauma is reported to occur in 20% of multiple trauma patients and accounts for 20–40% of all trauma deaths. Kulshrestha et al. [1] conducted a study with a sample of 1359 chest trauma patients and among them 49% had rib fractures, 20% had pneumothorax, 12% had lung contusion, and 6% thoracic vascular injury. The mortality rate was found to be 9.4%, of which 5.6% died in the first 24 h. Lung function is impaired after chest trauma primarily by direct parenchymal damage and subsequently by activation of systemic inflammation.

Intubation rates reported in patients with chest trauma range from 23% to 75%, mainly depending on trauma severity, the presence of underlying pulmonary disease, associated injuries, and the intensity of monitoring and management [2].

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Case Report

A 45-year-old male cyclist was hit by a vehicle and trapped under it. The extraction from the vehicle was arduous and lengthy. The first clinical assessment revealed a level of pain of 8 (VAS scale), the patient presented a tachypnea of 40 b/min, a Glasgow Coma Scale (GCS) of 15, an oxygen saturation of 82% on surrounding air requiring oxygen therapy at 15 L/min. He was tachycardic (HR 130 bpm) but not hypotensive (PAS 100 mmHg). His Revised Trauma Score was 8. Inspection revealed head injury with superficial wound and chest wall asymmetry but not subcutaneous emphysema. The breath sound on auscultation was absent in the basal right side of the thorax. In the ambulance the patient benefited of an echographic assessment that excluded a pneumothorax and revealed a moderate right pleural effusion; no fluid was visible in the pericardium, right upper and left upper quadrant recesses and the pelvis.

During prehospital management, the patient received morphine and ketamine to relieve pain. We opted for this kind of treatment considering that non-opioid analgesics do not provide sufficient analgesia and intravenous opioids are routinely mandatory even in the absence of intubation and despite one of their main adverse effects is the depression of the central respiratory centers, which causes the increase of hypoventilation and the reduction of the coughing reflex. Adding ketamine to morphine has been shown to reduce the morphine consumption preserving respiratory and hemodynamic function. The optimal drugs combination has been reported to be a ratio of 1:1 [3]. The patient received bolus doses of morphine-ketamine at the dosage of 0.015 mL/kg every 10 min.

After admission to the Emergency Department, the patient maintained his hemodynamic and neurologic status stable. At the emogasanalysis (EGA) the patient presented a mild Acute Respiratory Failure (PaO_2 52 mmHg with FiO_2 40%; P/F: 130) without hypercapnia ($PaCO_2$ 42 mmHg).

Total body CT scan revealed right pulmonary contusion with pleural effusion (estimated at 250–300 cc), four right ribs with no chest flail, first and second lumbar vertebrae with no spinal cord injury, right ankle and humerus fractures. A retrospective observational study published by Baker et al. [4] shows that patients who developed pneumonia after admission to hospital presented initially with more thoracic fractures on CT (8.1 vs 5.7, $P < 0.001$) and higher Injury Severity Score (ISS) when compared to those who did not develop pneumonia (29.1 vs 23.0, $P < 0.001$). Patients who developed pneumonia after blunt chest injuries had significantly higher invasive ventilation requirements in hospital and in prehospital environment ($P < 0.001$). These patients also had prolonged intensive care stays and required longer episodes of invasive and non-invasive ventilation ($P < 0.05$). In trauma patients actually, the risk of intubation depends not only on the severity of gas exchange impairment, but also on the severity of trauma, on the extension of lung contusion and on the hemodynamic status. However, early use of NIV might prevent the failure of spontaneous breathing and avoid the need for intubation by favoring chest stabilization and lung recruitment. In a prospective multicenter cohort study of hypoxemic patients after pulmonary contusion, the intubation rate was 18%, which is significantly lower compared to patients with community acquired

pneumonia or ARDS, the risk of failure with NIV was associated with a higher SAPS II score and with persistent hypoxemia after 1 h of NIV [5]. For these reason ERS/ATS guidelines suggest cautious NIV trial in patients with chest trauma when pain is controlled and hypoxaemia not severe [6]. In the case we are reporting here, the patient's hemodynamic status was stable, his Injury Severity Score (ISS) was 26, the SAPS II score at admission was 28, the grade of hypoxaemia was moderate (P/F: 130) and he did not have a multi-organ dysfunction. We therefore decided to hospitalize the patient in High Dependency Unit (HDU) to treat him with non-invasive mechanical ventilation. The HDU is an intermediate care unit; in accord to the ERS requisites, the levels of care in HDU include monitoring and intervention, with possibility to convert NIV promptly to invasive ventilation and recovery the patient in ICU [7]. Patient security management was guaranteed by a shared hospital protocol.

Non-invasive ventilation was continuously delivered after admission to HDU. The levels of starting inspiratory (IPAP) and expiratory (EPAP) positive airway pressure were 12 cmH_2O and 6 cmH_2O. PAP was titrated to achieve a tidal volume of 8 mL/kg and respiration rate of <25/min. Expiratory positive airway pressure (EPAP) was titrated to maintain SpO_2 >90% with Fi = 0.5.

During NIV, Pain Controlled Analgesia (PCA) was attempted with dexmedetomidine at 0.5 mcg/kg/h and morphine at 1 mL/mg at 5 min intervals titration; the goal of PCA analgesia was that of maintaining the VRS ≤4. This choice was based on the fact that dexmedetomidine (DEX), a selective α2 adrenergic receptor agonist, has analgesic, sedative, and sympatholytic properties without causing respiratory depression. The preoperative or intraoperative use of DEX has been shown to potentiate analgesia and reduce postoperative opioid requirements.

The dexmedetomidine-morphine mixture reduces morphine consumption while yet improving the quality of analgesia. The addition of dexmedetomidine to i.v. PCA morphine results in superior analgesia, significant morphine sparing, less morphine-induced nausea, and is devoid of additional sedation and untoward haemodynamic changes in patients undergoing abdominal surgery [8].

Non-invasive monitoring was attempted with Oxygen saturation, arterial blood gas analysis every hour during first 4 h and every 4 h during first 24 h (pH, $PaCO_2$, PaO_2), blood pressure monitoring, ECG and lung ultrasound (LUS). This technique is becoming an essential part of the chest imaging in every setting (prehospital, emergency department, high dependency unit, intensive care unit). It is portable, real time, bed side, and repeatable. In the supine position, six regions should be systematically examined: upper and lower parts of the anterior, lateral and posterior chest wall. The use of ultrasound reduces the necessity of intra-hospital patient's transport for diagnostic procedures; moving patients from the safety of an intensive care unit is associated with an overall complication rate of up 70% and a mortality rate of 2% [9]. We observed at 1, 6 and 24 h consolidation, pleural effusion and LUS reaeration score (LUS-ReS). This score could be a useful tool in predicting non-invasive ventilation effectiveness for acute respiratory failure treatment [10].

Heart rate (HR) dropped and P/F ratio improved significantly within 1 h of initiation of non-invasive mechanical ventilation. Non-invasive ventilation was delivered

continuously for 3 days, when patient tolerated FiO_2 <0.5 with IPAP <6 and IPAP <12 (without signs of respiratory distress like agitation) withdrawal from NIV was attempted. Non-invasive ventilation withdrawal was attempted with gradual reduction (2 cmH_2O) of inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) every 12 h.

After 10 days the patient was transferred to the orthopedic department for humerus surgery.

Key Teaching Points

- Adding ketamine to morphine reduces the morphine consumption preserving respiratory and hemodynamic function.
- Lung Ultrasound was an optimal tool to evaluate and monitor a patient with blunt chest trauma during noninvasive ventilation.
- Dexmedetomidine as an adjunct therapy to facilitate the acceptance of the non-invasive ventilation in patients with blunt chest trauma.

Questions and Answers

1. Why dexmedetomidine-morphine mixture should be used during non-invasive ventilation in chest trauma pts?

   (a) To reduce morphine consumption while yet improving the quality of analgesia
   (b) To increase morphine consumption while yet improving the quality of analgesia
   (c) It is not recommended

   Answer: (a) To reduce morphine consumption while yet improving the quality of analgesia
2. When do ERS/ATS guidelines suggest cautious NIV trial in chest trauma pts?

   (a) When pain is controlled and hypoxaemia is severe
   (b) When hemodynamic status is stable
   (c) All of the above

   Answer: (c) All of the above
3. Which are the risk factors for the NIV failure in pulmonary contusion pts?

   (a) Higher SAPS II score
   (b) Persistent hypoxemia after 1 h of NIV
   (c) All of the above

   Answer: (c) All of the above
4. Which of the following is correct?

   (a) Chest trauma is reported to occur in 20% of multiple trauma patients and accounts for 20–40% of all trauma deaths

(b) Chest trauma is reported to occur in 60% of multiple trauma patients and accounts for 10–20% of all trauma deaths
(c) Chest trauma is reported to occur in 5% of multiple trauma patients and accounts for 80% of all trauma deaths

Answer: (a) Chest trauma is reported to occur in 20% of multiple trauma patients and accounts for 20–40% of all trauma deaths

5. Why ketamine should be added to morphine in pre-hospital treatment in chest trauma pts?

(a) To reduce the morphine consumption
(b) To preserve respiratory and hemodynamic function
(c) All of the above

Answer: (c) All of the above

6. Which of the following score should be used to predict NIV effectiveness for acute respiratory failure treatment in chest trauma pts?
(a) LUS reaeration score (LUS-ReS)
(b) SOFA score
(c) ECHO score

Answer: (a) LUS reaeration score (LUS-ReS)

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Chapter 36
Thoracic Surgery, a Clinical Case in Non-invasive Ventilation: Clinical Conditions in the Perioperative Period

Jakob Wittenstein and Martin Scharffenberg

Abbreviations

CO_2	Carbondioxide
ECG	Electrocardiogram
EPAP	End-expiratory positive airway pressure
HFNC	High flow nasal cannula
IPAP	Inspiratory positive airway pressure
NIV	Non-invasive ventilation
PaO_2	Arterial partial oxygen pressure
PPC	Postoperative pulmonary complications
SpO_2	Peripheral oxygen saturation
VATS	Video-assisted thoracoscopy

36.1 Introduction

The following chapter will look at the use of non-invasive positive pressure ventilation (NIV) in the perioperative period of thoracic surgery and a standard teaching case will be presented.

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Despite advances in surgical techniques, anaesthesia, and perioperative care, patients undergoing thoracic surgery are still at high risk of developing postoperative pulmonary complications (PPC) [1]. Risk factors for PPC are divided into patient-side risk factors such as obesity, history of lung disease and anamnesis of smoking and procedure-related factors such as abdominal and thoracic surgery. Furthermore, the phenomenon of minor surgery under major anaesthesia in thoracic surgery is common. Even relatively small procedures, e.g. pleurodesis, usually still require general anaesthesia, full monitoring including an arterial line, and one-lung ventilation with either a double-lumen tube or a bronchus blocker, with the associated risks of airway injury and hypoventilation. Furthermore, the adverse effects of intubated general anaesthesia are impaired cardiac performance and postoperative nausea and vomiting. Awake surgery with the use of NIV and a combination of local and regional anaesthesia can offer an alternative approach. Local and regional anaesthesia is a combination of thoracic epidural anaesthesia, paravertebral blocks, intercostal nerve blocks and intrathoracic vagal blockade to reduce the cough reflex. Nebulized lidocaine given 30 min before the start of the intervention can further reduce cough reflex [2].

However, the technique presents a greater technical challenge for the anaesthetist and surgical team. Thorough patient selection, strict planning, preparation and vigilance are essential [3]. Lung collapse with awake surgery seems not to be a problem [3]. Nevertheless, general anaesthesia should be in stand by and ready as a backup plan. Even though, the conversion rate from awake surgery to general anaesthesia is low and ranges between 0% and 10% [4]. Reasons for conversion are extensive pleural adhesion, persistent hypoxia and severe intrathoracic bleeding. It is important to define the conversion criteria beforehand and follow them strictly to avoid major risks. Nevertheless, patients must be suitable for general anaesthesia, since it is the only backup option. Therefore, anaesthetists should be well trained and able to place an endotracheal tube also with the patient lying in the lateral decubitus position. Furthermore, all team members have to be aware of the potential risks and have to be prepared. Awake surgery should not be considered as an anaesthetic approach when symptomatic gastro-oesophageal reflux or inadequate fasting is present. Overall, the evidence is low as well as the amount of randomized controlled trials.

Advantages of awake procedures are an efficient contraction of the diaphragm with a favourable ventilation-perfusion matching, a shorter hospital stay and reduction of postoperative morbidity rate [4]. On the other hand, disadvantages are reduced compliance of the ventilated lung due to the pneumothorax, a reduced tidal volume and possible rebreathing of CO_2 from the surgical lung. These disadvantages may be resolved with NIV or so-called high flow nasal cannula (HFNC) oxygen therapy. Mostly benefit from awake non-tube anaesthesia will those patients who suffer most from general anaesthesia, e.g. elderly patients and patients with known cardiorespiratory disease, emphysema and muscular diseases (Table 36.1).

Table 36.1 Awake thoracic procedures

Consider for	Intervention	Key factors
Elderly patients	Non-tubed awake thoracic surgery	Careful planning together with patient and surgeon
Patients with known comorbidities	Combination of local and regional (e.g. epidural catheter) anaesthesia	Close patient monitoring
Patients with known muscular disease	Perioperative non-invasive ventilation (NIV) or high flow nasal cannula (HFNC) oxygen therapy	Readiness to convert to general anaesthesia
Palliative patients	General anaesthesia in stand-by	Well experienced surgical and anaesthetic team

36.2 The Teaching Case

We will describe a standard teaching case of an 85-year-old man, weighing 83 kg, with a height of 180 cm, and with a suspected malignant tumour of the right lower lobe planned for a video-assisted thoracoscopy (VATS) for atypical lung resection. The patient has a history of smoking with 50 pack years. Furthermore, the patient suffers from a coronary artery disease with a condition after placement of a drug-eluting stent, an arterial hypertonus and a diabetes mellitus type 2. The American Society of Anesthesiologist (ASA) status is classified as ASA III.

36.3 Preoperative Phase

During the premedication visit, the anaesthetist discusses with the patient the use of epidural anaesthesia, sedation and NIV for the intervention. The patient gives his informed consent. As in general, premedication should be risk-adapted. The focus should lie on determining the cardiopulmonary reserve. In order to make the situation as comfortable as possible for the patient, it can be very helpful that the patient and anaesthetist get to know each other before surgery. Especially in case of complications, this can ease the situation. Furthermore, the anaesthetic procedure should be explained systematically to the patient before, to familiarize the patient with the proceedings.

Cough reflex due to manipulation of the lungs during awake procedures can be a problem. *However, it can be successfully reduced when aerosolized lidocaine 2% with an oxygen flow of 8–10 l/min is given for about 30 min preoperatively as a topical anaesthetic, which is started as soon as the patient arrives in the OR.* Alternatively, intravenous lidocaine administration can be considered. In contrast to inhalation, there is no initial temporary bronchial irritation after intravenous injection. However, with a comparable effect, higher plasma levels are reached when intravenously

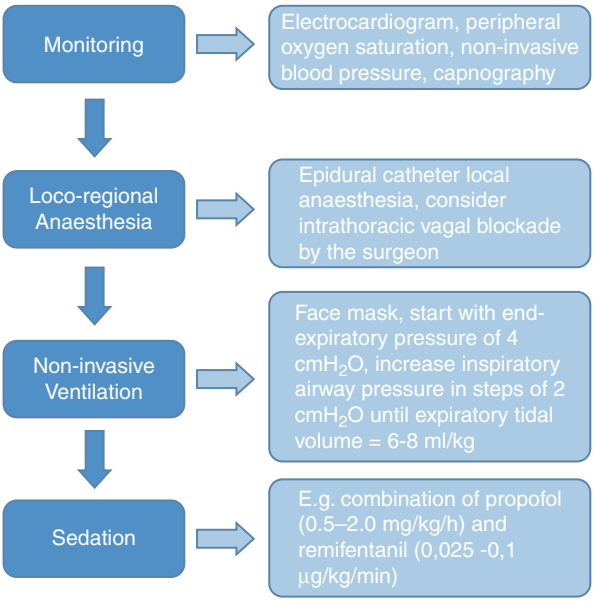

Fig. 36.1 Pre- and intraoperative phase

given with an increased risk of systemic side effects. Prior intravenous application, normal electrocardiogram has to be confirmed and if liver function is impaired, reduced metabolism must be expected and the dose adjusted if necessary.

Monitoring is established, including an electrocardiogram (ECG), peripheral oxygen saturation (SpO_2) and non-invasive blood pressure (Fig. 36.1). Peripheral venous access is placed. The epidural catheter for regional anaesthesia is placed in the Th5/6–Th6/7 thoracic interspace with a loss of resistance technique. After confirmation of the correct position, continuous epidural anaesthesia is started and titrated until a sensory blockade in the range from Th2 to Th8 is reached. Epidural anaesthesia increases diaphragmatic activity, while not effecting airway resistance [5], but it reduces the respiratory response to hypercapnia [6].

We are describing a case without the use of general anaesthesia. However, if general anaesthesia is unavoidable, extended preoxygenation is recommended, especially for critically ill patients as well as obese patients with a low respiratory reserve. In these patients, a combination of HFNC with NIV face mask for preoxygenation might be advantageous. NIV ensures effective nitrogen washout and HFNC application allows apnoeic oxygenation and thus more time to critical desaturation of the patient [7]. Furthermore, NIV should not be discontinued for preoxygenation in the cases of patients treated with NIV before intubation [8]. HFNC oxygen therapy has been demonstrated to generate a positive airway pressure, improve oxygenation and dyspnoea, reduce dead space, the work of breathing and the respiratory rate and improve patient comfort [9].

After verifying the local anaesthetic effect and before starting sedation, the anaesthetist starts the non-invasive ventilation with a facemask and an

end-expiratory positive airway pressure (EPAP) of 5 cmH_2O. Inspiratory positive airway pressure (IPAP) is slowly increased until 11 cmH_2O is reached and a back-up rate of four per min is set. Oxygen is titrated to achieve a saturation of ≥92%. Patient comfort and interface acceptance can be improved by starting with EPAP alone and then slowly increasing the EPAP and IPAP level once the mask is applied. IPAP can be increased in steps of 2 cmH_2O to achieve an expiratory tidal volume of 6–8 ml/kg ideal body weight [10]. NIV reduces the work of breathing, improves alveolar recruitment and ventilation and results in better gas exchange. Positive extra-pulmonary effects are a reduced right ventricular preload and a reduced left ventricular afterload.

36.4 Intraoperative Phase

The anaesthetist starts the sedation with a propofol bolus of 20 mg followed by a continuous infusion of 0.5–2.0 mg/kg/h and a continuous infusion of remifentanil of 0.025–0.1 µg/kg/min. The aim is to reach a level of sedation at which the patient is calm and tolerates NIV well. Other drugs which can be used for analgosedation are midazolam, ketamine, fentanyl and piritramid.

As soon as the pleural space is open and iatrogenic pneumothorax is induced during VATS, spontaneous one-lung breathing starts. There are physiologic alterations due to spontaneous one-lung breathing in an open pneumothorax: The compliance of the ventilated lung is reduced as well as tidal volume and rebreathing of CO_2 from the surgical lung may occur. Furthermore, when the pneumothorax is established, patients may become dyspnoeic or even tachypnoeic. In this case, it is important to coach the patient well. Additionally, titrated opioids according to respiratory rate, e.g. remifentanil, may be used to attenuate respiratory response after opening of the pleural space. During spontaneous one-lung ventilation an oxygen saturation, greater than 90% and permissive hypercapnia with arterial pH above 7.25 should be targeted.

As an alternative to NIV, HFNC oxygen therapy may be used during awake thoracic surgery. A flow of about 20 l/min increases PaO_2 without recruiting the surgical lung. At the end of the surgery, the flow can be increased to 70 l/min to recruit the surgical lung. Until now, the evidence is low and large clinical trials are missing.

Monitoring is essential throughout the whole perioperative period. Measuring respiratory rate, observing chest and abdominal wall movement and obtaining blood gas samples are key factors. The team must be ready at any time to switch from an awake procedure to general anaesthesia. According to a review by Tacconi and colleagues, most frequent causes of conversion are thick adhesions and respiratory movements (incidence: 1.3%), significant bleeding (incidence: 0.34%), impairment of gas exchange (incidence: 0.34%) and cardiac arrest (incidence <0.1%) [4].

The patient is turned to the right side and the VATS is performed without any problems. An atypical lung resection of the right lower lobe is performed.

36.5 Postoperative Phase

Postoperatively, non-invasive ventilation is continued for about 3–4 h and then stopped at normal blood gas levels and a stable hemodynamic situation. The postoperative algorithm includes furthermore intravenous fluid maintenance for 12 h postoperatively, the start of oral fluids and light cost within 4 h, and substantial multimodal pain management including the patient-controlled epidural analgesia and a peripheral analgesic such as ibuprofen, physiotherapy and early mobilization.

Thoracic surgeries are frequently associated with postoperative acute respiratory failure. After lung resection, lung function is more impaired compared to other types of surgery. The surgery itself leads to loss of parenchyma, anaesthesia and post-operative pain all have deleterious effects on the respiratory system causing diaphragm dysfunction with a decrease in lung volume and atelectasis. These modifications are maximum in the initial hours following surgery and generally regress after 1–2 weeks thereafter.

With the use of NIV, these effects can be attenuated by reducing the work of breathing, improving alveolar ventilation associated with increased gas exchange and reducing atelectasis [10]. NIV use can decrease mortality, the need for intubation and the incidence of nosocomial pneumonia in the postoperative period [11]. Various concepts for postoperative NIV application are currently being discussed. An approach of 60–120 min NIV episodes combined with phases of oxygen substitution by face mask can be chosen. Total daily NIV use ranges between 3 and 12 h. The length of the NIV episodes will be further reduced and finally terminated when good blood gases have been reached (Fig. 36.2). NIV provided by a trained team can reduce the intubation rate in the postoperative period. Nevertheless, an intensivist should be available within a few minutes from the patient in case of NIV failure to allow rapid intubation and transfer to an ICU for invasive mechanical ventilation. In any case, surgical complications, e.g. anastomotic leak, intra-abdominal sepsis etc., have to be addressed first and NIV only applied when the patient is cooperative and able to protect the airway.

The most common thoracic surgeries are lung and oesophagus resection. In theory, both surgeries represent a contraindication for NIV due to possible anastomosis

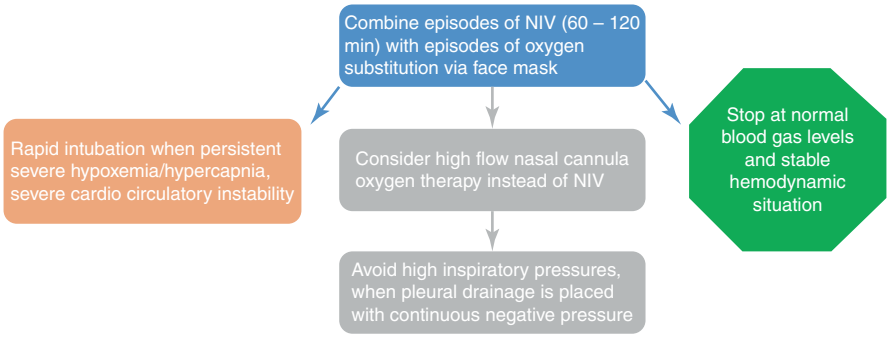

Fig. 36.2 Postoperative phase

insufficiency and aspiration. Concerning oesophagostomy, Raman and colleagues showed in a porcine model air pressure tolerance of an oesophageal anastomosis without air leaks to pressures of up to 84 cmH_2O, which is high above the pressures reached during NIV.

A current hot topic is the role of transpulmonary pressure in the development of ventilator-induced lung injury and so-called patient self-inflicted lung injury. The transpulmonary pressure (Ptrans) is calculated according to the following formula: Ptrans = Pairway–Ppleura, where Pairway represents the airway pressure and Ppleura represents the pleural pressure. After thoracic surgery, a pleural drainage is placed often. When negative pressures are applied at the drainage, pleural pressure is reduced. In combination with NIV, constant positive airway pressure is reached, with the risk of high transpulmonary pressures. However, studies investigating this effect on lung injury are still lacking. Nevertheless, high IPAP should be avoided in general, not only when thorax drainage with negative pressure is used.

HFNC oxygen therapy can be used instead of NIV after thoracic surgery. In a non-inferiority study among cardiothoracic surgery patients with or at risk for respiratory failure, the use of HFNC oxygen therapy compared with intermittent NIV did not result in a worse rate of treatment failure [12]. This is in line with other multicenter trials, showing that the application of HFNC oxygen therapy in patients with thoracoscopic lobectomy after extubation was able to reduce the risk of hypoxemia and reintubation as well as to improve gas exchange [13].

Key Teaching Points

- Awake thoracic surgery offers a promising alternative to general anaesthesia, especially for those patients who suffer most from general anaesthesia, e.g. elderly and patients with known cardiorespiratory disease, emphysema and muscular diseases
- Careful patient selection, strict planning, preparation and vigilance are essential for safe awake thoracic procedures
- Anaesthetists should be well trained and able to intubate the patient lying in the lateral decubitus position in case of conversion from awake to general anaesthesia
- Postoperative non-invasive ventilation can improve patient's outcome, but an intensivist should be available within a few minutes from the patient, to allow rapid intubation and transfer to an ICU for invasive mechanical ventilation in case of NIV failure

Questions and Answers

1. Risk factors for postoperative pulmonary complications are. Which answer is not correct?

   (a) Smoking
   (b) COPD
   (c) Obesity

(d) Abdominal surgery
(e) Epidural anaesthesia

Answer: (e) Epidural anaesthesia

2. What are contraindications for NIV in thoracic procedures

(a) Patients with cardiorespiratory disease
(b) Patients with muscular disease
(c) Palliative patients
(d) Patients with presence of gastro-oesophageal reflux

Answer: (d) Patients with presence of gastro-oesophageal reflux

3. Essential for NIV application in thoracic surgery is. Which answer is not correct?

(a) Careful patient selection
(b) Readiness to perform intubation
(c) Close patient monitoring
(d) Placement of a central venous catheter

Answer: (d) Placement of a central venous catheter

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Chapter 37
Non-invasive Ventilation Following Thoracotomy: Clinical Case

Yerosimou Fotis and Schizas Nikolaos

Abbreviations

ABGs	Arterial blood gases
ALI	Acute lung injury
ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CXR	Chest X-ray
DLT	Double lumen tube
ETI	Endotracheal intubation
FCV	Forced vital capacity
FEV_1	Forced expiratory volume in one second
ICU	Intensive care unit
NIV	Non-invasive ventilation
NPPV	Noninvasive positive-pressure ventilation
PEEP	Positive end-expiratory pressure
VAP	Ventilator associated pneumonia

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37.1 Introduction

Patients undergoing lung surgery are thought to be at high risk for the development of postoperative pulmonary complications [1]. Surgical procedures in thoracic surgery have a major effect on the respiratory system, impaired by multiple factors, both surgery- and patient-related. Patient-related factors include patients with a history of smoking and chronic obstructive pulmonary disease (COPD). The effects of anesthesia and thoracic surgery procedures include respiratory muscle impairment, reduced tidal volume and atelectasis. Impaired pulmonary oxygen transfer is primarily attributed to a decrease in functional residual capacity in about 70% of patients following thoracotomy [2].

The two lungs on each side of the thoracic cavity are two separate organs morphologically, but act as one functional unit, inflating and deflating in unison to maintain the normal levels of oxygen and CO_2 in the blood [3]. During thoracic procedures, in order to improve surgical field exposure, lung isolation is necessary. To achieve that, one-lung ventilation technique is used. Lung isolation requires advanced knowledge of the maintenance of gas exchange and specialized skills for airway management.

One of the biggest concerns with one-lung ventilation is hypoxemia and acute lung injury (ALI). Hypoxemia is usually the result of alveolar hypoventilation and an increasing shunt fraction, whereas ALI is caused by ventilatory stress (volutrauma, atelectrauma, and barotrauma), re-expansion pulmonary injury, and the lung surgery itself [4].

Although NIV can refer to any ventilator support method without the use of ETI, we are only going to discuss the use of Noninvasive Positive-Pressure Ventilation (NPPV). In NPPV, there are controlled modes and assisted modes. In controlled modes only the ventilator applies pressure to the respiratory system while in assisted modes the pressure is applied by both the ventilator and the respiratory muscles. In the following paragraphs we are going to discuss a clinical case regarding the use of NIV in patients presenting with postoperative pulmonary complications following thoracic surgery.

Case Presentation

A 77-year-old male underwent right thoracotomy because of an abnormal shadow in chest radiography. The pre-operative computed tomography (CT) scan with contrast enhancement revealed a 2.9 cm × 2.6 cm × 2.2 cm mass shadow in the right upper lobe posterior segment. The CT scan also provided evidence of emphysema. Patient was a former smoker (20 cigarettes per day for at least 15 years), but had stop 30 years before surgery (Fig. 37.1).

Patient's pulmonary function tests revealed Forced Vital Capacity (FCV) 2.02–65% and Forced Expiratory volume (FEV_1) in 1 s 1.90–81%. His medical history included COPD, hypertension, dyslipidemia, hepatitis C virus and benign prostate hyperplasia.

The operation was performed using the right posterolateral thoracotomy procedure, where an incision was performed over the fifth intercostal space for optimal

access to the pulmonary hilum (pulmonary artery and pulmonary vein). The procedure included posterior segmentectomy of the right upper lobe and sampling biopsy of mediastinal lymph nodes. Segmentectomy was chosen over lobectomy in order to preserve as lung parenchyma as possible and to achieve the oncological outcome.

During the anesthesia the patient was under protective lung ventilation in both one-lung and two-lung ventilation with low Tidal volume (<6 mL/kg) and Positive end-expiratory pressure (PEEP) (6-8 cm H_2O) and FiO_2 50% and 80% respectively. The patient was intubated with a left double lumen tube (DLT) 39F with complete isolation of the pathological lung. Throughout the course of anesthesia there were no complications.

After the procedure, the patient was extubated and transferred to the ICU for close monitoring and pain management. During that time an air-entrainment mask was used on the patient with a flow of 5lt of O_2 and analgesia was controlled with continuous intravenous infusion of morphine, paracetamol and NSAIDs.

Patient presented with symptoms and signs of acute respiratory failure 6 h approximately after admission to the ICU, including hypoxia $SpO_2 > 85\%$, shortness of breath and tachypnea. During this time the patient was fully aware and conscious. Patient was quickly placed on non-invasive ventilation and ventilator settings were adjusted according to the arterial blood gases (ABGs) values (Table 37.1).

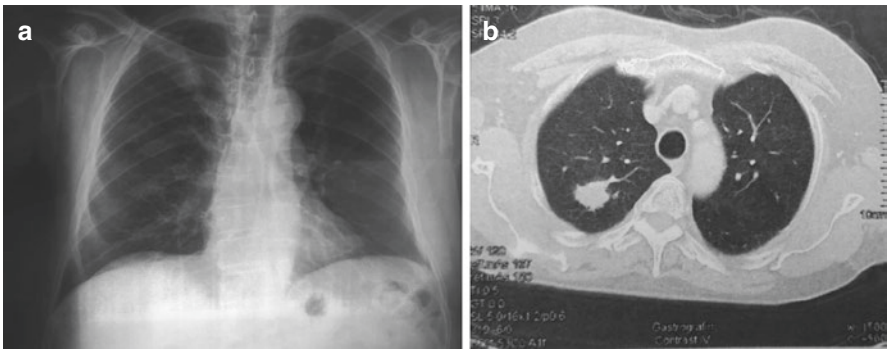

Fig. 37.1 (**a**) Preoperative chest x-ray (CXR) depicting lesion in the right upper lobe, without signs of atelectasis or infection. (**b**) Preoperative CT depicting right upper lobe nodule and diffused signs of emphysema

Table 37.1 ABGs of the patient before, during and after NIV

	pH	pO_2 (mmHg)	pCO_2 (mmHg)	SO2 (%)	FiO_2	Respiratory rate
Simple O_2 mask	7.274	66.2	58.6	89.3	7lt 0_2 (~50%)	22/min
2 h NIV	7.250	78.6	53.0	93.1	80%	14/min
4 h NIV	7.353	73.1	54.4	93.5	40%	17/min
Simple O_2 mask 6 h after NIV	7.446	78.9	45.1	96.1	5lt 0_2 (~40%)	11/min

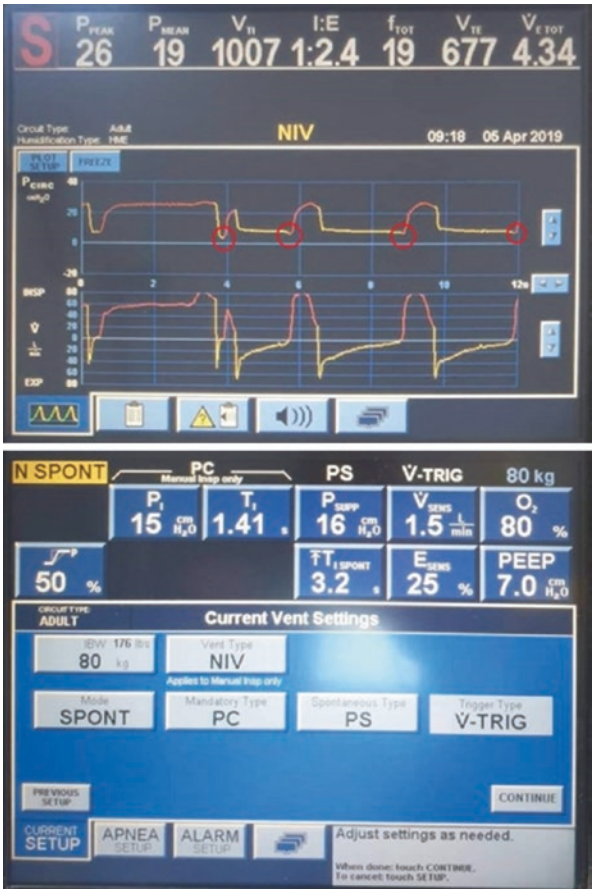

Fig. 37.2 The red circles show the negative pressure created by the patient as he tries to initiate a breath

It is worth mentioning that the patient was very cooperative and tolerated NIV extremely well, which is the main reason of his quick improvement and transitioning from NIV to simple oxygen mask in just a few hours. The patient was monitored for 48 h, following the thoracotomy. After remaining stable with no more complications, the patient was transferred to the thoracic surgery clinic for further monitoring (Fig. 37.2).

37.2 Discussion

The aims of NIV [5] are (1) to partially compensate for the affected respiratory function by reducing the work of breathing, (2) to improve alveolar recruitment with better gas exchange (oxygenation and ventilation), and (3) to reduce left ventricular afterload, increasing cardiac output and improving hemodynamics.

Short-term NIV with a ventilator support system improves the efficiency of the lung as a gas exchanger without noticeable non-desired side effects in patients submitted to lung resectional surgery [6]. There are some risks with the use of positive pressure ventilation following thoracic surgery such as air leakage and bronchial stump disruption but with careful regulation and modest use of PEEP, these risks are minimized. Most patients presenting with respiratory complications after thoracic surgery, have been benefited from non-mechanical ventilation showing improvement in just a short period.

However, NIV fails in about 20% of patients [7]. Failure of NIV is not always related to the patient. The success of NIV depends also on the medical personal, their knowledge and skills on this topic. Physicians must be able to overcome any issues that may arise from NIV and deal with the problems that accompany this ventilation technique which will determine the patient's outcome in most cases. The most common problems include (1) a lack of operating knowledge by the staff; (2) improperly fitted equipment (e.g., a mask with excessive leaks); and (3) the inability of the personnel to control oxygen therapy or manage the ventilator alarms [8].

NIV can have many advantages especially when endotracheal intubation (ETI) can be avoided together with the complications that follow ETI such as pulmonary infections, ventilator associated pneumonia (VAP), lung injury etc. It is important to remember though, that NIV is just a complementary method of ventilation and under no circumstances can replace ETI when there is indication for it.

Key Teaching Points

- Anesthesia and thoracic surgery procedures can impair respiratory function resulting in acute respiratory failure (ARF).
- Recognizing the symptoms of ARF and treating them as soon as possible reduces mortality rates and improve patient's respiratory function.
- NIV must be used as first line treatment and avoid ETI if possible.
- NIV does not replace ETI when there are indications for it.
- Constant knowledge and skill improvement of NIV are crucial for patient's outcome.

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Chapter 38
Noninvasive Ventilation in Acute Respiratory Distress Syndrome

Julie Lin and John P. Kress

Abbreviations

AHRF	Acute hypoxemic respiratory failure
ARDS	Acute respiratory distress syndrome
COPD	Chronic obstructive pulmonary disease
FiO_2	Fraction of inspired oxygen
IBW	Ideal body weight
ICU	Intensive care unit
NIV	Noninvasive ventilation
P/F ratio	Partial pressure of arterial oxygen/fraction of inspired oxygen ratio
PaO_2	Partial pressure of arterial oxygen
PEEP	Positive end expiratory pressure
P-SILI	Patient self-induced lung injury
SAPS II score	Simplified acute physiology score II score
SOFA score	Sequential organ failure assessment score

Noninvasive ventilation (NIV) is a widely used intervention in the intensive care unit (ICU) for patients with respiratory failure. Studies have shown benefit with utilizing NIV in patients with acute hypercapneic respiratory failure, such as chronic obstructive pulmonary disease (COPD) exacerbations, and cardiogenic pulmonary edema with decreased need for endotracheal intubation and reduced mortality [1].

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However, application of NIV in acute hypoxemic respiratory failure (AHRF) is less routinely used due to treatment failure rates leading to endotracheal intubation as high as 50%.

The most severe form of AHRF is acute respiratory distress syndrome (ARDS). An inciting insult causes an acute diffuse inflammatory response and results in epithelial and endothelial damage in the lung. The alveolar-capillary barrier is compromised which leads to alveolar edema, increase in dead space, decrease in lung compliance, and profound hypoxemia. Diagnosis is based on the Berlin criteria. Recognition of ARDS early in the patient's clinical course is extremely important because ARDS is associated with high mortality rates. While extensively studied in mechanically ventilated patients, where low tidal volume strategy and plateau pressures less than 30 cmH_2O are shown to be beneficial in improving mortality, less is known about the role of noninvasive ventilation in ARDS [2]. Prior studies have been published to evaluate the utility of NIV in ARDS.

In a multicenter observational study performed by Antonelli et al. and published in 2007, Antonelli and colleagues evaluated the use of NIV in patients who were diagnosed with ARDS. Patients with a diagnosis of early ARDS identified 24 h prior to ICU admission were treated with NIV as first-line management. Eligibility to participate in the study was based on predefined criteria: severe dyspnea with spontaneous breathing, elevated respiratory rate greater than 30 breaths/min, and the diagnosis of ARDS. The goal was to prevent progression to endotracheal intubation. In these patients, full face mask or helmet interfaces were used to deliver NIV [3].

The full face mask covers the nose and mouth and is secured with head straps. In contrast, the helmet is a PVC hood that goes over the patient's head and is sealed with a soft collar around the neck and held structurally by a plastic ring. The helmet is secured by two braces that are fastened to the plastic ring and go underneath the arm pits. The helmet is able to be pressurized [3].

In this trial, NIV failure was defined as the inability to maintain adequate oxygenation (partial pressure of arterial oxygen (PaO_2) >65 mmHg with a fraction of inspired oxygen (FiO_2) $\geq$0.60), excessive use of accessory muscles, altered mentation, inability to clear secretions, intolerance of mask or helmet, and hemodynamic instability. Of the patients admitted for ARDS, 147 patients (31%) were not receiving invasive mechanical ventilation at the time of ARDS diagnosis and were included in the study for using NIV as first line management. In this cohort, 54% of the patients treated with NIV did not progress to invasive mechanical ventilation via endotracheal tube. Patients that failed NIV had higher Simplified Acute Physiology Score (SAPS) II scores, were older, and required higher levels of PEEP and pressure support. Patients who avoided intubation had an initial mean PaO_2/FiO_2 (P/F) ratio of 116 which was similar to the group that progressed to intubation (mean P/F ratio was 105). Patients who avoided intubation showed an improvement in the P/F ratio 1 h after application of NIV. In terms of ICU mortality, those that progressed to intubation had a higher rate of mortality (OR 21, $p < 0.001$). Six percent of the patients who avoided intubation died in the ICU whereas of the patients that progressed to intubation, 56% of them died. A SAPS II score greater than 34 and a

persistent P/F ratio less than 175 were identified as independent risk factors associated with progression to intubation [3].

The study by Antonelli et al. concluded that NIV could be used cautiously in patients with ARDS in hospital centers that were skilled in NIV use. Using NIV as a first line therapy could prevent progression to invasive mechanical ventilation in approximately 50% of patients. However, NIV should be avoided in those with SAPS II score greater than 34 or a P/F ratio less than 175 as those were identified risk factors associated with NIV failure [3].

The Berlin criteria for diagnosis of ARDS stratifies severity based on the P/F ratio. Mild ARDS is classified as a P/F ratio of 200–300, moderate as a P/F ratio of 100–200 and severe as a P/F ratio less than 100. Studies have demonstrated the outcome of NIV use in each of these ARDS severity categories.

In an observational cohort study by Thille et al. published in 2013, investigators looked at the outcomes of patients who received NIV as their initial support in the management of AHRF. Eighty-two of the 113 patients receiving NIV met criteria for ARDS with 16 patients with mild (20%), 47 with moderate (57%) and 19 (23%) with severe ARDS. The majority of ARDS was secondary to pneumonia in this study. In this cohort, the rate of intubation was 62% for patients receiving NIV for ARDS in comparison to 35% for those that did not have ARDS and were treated with NIV ($p = 0.015$). Worsening P/F ratio and more severe ARDS led to increased rates of intubation—31% in mild, 62% in moderate and 84% in severe ARDS ($p = 0.0016$) (Table 38.1). Notably, patients with mild ARDS had comparable rates of intubation as those who did not have ARDS with AHRF (31%). Patients with moderate to severe ARDS were twice as likely to progress to intubation than patients with mild ARDS. ICU mortality was also higher in patients with moderate to severe ARDS (32%) in comparison to those with no or mild ARDS (15%) ($p = 0.041$). Patients that failed NIV and progressed to intubation had lower PEEP at NIV initiation and poor tolerance to NIV. Active cancer, shock, moderate to severe ARDS, higher SAPS score, and lower Glasgow coma scores were all risk factors for NIV failure. Thille et al. concluded that given the similar rate of intubation in patients with mild ARDS and non-ARDS, NIV could be used in mild ARDS as first-line management. NIV use in severe ARDS should be avoided due to the high failure rate and progression to invasive mechanical ventilation [4].

The largest study investigating the application of NIV in ARDS was the substudy of the LUNG SAFE (Large Observational Study to Understand the Global Impact

Table 38.1 Published studies evaluating NIV failure rates with severity of ARDS

Severity of ARDS	NIV failure rates (Thille et al. 2013 [4])	NIV failure rates (Bellani et al. 2017 [5])
Mild (200 mmHg < P/F ratio ≤ 300 mmHg)	31%	22%
Moderate (100 mmHg < P/F ratio ≤ 200 mmHg)	62%	42%
Severe (P/F ratio ≤ 100 mmHg)	84%	47%
p-Value	0.0016	0.008

of Severe Acute Respiratory Failure) cohort published in 2017 by Bellani et al. The LUNG-SAFE cohort was a multicenter prospective study of patients undergoing invasive or noninvasive ventilation and described the incidence of ARDS, clinical management, and mortality. This study described how NIV is used in ARDS, the characteristics of patients managed with NIV, factors associated with NIV failure, and mortality of patients with ARDS using NIV. This study also looked at the severity of ARDS and NIV use similar to Thille et al. In the LUNG-SAFE cohort, 15% of patients (436/2813 patients) were managed with NIV in the first 2 days after meeting diagnostic criteria for ARDS [5].

This study demonstrated that NIV use may delay the diagnosis of ARDS. NIV use was associated with a lower recognition and diagnosis of ARDS by clinicians in comparison to those receiving invasive mechanical ventilation. Several differences were observed between the NIV and invasive mechanical ventilation groups. Patients receiving NIV had lower PEEP and higher FiO_2 to address hypoxemia in comparison to the invasive mechanical ventilation group. Also, NIV patients were less able to control respiratory drive, had higher minute ventilation, and were less able to achieve lung protective strategy tidal volumes. NIV treatment failure was defined as the need for endotracheal intubation after 2 days of NIV use in ARDS which occurred in 30.7% of NIV group. The LUNG-SAFE study also observed that the greater the severity of ARDS, the higher the rate of NIV failure (22.2% to 42.3% to 47.1% in mild, moderate, and severe category respectively, $p = 0.008$) (Table 38.1). The rates of NIV use among the ARDS severity categories were similar. Risk factors associated with NIV failure included a higher nonpulmonary SOFA score, lower P/F ratio and rise in arterial carbon dioxide levels over the first 2 days of NIV use. Patients who had NIV failure had a significantly worse ICU and hospital mortality in comparison to those who were successfully managed with NIV (42.7% vs. 10.6%, $p < 0.001$). Risk factors for increased mortality in NIV patients was a declining P/F ratio in the first 2 days of NIV use in ARDS. Of note, in the severe ARDS category with a P/F ratio less than 150 mmHg, NIV use was associated with worse ICU mortality than invasive mechanical ventilation use [5].

Besides risk factors identified from prior studies that predict NIV failure, some investigators have questioned whether spontaneous breathing itself with NIV contributes to NIV failure. In the LUNG-SAFE study, patients managed with NIV had lower PEEP levels than patients receiving invasive mechanical ventilation. The lower PEEP achieved with NIV leads to higher driving pressures and high transpulmonary pressure that could induce lung injury, a condition called patient self-induced lung injury (PSILI). Tidal volumes greater than 9 ml/kg in NIV have been identified as a risk factor associated with progression to intubation and increased mortality. Obviously, such an observation does not prove cause. Nonetheless, for some patients, it may be difficult to achieve a consistent low (i.e. 6 ml/kg) tidal volume in NIV. Therefore, clinicians should be cognizant of the inspiratory efforts and tidal volumes achieved while patients are receiving NIV due to the possible risk of worsening lung injury [6].

Introduction of high flow nasal cannula (HFNC) oxygen delivery devices for management of hypoxemic respiratory failure has added another tool in the effort to avoid endotracheal intubation. Here, heated and humidified oxygen is delivered

through the nose at adjustable high flow rates and FiO_2. Frat et al. reported this strategy to be more favorable than NIV in AHRF. This FLORALI trial was a prospective, multicenter randomized controlled trial that compared the use of NIV, HFNC, or standard oxygen through a face mask in patients admitted with AHRF without hypercapnia and a P/F ratio of less than 300 mmHg. There was no statistically significant difference in intubation rates between the NIV, HFNC or standard oxygen groups. However, there were more ventilator-free days and lower mortality at 90 days in the HFNC group than the NIV group. This study suggested that HFNC therapy was more favorable than NIV in treatment of AHRF [7].

The use of different masks for positive pressure delivery in NIV treatment in ARDS has been studied. The traditional full face mask covering the nose and mouth widely used in ICU settings for NIV has many pitfalls that may hinder the efficacy of its use. In ARDS, higher levels of PEEP are oftentimes needed to maintain oxygenation and for alveolar recruitment; however, with the face mask, intolerance to the higher pressures and increased air leak may lead to ineffective use. As an alternative, use of the helmet interface that goes over the head of the patient and is sealed at the neck for NIV eliminates mask discomfort and air leak problems. In a single center, randomized trial by Patel et al. published in 2016, the use of a helmet interface for NIV was compared to the face mask for ARDS patients to prevent progression to endotracheal intubation. Adult patients receiving face mask NIV for at least 8 h for ARDS were included in the trial. Enrolled patients were randomized to either remain on face mask NIV (control) or switched to helmet NIV (intervention). The study was stopped due to efficacy and safety after 83 patients. In this study, 72% of patients had a P/F ratio of less than 200. Results showed that patients receiving helmet NIV were able to tolerate higher PEEP levels than the face mask group. The helmet group had a statistically significant reduction in respiratory rate after switching to this interface and the rate of endotracheal intubation was significantly reduced. The face mask group progressed to endotracheal intubation at a rate of 61.5% versus 18.2% with the helmet group ($p < 0.001$). Patients in the helmet group had significantly more ventilator free days than the face mask group (28 versus 12.5 days, $p < 0.001$) and had shorter ICU length of stays (4.7 vs 7.8 days, $p = 0.04$). Patients in the helmet group had significantly less hospital and 90 day mortality [8].

This study concluded that use of helmet for NIV in comparison to face mask NIV was associated with less progression to endotracheal intubation, reduced ICU length of stay, ventilator days and 90 day mortality. The main difference was likely due to the ability of patients on helmet NIV to be able to tolerate higher levels of PEEP. This study suggested that helmet NIV may have a beneficial and effective role in ARDS by reducing the rate of endotracheal intubation. Further studies should be conducted to evaluate the role of helmet NIV in ARDS [8].

In conclusion, there are a limited number of studies evaluating the role of noninvasive ventilation in ARDS. Studies suggest that noninvasive ventilation may have a role in management of ARDS, especially in early mild ARDS. The observed rates of preventing the need for invasive mechanical ventilation after using first-line NIV therapy in ARDS are variable. Antonelli et al. demonstrated that NIV may have a role early in the course of ARDS with 54% of patients not needing invasive mechanical ventilation if treated with NIV as first line therapy. Thille et al. reported

relatively worse rates of successful first-line NIV therapy for ARDS with 38% of patients not progressing to invasive mechanical ventilation. The LUNG-SAFE study reported success rates of almost 70% for patients treated with first-line NIV therapy in ARDS. However, although some of the observational studies sound promising for using NIV therapy in ARDS, clinicians should be quick to recognize risk factors that predict NIV failure. Several studies noted independent risk factors for NIV failure including SAPS II score greater than 34, P/F ratio less than 175, active cancer, shock, moderate to severe ARDS, lower Glasgow coma scores, and rising arterial carbon dioxide levels with NIV use. Observational studies noted an association between worsening ARDS severity and higher NIV failure rates. Authors suggest whether this is due to the inability to achieve lung protective, low tidal volume strategies with NIV which would worsen lung injury. Those that had more severe ARDS and had NIV failure with progression to invasive mechanical ventilation had higher ICU mortality rates than those who had initially received invasive mechanical ventilation. Therefore NIV use in moderate to severe ARDS should be avoided given the high likelihood of progressing to invasive mechanical ventilation and worse ICU mortality. Perhaps the progression to invasive mechanical ventilation is due to the face mask interface that is frequently used in ICUs for NIV delivery. Due to higher PEEP needed to achieve oxygenation in ARDS, patient discomfort and intolerance of high pressures could lead to need for mechanical ventilation. Thus far, a single center randomized trial by Patel et al. has shown promise in using the helmet interface for NIV delivery in ARDS in comparison to the facemask interface. In this pilot randomized trial, helmet NIV had significantly less progression to mechanical ventilation, more ventilator free days, a shorter ICU length of stay and reduced hospital and 90 day mortality in comparison to face mask NIV. This study suggests that the helmet interface could be used as the future NIV delivery modality for treatment of ARDS. Regardless of the NIV delivery modality, current studies suggest that NIV can be cautiously used in early mild ARDS in institutional centers that are skilled and equipped for careful monitoring of these patients with early recognition of those that are at high risk for progression to invasive mechanical ventilation.

Key Teaching Points

- Noninvasive ventilation used as first-line management of ARDS can potentially reduce the need for endotracheal intubation.
- Rates of NIV failure increase with severity of ARDS.
- Risk factors for NIV failure include a P/F ratio less than 175 and a higher severity of illness score.
- Patients using full face mask may be unable to achieve high pressure support and PEEP levels due to intolerance and air leak which can lead to NIV failure.
- Helmet interface for NIV delivery shows promise in reducing the need for endotracheal intubation.

Questions and Answers

1. Of the following, which patient with ARDS treated initially with noninvasive ventilation would least likely progress to need for invasive mechanical ventilation?

   (a) Patient with a PaO_2/FiO_2 of 50
   (b) Patient with a PaO_2/FiO_2 of 100
   (c) Patient with a PaO_2/FiO_2 of 150
   (d) Patient with a PaO_2/FiO_2 of 250
   (e) None of the above; patients with ARDS should not be treated with NIV

   Answer: (d) Patient with a PaO_2/FiO_2 of 250

2. In comparing helmet noninvasive ventilation with full face mask noninvasive ventilation in ARDS, how has the helmet interface shown advantage over the full face mask?

   (a) Less need for endotracheal intubation
   (b) Increased ventilator-free days
   (c) Decreased ICU length of stay
   (d) Decreased hospital mortality
   (e) All of the above

   Answer: (e) All of the above

3. Which of the following statements is true in regards to use of noninvasive ventilation in ARDS?

   (a) Noninvasive ventilation is the initial treatment of choice for patients with severe ARDS.
   (b) Patients with mild ARDS receiving noninvasive ventilation have similar rates of intubation as those with non-ARDS acute hypoxemic respiratory failure of similar P/F ratio severity.
   (c) Higher SAPs scores and lower PaO_2/FiO_2 ratios are not risk factors for noninvasive ventilation failure in ARDS.
   (d) The helmet interface in noninvasive ventilation has been shown to have worse outcomes than the full face mask interface and should not be used in ARDS.
   (e) None of the above statements are true.

   Answer: (b) Patients with mild ARDS receiving noninvasive ventilation have similar rates of intubation as those with non-ARDS acute hypoxemic respiratory failure of similar P/F ratio severity.

4. Which of the following has been identified as a risk factor for noninvasive ventilation failure in ARDS?

   (a) Low SAPS/SOFA score
   (b) Normal Glasgow coma score
   (c) Young adults

(d) Shock
(e) PaO_2/FiO_2 greater than 200

Answer: (d) Shock

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Chapter 39
Nasal High Flow Oxygen During Post-extubation Period in a Patient with Traumatic Brain Injury

Sibel Ocak Serin and Gulsah Karaoren

Abbreviations

APACHE	Acute physiologic assessment and chronic health evaluation
ASA	American society of anesthesiologists
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
FiO_2	Fraction inspired oxygen
GCS	Glasgow coma scale
HFNC	High-flow nasal cannula
ICU	Intensive care unit
NIV	Non-invasive ventilation
PEEP	Positive end-expiratory pressure

39.1 Introduction

High-flow nasal cannula (HFNC) oxygen therapy is an innovative and useful method for treating patients with respiratory failure. In HFNC, the aim is to decrease the respiratory frequency and increase oxygen saturation (RR <25 and SaO_2 >90%). HFNC device includes an air (oxygen mixer), active heater, humidifier, and nasal cannula [1]. It delivers heated and humidified air providing higher and more

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expected gas flow rates and fraction inspired oxygen (FiO_2) than traditional oxygen therapy [2]. By air/oxygen mixer, room air (FiO_2: 21%) can be replaced with pure oxygen (FiO_2: 100%). Humidifier saturates oxygen by water vapor. Humidified oxygen is delivered to the nasal cannula after heating up to 37 °C by a one-way inspiratory transfer tube [3]. HFNC is a quick, easy, and relatively inexpensive method that is significantly easier for nursing staff regarding management. It includes some advantages for the patient, such as allowing speaking, eating, and sleeping without interrupting therapy. In previous studies, HFNC considered an alternative to invasive ventilation in patients intolerant to non-invasive ventilation (NIV). In comparative studies, pressure ulcers related to the device were seen as less common than NIV [4].

HFNC supplements nasopharyngeal dead space and provides PEEP of 4–8 cmH_2O, creates a recruitment effect and decreases inspiratory resistance. Also, improves mucus-related atelectasis via improved mucus drainage and decreased retention by humidification. Controlled oxygen concentration by HFNC results in decreased hypoxemia attacks compared to standard oxygen therapy via mask [5].

The primary use of HFNC is to provide a relatively high FiO_2 to patients with severe non-hypercapnic hypoxemic respiratory failure from medical causes. HFNC indications and contraindications are shown in Table 39.1.

Clinicians should be alert to symptoms of respiratory failure requiring intubation and mechanical ventilation during HFNC. These include increased respiratory frequency, presence of thoraco-abdominal asynchrony (15 and 30 min after initiation of HFNC therapy), and lack of marked improvement in oxygenation within 1 h. Clinicians should also be careful of abdominal distention, aspiration, and rarely barotrauma (pneumothorax). However, barotrauma risk is lower than those observed in NIV or invasive mechanical ventilation [6, 7]. Re-intubation is observed in 10–20% of patients after extubation despite advances in protective ventilation, sedation, and early mobilization. Extubation failure can lead to re-intubation, prolonged ICU and hospital stay, and increased costs, resulting in higher mortality and morbidity.

Table 39.1 HFNC indications and contraindications

HFNC indication	HFNC contraindication
COPD exacerbation	$PaCO_2$ >48 mmHg
Pneumonia	Mid-maxillar facial trauma
Pulmonary edema	Suspected pneumothorax
Acute cardiac failure	
Asthma	
Lung contusion, ARDS	
Bronchoscopy	
Pre-intubation oxygenation	
Post-extubation	

COPD chronic obstructive pulmonary disease, *ARDS* acute respiratory pulmonary disease

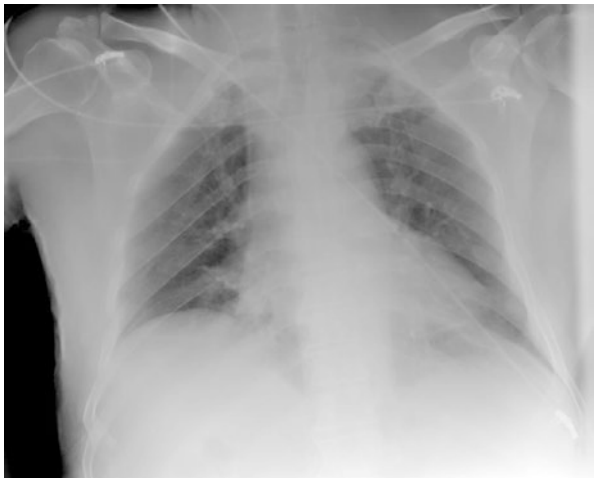
There are three non-invasive methods to increase PaO_2 in patients experiencing desaturation after extubation: conventional oxygen therapy, high-flow oxygen therapy, and NIV [8].

When compared to conventional oxygen therapy, HFNC improves oxygenation and patient comfort after extubation. Also, it decreases the post extubation re-intubation risk in critically ill patients. However, the evidence is not sufficient to support HFNC in patients at high-risk for re-intubation. Controversial results have been reported in studies comparing HFNC and NIV after extubation in high-risk patients [9].

Here, we presented our experience with HFNC in a patient with moderate chronic obstructive pulmonary disease, who was considered at high risk for extubation failure due to a GKS of 7–8, insufficient cough reflex, and respiratory secretions.

Case

A 60 years old man presented to the emergency department with a head injury and a GCS score of 14. The patient had a history of diabetes, hypertension, and chronic obstructive pulmonary disease (COPD) over 20 years and underwent intubation under emergent conditions because of decreased GCS 14 to 10 with superficial respiration. On cranial computed tomography (CT) scan, compression fracture, diffuse traumatic subarachnoid hemorrhage, and gross epidural hematoma were detected; thus, the patient underwent decompression craniotomy with American Society of Anesthesiologists (ASA) of 4E. Hemodynamics were normal during surgery, and the patient was admitted to ICU for close hemodynamic monitorization at the post-operative period. At the ICU admission, The acute physiologic assessment and chronic health evaluation (APACHE) score was 22 with a GKS 3. The patient was sedated with midazolam and remifentanil, and mechanical ventilation was started with volume-controlled mode. The patient had spontaneous respiration effort, and ventilation mode was converted to assisted-controlled mode on day 3; however, he was extubated during positioning (Picture 39.1). Midazolam and remifentanil infusions were cessated, but conscious sedation was initiated with the infusion of

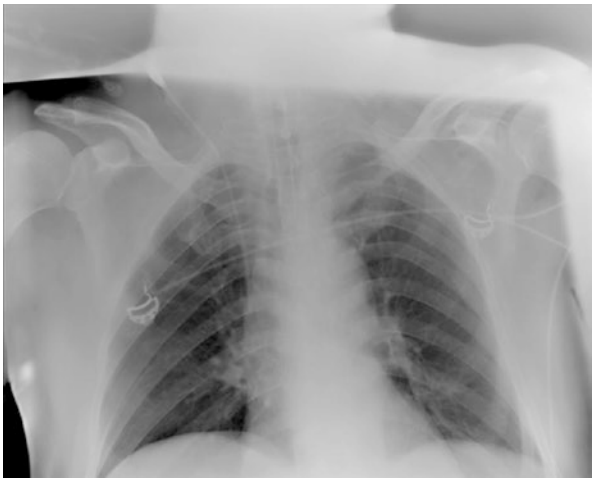


Picture 39.1 X-ray image before accident extubation

dexmedetomidine (0.2 mcg/kg) due to the presence of agitation. However, the patient had a GCS score of 7–8 and low oxygen saturation with O_2 supplementation via mask; thus, HFNC oxygen supplementation (the flow rate was 50–30 L/min FiO_2 titrated between 60% and 40%) was started. A silicone nasal airway (No: 7.5) was inserted. Dexmedetomidine was cessated on the hour 24, and no sedation was given as agitation was disappeared. During HFNC therapy, it was seen that the patient had no desaturation episodes with improved neurological scores and cooperation; the breathing sounds were normal at upper zones while decreased at lower zones. Frequent nasotracheal aspiration, tapotement, and postural drainage were performed. The patient was monitored by arterial blood gases and peripheral oxygen saturation during the next 10 days. In this period, it was observed that there were bilateral coarseness and rhonchus; however, peripheral oxygen saturation was 94–96% during follow-up (Picture 39.2). No additional respiratory support was required. On day 16, the patient was transferred to the ward with 2 L/min oxygen supplementation via mask after removing the nasal airway with the following vital signs: blood pressure, 110/68 mmHg; heart rate, 94/min; and oxygen saturation, 97%.

In this patient, avoiding re-intubation after accidental extubation resulted in the following gains:

1. Preventing the development of reintubation or ventilator-associated pneumonia
2. Allowing beat-to-beat GCS monitorization by avoiding deep sedation after HFNC
3. Early mobilization of the patient within the bed, preventing pressure ulcers
4. Easier performance of Tapotement and respiratory rehabilitation methods due to readily positioning of the patient
5. Preventing increased intracranial pressure due to lack of discomfort related to intubation; which is avoided in patients with subarachnoid hemorrhage



Picture 39.2 X-ray image on day 10 of HFNC

39.2 Conclusion

In conclusion, the monitorization of consciousness, GCS score, and pupils are of importance in patients with traumatic brain injury. Shift or herniation caused by acute bleeding or edema may require emergent intervention. In severe traumatic brain injury, ventilation support could be required due to low GCS Scores (<7–8); however, mechanical ventilation requires concurrent sedation, making monitorization of consciousness difficult, delaying treatment.

HFNC should be kept in mind as an advantageous method in which monitoring of consciousness is essential since HFNC does not require sedation.

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Part VII
Clinical Conditions: Sleep Breathing Disorders

Chapter 40
Treatment-Emergent Central Sleep Apnea: Always Look for an Air Leak

Abdul Rouf Pirzada and Ahmed Salem BaHammam

40.1 Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder. Over the years, extensive research has fostered a better understanding of its pathogenesis and defining its different phenotypes; nevertheless, positive airway pressure (PAP) therapy has remained as the 'gold standard' treatment option. Perceptibly, PAP therapy is fraught with challenges and, at times, undesired side effects. All these therapeutic pitfalls not only determine the outcome but also have a close correlation with patient compliance. Treatment-emergent central sleep apnea (TECSA) (complex apnea) is one of such challenges that needs to be prognosticated in high-risk patients, and cautiously managed, whenever it does not follow the common course of gradual remission over time.

Case Report

A 39 years old male presented to the sleep medicine clinic with complaints of loud snoring, choking, and witnessed apneas. Additionally, the patient had non-refreshing, interrupted sleep, excessive daytime sleepiness with an Epworth sleepiness scale score of 13/24. The patient had been a smoker and had bronchial asthma, which was fairly controlled on inhaled steroid and long-acting beta-2 agonist inhalers. The relevant examination was unremarkable except for a Mallampati score of 4 and a body mass index of 39.6 kg/m^2. Blood gases, pulmonary function tests and echocardiography were unremarkable.

With this symptom conglomeration, a preliminary diagnosis of OSA was made, and the patient was taken for further evaluation, including attended in-house

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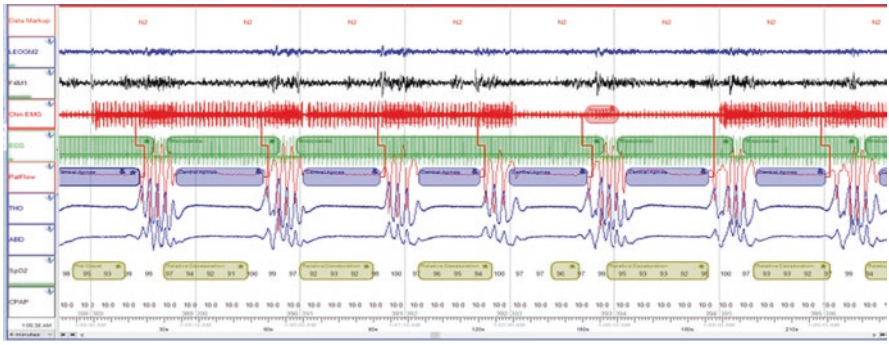

Fig. 40.1 An 8-min epoch showing the development of central sleep apnea on CPAP pressure of 10 cmH_2O

polysomnography (PSG). The diagnostic PSG demonstrated severe OSA with an apnea-hypopnea index (AHI) of 120/h, with minimum oxygen saturation of 79% and a desaturation index of 121.5/h. The diagnostic PSG also showed a central apnea index of 8.7/h.

The titration study was carried out using conventional continuous positive airway pressure (CPAP), which results in the elimination of the obstructive respiratory events; however, the central sleep apnea index increased to 19.2/h (Fig. 40.1). The patient was prescribed CPAP device pressure of 10 cmH_2O. The patient was planned for a close follow-up in the PAP clinic to evaluate the course of the central apneas.

During follow-up, 1 month later, in the PAP clinic, the patient was uncomfortable with the device use and complained of persistent air hunger and daytime somnolence; consequently, he had bad adherence to CPAP. The device data card analysis showed persistence of central sleep apnea with a central apnea index of 10.8/h. Additionally, analysis of the device stored data revealed that the overall mask leak was high, with the average leak of 127 l/min, and the percentage of time with a large leak of approximately 97% (Fig. 40.2).

The mask was changed, and a good mask fit was assured without adjusting the pressure settings. On the next follow-up (1 month later), the patient reported better tolerance of the CPAP therapy and improvement in daytime sleepiness. Analysis of the CPAP stored data revealed an AHI of 2.3/h average leak of 5 l/min. The central apnea index came down to zero. The condition was diagnosed as TECSA secondary to air leak.

40.2 Discussion

Since the introduction of PAP therapy for OSA in the early 1980s, a better understanding of the disorder as well as treatment modalities, including the complications and pitfalls emerging from it, are coming forth. Nonetheless, it has resulted in the

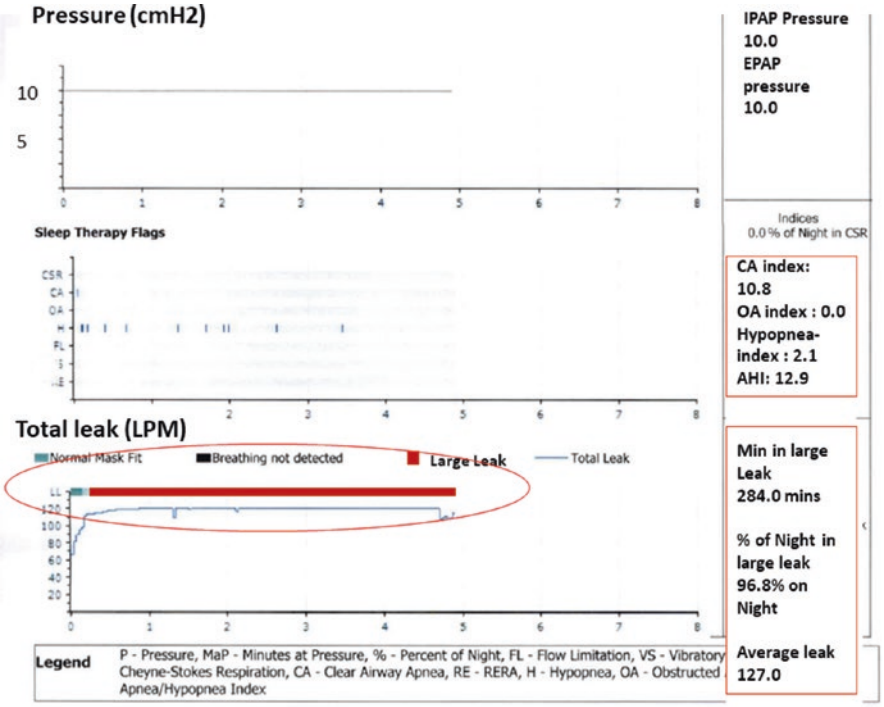

Fig. 40.2 Downloaded data from the positive airway pressure divide showing the pressure used, the air leak levels, and the residual respiratory events. The patient has significant air leak for a long-time during sleep and persistence of central sleep apnea

emergence of more sophisticated and intelligent devices to manage different phenotypes of OSA.

TECSA, sometimes referred to as complex sleep apnea, is one of the PAP therapy-associated complications seen in a certain subset of patients of OSA, resulting in poor adherence and therapeutic failure [1]. It is defined as the emergence or persistence of central apneas while undergoing treatment for OSA using PAP therapy in the form of CPAP, bi-level positive airway pressure (BPAP), or auto-titrating PAP; nevertheless, it has been reported after alternative treatment modalities such as adenotonsillectomy [2]. The typical occurrence of TECSA is seen following a substantial resolution of previously witnessed obstructive respiratory events that were identified during a prior diagnostic sleep study or diagnostic portion of a split-night sleep study. However, to minimize the diagnostic ambiguity and to refine the understanding, diagnostic criteria have been put forth (Table 40.1) [3].

The reported prevalence rate of TECSA has been vividly variable; a systemic review that included nine studies reported prevalence rates of 5.0–20.3% [4]. The prevalence of TECSA during full night titration studies ranges from 5.0% to 12.1%, whereas it was between 6.5% and 20.3% during split-night titration studies [4]. However, the aggregate point prevalence of TECSA was 8% [4]. This wide variation

Table 40.1 Diagnostic criteria for TECSA [3]

Diagnostic criteria: *Criteria A–C must be met*
A. Diagnostic PSG shows five or more predominantly obstructive respiratory events[a] (obstructive or mixed apneas, hypopneas or RERAs) per hour of sleep
B. PSG during use of positive airway pressure without a backup rate shows significant resolution of obstructive events and emergence or persistence of central apnea or central hypopnea with all of the following: 1. Central apnea—central hypopnea index ≥5/h. 2. Number of central apneas and central hypopneas is ≥50% of total number of apneas and hypopneas.
C. The central sleep apnea is not better explained by another CSA disorder (e.g., CSA with CSB or CSA due to a medication or substance).

Adapted from 2014 American Academy of Sleep Medicine, 2510 North Frontage Road, Darien, IL 60561, USA [3]

[a]Respiratory events defined according the most recent version of the AASM Manual for the Scoring of Sleep and Associated Events

[b]A diagnosis of treatment-emergent central sleep apnea does not exclude a diagnosis of OSA. That is, a diagnosis of OSA can be made based on the diagnostic sleep study

in prevalence can be ascribed to the characteristics of the study groups such as patient demographics, body mass index (BMI), gender, age and comorbidities, and factors related to the diagnostic procedure such as split-night titration and titration in the supine position [5].

In a large study that followed patients with OSA for 90 days after the initiation of CPAP therapy found that the older age, higher residual AHI and central apnea index (CAI), and higher leak are the main predictors of TECSA; hence patients with these conditions should always warrant early and close follow up [5].

Symptomatically, TECSA presents with the persistence of OSA symptoms, including daytime sleepiness and disturbed non-refreshing sleep despite PAP treatment. Air hunger is not an uncommon symptom in these patients. Additionally, patients with TECSA have lower adherence to PAP therapy. Basically, TECSA is a central sleep apnea disorder that is characterized by cessation of airflow and the absence of a respiratory effort.

40.2.1 Pathophysiology of TECSA

To comprehend the pathophysiology of TESCA, we need to look into the pathophysiology of central sleep apnea. During sleep, in the absence of wakefulness drive to breathe, metabolic control is solely responsible for breathing. Additionally, the hypercapnic and hypoxic drives are reduced, and there is also increased upper airway resistance. The pathophysiological mechanism of this phenomenon revolves

around the 'loop-gain', which has two components, plant gain, and controller gain. Controller gain refers to the chemosensitivity and ventilatory responses to hypoxia and hypercapnia. On the other hand, plant gain refers to the changes in $PaCO_2$ levels resulting from a given change in ventilation. Central sleep apnea can result secondary to unstable breathing caused by high loop gain, or secondary to reduced output from the central neurons. Therefore, high loop gain results in hyperventilation and a lower $PaCO_2$ level below the apneic threshold. When the $PaCO_2$ level drops below the apneic threshold, ventilation will cease, and apnea will occur and last until the $PaCO_2$ level increases above the threshold [1]. This phenomenon is more profound and common during nonrapid eye movement sleep when the CO_2 reserve, which is the difference between eupneic $PaCO_2$ and the apneic threshold, is highly labile. Generally, PAP therapy settings have little bearing on the emergence of TECSA; however, high PAP pressure, rapid titration, and the use of BPAP therapy is presumed to be associated with more mask leaks and pressure intolerance and hence sleep fragmentation and subsequent central sleep apnea. The exact cause of this type of central sleep apnea cannot be discerned from these clinical correlates; nonetheless, several hypotheses have been proposed. One causative theory is that the upper airway resistance due to OSA can weaken the ventilatory control system, thereby reducing the efficiency of CO_2 excretion; once the resistance is overcome by PAP therapy, $PaCO_2$ washout takes place thus reducing the $PaCO_2$ tension to a value below the CO_2 apnea threshold results in CSA. Over several days to weeks, the CO_2 apnea threshold is known to change, resulting in the resolution of central sleep apnea. Similar changes have been reported after relieving the obstructive events using tracheostomy, maxillomandibular advancement surgery, and mandibular advancement device. Another proposed mechanism is that, in the presence of significant mask leak or mouth breathing, in case of a nasal mask, this may result in a washout of CO_2 from the anatomical dead space, which results in a drop in CO_2 below the apnea threshold. Another proposed theory, though less plausible, is that PAP therapy initiation may worsen sleep quality causing frequent transitions from sleep to wake and wake to sleep states, resulting in frequent arousals with consequent stimulation of the ventilatory response, which reduces $PaCO_2$ below the CO_2 apnea threshold and the emergence of CSA during subsequent sleep. However, these associated CO_2 fluctuations also tend to resolve over time as patients adjust to the interface and the application of PAP therapy. In an almost similar fashion when BPAP is used, inspiratory PAP can lead to augmented tidal volumes, which decrease $PaCO_2$. If the fall in the $PaCO_2$ level goes below the CO_2 apnea threshold, central sleep apnea may ensue. Thus, several phenomena can theoretically contribute to fluctuations of CO_2, and consequent TECSA, and these factors can be easily overcome with careful attention to the underlying mechanism. TECSA may occur at any PAP setting [4]. In general, PAP therapy settings in patients demonstrating TECSA are not much different from those in patients without central apneas [4]. Figure 40.3 presents a proposed algorithm of the possible mechanisms of TECSA.

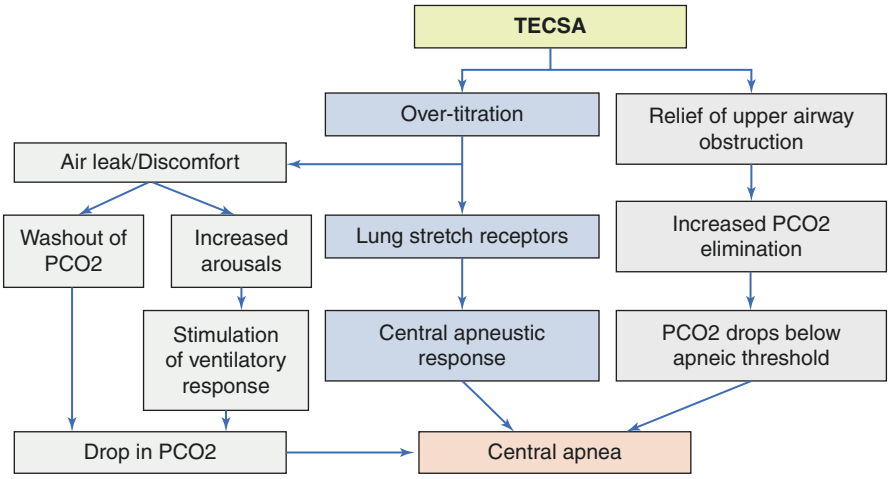

Fig. 40.3 A proposed algorithm of the possible mechanisms of TECSA

40.2.2 Time-Course of TECSA

The general outcome of TECSA is a complete resolution on the long term. This has been duly demonstrated in a recent systemic review [6]; over a few weeks to several months, about two-thirds of these patients had complete resolution of central apneas [6]. However, some patients, continues to exhibit persistent TECSA.

It important here to mention that a small proportion of patients (0.7% and 4.2%) may have delayed development of TECSA after at least 1 month of PAP therapy initiation [6].

40.2.3 Treatment

As stated above, in most TECSA cases, apnea events during initial PAP titration are self-limited and disappear over time [7]. Nevertheless, follow up is needed to make sure that the emergent central events disappear with continued therapy. This can be done by tracking the PAP stored data. However, the therapist should always look for possible problems causing treatment-emergent CSA and solve them. In the case of overtitration, PAP should be reduced to solve the problem, and titration should be done slowly. When a substantial mask leak is detected, the interface should be adjusted or changed. PSG can be repeated in difficult cases.

Most TECSA will spontaneously disappear in the first 3 months of treatment or after treating associated causes such as air leak. However, in the rarely reported persistent cases, adaptive servo-ventilation (ASV) has been shown to rapidly resolve

the disorder and relieve the symptoms of TECSA with the potential of increasing early adherence to therapy [8]. Additionally, ASV has been shown to maintain an effective suppression of CSA over time [9].

ASV is a novel method of automated pressure support that performs breath-to-breath analysis and delivers ventilatory needs accordingly, in order to prevent the hyperventilation that drives TECSA. During ASV ventilation, the end-expiratory pressure is set, and during inspiration, the device determines the degree and timing of ventilatory support. As breath-to-breath analysis is done, when significant reductions or pauses in breathing occur, the device interferes with enough support to maintain the patient's breathing. Once the breathing problem resolves, the machine returns slowly to baseline [8]. When the breathing pattern is stable, ASV provides just enough pressure to maintain airway patency and remove obstructive events.

Nevertheless, not all TECSA patients need an expensive and complicated device [8]. It is recommended that ASV should only be considered after a period of CPAP treatment of at least 3 months [10, 11].

Figure 40.4 shows a proposed algorithm to approach to the management of TECSA.

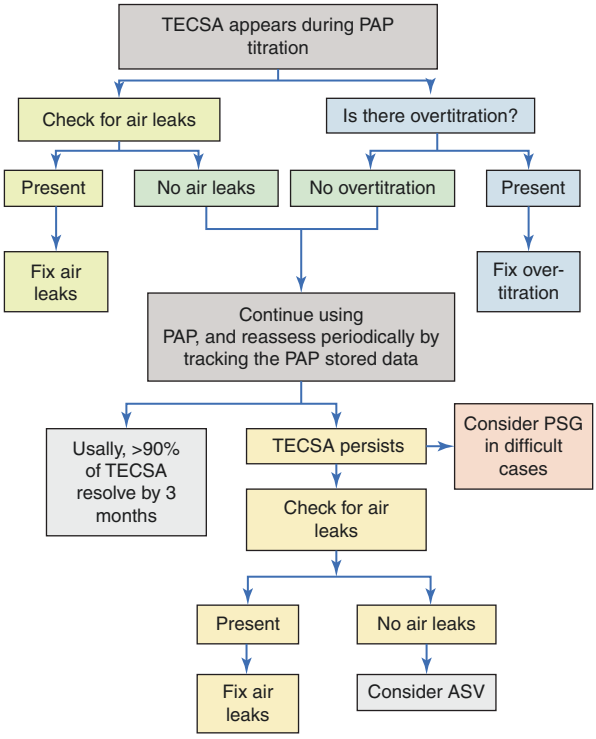

Fig. 40.4 A proposed algorithm to approach to the management of TECSA

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Chapter 41
Non Invasive Ventilation in Sleep Apnea Syndrome

C. M. Acosta Gutiérrez, C. Matesanz López, and J. Montoro Ruiz

Abbreviations

BMI	Body Mass Index
BP	Blood pressure
CPAP	Application of continuous positive pressure
ES	Excessive sleepiness
IAH	Index of apnea-hypoapnea
OSAS	Obstructive sleep apnea syndrome
PSG	Polysomnography
RSD	Respiratory sleep disorder

Clinical Case

Obstructive Sleep Apnea Syndrome (OSAS) is the most common respiratory sleep disorder (RSD). It is characterized by the presence of intermittent upper airway total (apneas) or partial (hypoapneas) collapse during the night [1, 2]. The existence of an index of apnea-hypoapnea (IAH) >5 (sum of apneas and hypopnea, per hour of sleep), associated with excessive sleepiness (ES), neurocognitive or behavioral disorders not explained by other causes, define this syndrome [1]. Epidemiological studies indicate an OSAS prevalence of 5–15% in adults [2]. The supine body position contributes to apnea and hypopnea to occur during sleep [3]. Risk factors are

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well known: obesity (considered as BMI >28, that is present in 60–90% of patients, having male sex a ratio of 2:1 or 3:1 ratio over female), smoking, alcoholism, associated diseases such as hypothyroidism, and usage of central nervous system depressant drugs [4].

The gold standard treatment is the use of CPAP. This pressure corrects obstructive, mixed and, in not a few cases, central apneas. It is caused by a mechanical phenomenon that results in an increase of the upper airway section, in turn causing an increase in functional residual capacity [1]. It is therefore not a ventilatory mode per se, since it does not generate any help in inspiration but increases residual functional capacity and recruits alveoli [4]. We only handle two variables, the level of positive pressure and the flow of oxygen provided, besides there are devices with the possibility of humidification. In this way, it avoids the desaturation of oxygen, the electroencephalographic awakenings (known as arousal) secondary to respiratory events and, therefore, normalizes the architecture of sleep. It also produces remission of OSAS symptoms, decreased and/or elimination of excessive daytime sleepiness (ES) measured with clinical scales [1, 2], recovery of attention span among other cognitive variables and, with all this, an improvement of quality of life. Another noticeable effect is that it reduces the risk of traffic accidents in patients with this pathology and normalizes blood pressure (BP) figures in a relevant percentage of hypertensive subjects with this associated disease [2]. A role of this treatment has even been suggested in heart failure and others cardiovascular diseases [1–3].

We would like to present a 62 years old male, with a profession into the financial sector. He does not have any known allergies to medications. Ex-smoker with an accumulated packages years of 15 and not an alcohol drinker. No history of hypertension, dyslipidemia or DM. On his medical history there is only a resolved chronic pharyngitis and a surgical intervention for a prostatic hyperplasia.

His first consultation was in 2014 for conciliation insomnia already in treatment with benzodiazepines. A polysomnography (PSG) was performed, showing OSAS in severe grade (IAH—43/h CT90—26%) and insomnia. CPAP was offered as treatment but patient ended refusing as it worsened his pharyngitis, so cognitive-behavioral therapy was performed in association with Clonazepam, with a good response.

It should be taken into account that CPAP is not a curative treatment. For this reason its application must be continuous; so it is key to get an adequate compliance. To achieve this, a close follow-up is recommended during the first few months. It has no absolute contraindications, except the cerebrospinal fluid fistula, but we must know that this is an uncomfortable treatment, especially for the first few weeks. For this reason it is essential, first of all, to ensure that the indication of treatment is correct, that the information to the patient is sufficient, to obtain a good doctor-patient relationship and, finally, to effectively control the adverse effects. The most common are [1]:

– Congestion and/or nasal obstruction: It is the most frequent. The treatment depends on the factor that causes it. It is generally caused by edema and inflam-

mation of the nasal mucosa and often vanish spontaneously. It is treated with local instillations or the use of corticosteroids in aqueous solution by nasal route.
- Skin irritation: It is produced in the area of contact with the CPAP mask. With modern masks it is, in general, of little importance and usually disappear over time as the skin hardens.
- Pharyngeal dryness: It mostly goes away spontaneously and it is a frequent complaint of patients with OSAS before being treated and it is due to the loss of soft palate water as a result of snoring and apnea.
- Noise: Especially on the first weeks, patients and their partners tend to complain about the noise produced by the intentional leak of the mask, as the air flows through it at inspiration and expiration. It does not have a special treatment and requires the adaptation of the patient and the partner.
- Conjunctivitis: In general it is produced as a consequence of a non intentional air leakage through the mask, which impacts on the conjunctiva and produces a certain degree of irritation. It usually indicates that the mask is poorly adjusted. Disappears with proper adjustment of the mask by the patient.
- Headache: It is not frequent. Its origin is not clear and normally disappears over time.
- Epistaxis: Although it is not very frequent its appearance can be very conditioning and in certain circumstances hinder the application of CPAP. Most of the time it originates in the anterior part of the nostrils and its most frequent cause is nasal dryness.
- Aerophagia: It is very rare. It is produced by the patient partially swallowing the air flow produced by the CPAP.

The appearance of these adverse effects is frequent during the first weeks of CPAP use. In general they will be mild, transitory and with good response to local measures [1].

The next medical consultation of our patient was 2 years later for snoring, apnea pauses, non-restorative sleep, nocturia and excessive sleepiness, without asphyxical arousals nor morning headache. At that moment his sleeping schedule was from 00:00 to 07:00 a.m.

Physical examination: Weight—75 kg, Measuring—175 cm, BMI—24 kg/m^2, Epworth test: 13. Cardiac and pulmonary auscultation within normal range.

The following diagnostic tests were performed with the following results:

- PSG: showed decreased sleep efficiency due to prolonged sleep wakefulness. It showed a slight decrease in deep sleep. No PLMS were observed. The respiratory analysis showed the presence of apneas and hypopneas with an IAH of 38.1/h, a supine IAH of 43.7/h and a RDI (including Reras) of 38.1/h. The mean O_2 Sat during the whole sleep was 90% and the minimum O_2 Sat was 66%, with a CT-90 of 49.59%. The heart rate during sleep varied between 87 and 48 lpm, with an average of 59 lpm. No significant changes in heart rhythm were observed.
- Conclusion: From the respiratory point of view, a severe number of respiratory events were observed, and those were compatible with severe sleep apnea with mild secondary oximetric alteration (IAH 44/h ODI 38/hTC90 50%).

– Suggested immobilization test: 14 periodic movements on the lower extremities were detected throughout the test. The study was interpreted as normal.
– Maintenance of wakefulness test: There was evidence of an average sleep latency of 23 min along the two tests. The study was interpreted as normal.
– AutoCPAP titulation: We conducted an autoCPAP titulation study to our patient once OSAS was diagnosed by polysomnographic record (Fig. 41.1). Normally pressure is increased by 1 cmH_2O every 5 min until respiratory events are resolved, but in some cases we can find patients that require high variable pressures throughout the night. There was a high average leak throughout the nights of the study, but an adequate average leak at the selected days (see graph), indicating therefore a good mask fit. Residual IAH was <5/h so it indicated that obstructive events were corrected with the administered pressures. Taking into account the variability of those, autoCPAP was the choice of treatment.

Titulation results showed high pressure variability to achieve an optimal residual IAH, so it was not possible to determine an optimal fixed pressure for proper treatment. Therefore treatment with autoCPAP was recommended with a minimum limit of 4 cmH_2O and a maximum of 15 cmH_2O.

Given the evidence, is was concluded that the diagnosis of severe postural OSAS persisted. Due to his nasal pathology it was recommended to the patient to reengage with the treatment using an autoCPAP instead of a fixed CPAP, along with an humidifier and a nasal interface. Patient agreed to reinitiate ventilation.

Recent studies have documented the possibility of treating patients with auto-adjustable pressure devices, called autoCPAP, being the most acceptable those that modifies pressure according to inspiratory flow wave. The starting hypothesis in the development of these devices was that a fixed CPAP pressure, obtained by conventional methods, does not represents the real needs of a patient during all their nights of sleep with all the positions they may use. Therefore autoCPAP may have the potential to be more effective and convenient than CPAP, by better matching the varying needs of the patient and by improving comfort through only applying the minimally required pressure, however there is no strong evidence of this at the moment. Another thing to be considered is that their price is higher than CPAP [1, 3, 5].

Ventilation is deeply modified during sleep. Body position, control of respiratory rate, resistance of the airway to the air flow and coordination of inspiratory and expiratory muscles have influence into the proper functioning of the ventilatory system. Application of non-invasive mechanical ventilation may contribute to a better ventilation and sleep quality [4]. Application of CPAP was described by Sullivan in 1981 and, since then, it has become the standard treatment of OSAS along with hygienic sleep measures.

Bloch et al. [2] showed that treatment with autoCPAP is equivalent to treatment with fixed CPAP in improving subjective and objective sleepiness, quality of life, sleep-related breathing disturbances, blood pressure among others, without observing differences in therapeutic adherence (>5 h/night) [2, 5, 6].

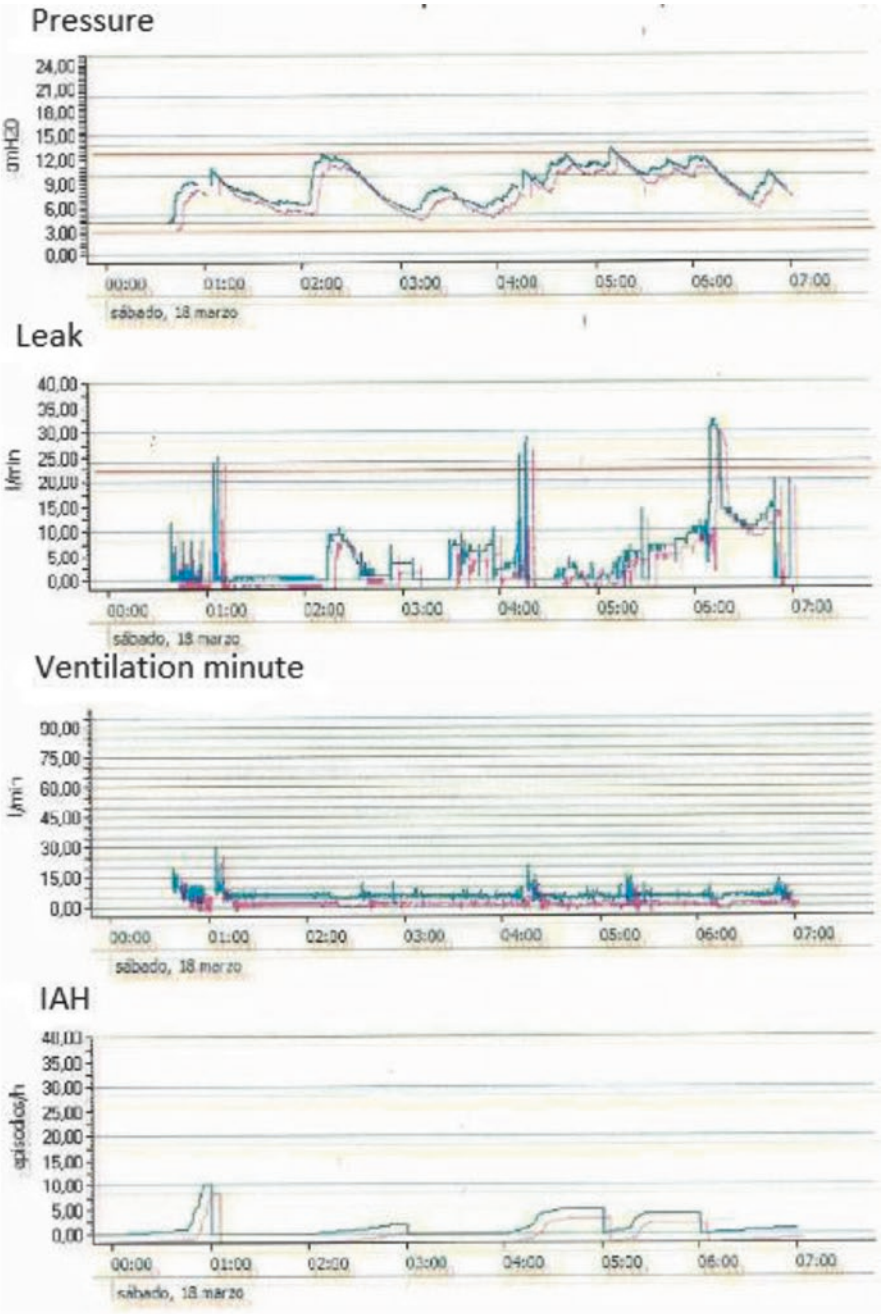

Fig. 41.1 AutoCPAP

In the case of our patient, the respiratory events appeared mostly in supine decubitus. It was found that, in the supine decubitus position, the upper airway was reduced in size and could increase its resistance [7]. Therefore, some patients suffer only apneas and hypopneas in this position aggravating the OSAS. Thus, keeping the patient in a lateral position could solve the problem [8].

Questions and Answers

1. What is the correct answer?

   (a) The gold standard treatment of OSAS is CPAP
   (b) OSAS is the rarest respiratory sleep disorder
   (c) The use of CPAP increases the risk of traffic accidents in patients with OSAS

   Answer: (a) The gold standard treatment of OSAS is CPAP
2. Which of the following pathologies are not OSAS risk factors?

   (a) Obesity (considered as BMI >28)
   (b) Hypothyroidism
   (c) Arterial hypertension

   Answer: (c) Arterial hypertension
3. Which of the following pathologies is an absolute contraindication for the use of CPAP?

   (a) Nasal obstruction
   (b) Cerebrospinal fluid fistula
   (c) Aerophagia

   Answer: (b) Cerebrospinal fluid fistula
4. Which of the following diagnostic tests are not indicated in sleep breathing disorders?

   (a) Polysomnography
   (b) Maintenance of wakefulness test
   (c) AutoCPAP titulation

   Answer: (b) Maintenance of wakefulness test

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Chapter 42
Nocturnal Hypoventilation and Sleep Breathing Disorders

David Barros Coelho

Abbreviations

AIH	Apnea Hipopnea Index
ALS	Amyotrophic lateral sclerosis
ASV	Adaptive servoventilation
BMI	Body mass index
CCHS	Congenital central alveolar hypoventilation syndrome
CO_2	Carbon dioxide
CSA	Central sleep apnea
EPAP	Expiratory positive airway pressure
ESS	Epworth sleepiness scale
IPAP	Inspiratory positive airway pressure
NIV	Non-invasive ventilation
NMD	Neuromuscular diseases
NREM	Non-REM sleep
OHS	Obesity-hypoventilation syndrome
OSA	Obstructive sleep apnea
$PaCO_2$	Arterial carbon dioxide
PAP	Positive pressure ventilation
$PetCO_2$	End-tidal CO_2
$PtcCO_2$	Transcutaneous CO_2
REM	Rapid-eye movement sleep
RF	Respiratory failure

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Clinical Case

Male patient, 47 years-old, with Nanism. Body Mass Index (BMI) 41.7 kg/m^2. Diagnosed 16 years ago with OHS—severe Obstructive Sleep Apnea (OSA). With an Apnea Hypopnea Index (AIH) 76/h, mean nocturnal SpO_2 58%, Epworth Sleepiness Scale (ESS) 20, type 2 respiratory failure (RF) (pH 7.408 PCO_2: 54.5 PO_2 58). The patient was started on Non-Invasive Ventilation (NIV) (nasal mask) with Inspiratory Positive Airway Pressure (IPAP) 20 cm H_2O and Expiratory Positive Airway Pressure (EPAP) 12 cm H_2O, without oxygen, with symptomatic improvement and normalization of blood gases. Residual AHI between 10 and 14/h, nocturnal oximetry with mean SpO_2 96% and time < 90: 6.1%.

Ten years later, the patient gained 8 kg, started on regular and sometimes abusive alcohol intake and residual AHI gradually raised to 29/h in 2014, with nocturnal oximetry with t < 90: 15.4%. The mask was changed to oronasal and re-titrations were performed with increase in pressures (until IPAP 29 e EPAP 17). Later the patient was re-adapted to BiPAP ST IPAP 2 EPAP 16. However, nocturnal oximetry revealed a pattern of frequent desaturation during the first half of the night (see Fig. 42.1), minimum SpO_2 62%, t < 90: 12.4%. This pattern continued despite raising pressures.

The patient was several times advised to stop drinking. After an admission for acute pancreatitis, he stopped alcohol intake. There was an improvement of nocturnal oximetry (mean SpO_2 96.3%, min 88%, t < 90: 0.2%) and AHI (6/h).

42.1 Definitions

The American Academy of Sleep Medicine scoring rules for respiratory events define hypoventilation during sleep as follows: (1) arterial carbon dioxide ($PaCO_2$) (or transcutaneous or end-tidal carbon dioxide as surrogates) 55 mmHg for 10 min; or (2) there is an increase in PCO_2 of 10 mmHg from the awake supine value to a value exceeding 50 mmHg for 10 min [1].

For pediatric patients, hypoventilation is scored when $PaCO_2$ is 50 mmHg for more than 25% of the total sleep time.

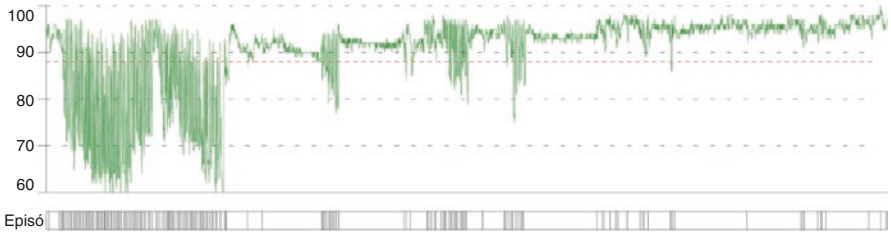

Fig. 42.1 Hypoventilation predominantly on the first quarter of the night due to alcohol ingestion

Table 42.1 Staging of hypoventilation in obese patients (BMI >30 kg/m^2)

0	Obesity-associated sleep hypoventilation	No hypercapnia
1	Obesity-associated sleep hypoventilation	Intermittent hypercapnia during sleep. Normal diurnal P_{CO2} or P_{tcCO2}. Bicarbonate <27 mmol/L.
2	Obesity-associated sleep hypoventilation	Intermittent hypercapnia during sleep (P_{CO2} or P_{tcCO2}) morning > evening. Bicarbonate >27 during wake. Bicarbonate increased during day.
3	Obesity hypoventilation	Sustained hypercapnia. P_{CO2} >45 mmHg while awake.
4	Obesity Hypoventilation Syndrome	Sustained hypercapnia while awake, cardiometabolic comorbidities.

According to the European Respiratory Society task force from 2018, other markers of gravity should be taken into account, including bicarbonate, cardiovascular and metabolic comorbidities. Since hypoventilation precedes the development of daytime hypercapnia, milder forms of the disease (without raised PCO_2) should be evaluated. A staging system with 5 possible degrees is represented in Table 42.1.

42.2 Pathophysiology of Hypoventilation During Sleep

Minute ventilation is essential to keep $PaCO_2$ between 35 and 45 mmHg. An increase and decrease in ventilation lead to decrease or accumulation of CO_2. Respiratory acidosis leads acutely to pH changes, while chronically there is a renal compensation by regulating bicarbonate renal excretion. Therefore, chronic hypoventilation can be characterized by low minute ventilation (e.g. breathing frequency), raised $PaCO_2$ (>45 mmHg) or high bicarbonate despite normal pH. It is therefore a result of a mismatch between elimination of CO_2 by the ventilatory system and metabolic production of CO_2.

The development of hypoventilation is evident initially during sleep. In healthy individuals, minute ventilation decreases from wakefulness to Non-REM Sleep (NREM) sleep and REM sleep by about 15%. There is a lower tidal volume and consequently lower minute-ventilation (without proper compensation through breathing frequency). During sleep, and particularly during REM sleep there is lowered muscle tone and blunted hypoxic and hypercapnic ventilatory responses. In neuromuscular diseases (NMD), for example, PSG studies reveal a decrease in REM sleep, which may be a protective mechanism [2–4].

42.3 Clinical Presentation and Evaluation

There are huge differences in the clinical presentation among patients, so a complete medical history, clinical examination with assessment of sleep quality, morning symptoms, dyspnea and daytime sleepiness. This evaluation is of extreme importance since chronic hypoventilation usually develops during sleep or exertion.

Polysomnography is essential in diagnosing, guiding treatment and follow-up of treatment non-responders. It enables to distinguish sleep and wakefulness, sleep stages, arousal and their relation to breathing disturbances [5].

Measurement of CO_2 can be made both invasive or non-invisibly. Arterial samples or samples from arterialized ear lobe are goldstandards, however not feasible in the evaluation of the sleeping patient, due to sleep disturbance and hyperventilation. Methods like end-tidal CO_2 ($PetCO_2$) and the transcutaneous CO_2 ($PtcCO_2$) can overcome this problem. $PetCO_2$ can be influenced by nasal congestion, oxygen insufflation, NIV and mask-leaks. $PtcCO_2$ correlates with $PaCO_2$, although it is systematically higher than $PaCO_2$, which has to be considered when interpreting the results. This happens because it is influenced by the metabolism and heating of the skin [5].

42.4 Classification and Causes of Sleep Related Hypoventilation

Hypoventilation can appear as a result of problems affecting the brain, spinal cord, nerves, muscles, heart, lungs, or airway.

The International Classification of Sleep disorders (third edition) describes six subtypes of sleep related hypoventilation disorders:

- Obesity-hypoventilation syndrome (OHS);
- Congenital central alveolar hypoventilation syndrome (CCHS);
- Late-onset central hypoventilation with hypothalamic dysfunction;
- Idiopathic central alveolar hypoventilation;
- Sleep related hypoventilation due to a medication or substance;
- Sleep related hypoventilation due to a medical disorder.

In addition, there are entities related to Central Sleep Apnea (CSA) such as follows:

- CSA with Cheyne–Stokes breathing
- Central apnea due to a medical disorder without Cheyne–Stokes breathing CSA due to high-altitude periodic breathing
- CSA due to a medication or substance
- Primary CSA

- Primary CSA of infancy
- Primary CSA of prematurity
- Treatment-emergent CSA

42.4.1 OHS

OHS is defined as the presence of daytime hypercapnia in an obese patient (BMI ≥30 kg/m^2), after excluding other conditions associated with alveolar hypoventilation. Patients have a sleep breathing disorder, OSA in 90% of cases. There are also impaired pulmonary mechanics (ventilation/perfusion mismatching and reduced respiratory muscle strength) and impaired ventilatory control (reduced neural dive, reduced ventilatory responsiveness, leptin resistance and carbon dioxide overproduction).

Leptin is a protein produced by adipose tissue. Leptin crosses the blood-brain barrier and is a stimulant of ventilation. It correlates positively with BMI, however in hypercapnic patients with OHS, a mechanism of central resistance to leptin seems to be involved [5].

OHS should be suspected in following situations, in an obese patient (BMI ≥30 kg/m^2):

- Reduced lung function due to obesity
- Reduced inspiratory muscle strength
- Diurnal O_2 saturation (SpO_2) ≤94% or an overnight nadir saturation <80%
- Severe OSA (AIH >50)
- Exertion dyspnea
- Pulmonary hypertension and/or right-sided heart failure without a recognisable reason
- Facial plethora
- Raised bicarbonate on venous blood sampling.

42.4.2 CCHS

CCHS is a congenital disease, due to a defect in the PHOX2B-gene, in an autosomal dominant mode, leading to a diffuse imbalance of the autonomic system. It can be accompanied by other diseases as Hirschsprung's disease, cardiac arrhythmia, and tumors. It usually begins during childhood, despite reports of late onset, adult cases. There is a failure in central respiratory drive, which is more pronounced during sleep. Late-onset cases can present as a respiratory failure after use of respiratory depressors such as after general anesthesia [5].

42.4.3 Late Onset Central Hypoventilation with Hypothalamic Dysfunction

The patients with late onset central hypoventilation with hypothalamic dysfunction present with obesity, endocrine abnormalities of hypothalamic origin, severe emotional or behavioral disturbances or a tumor of neural origin (two of these four findings are required). Diabetes insipidus, inappropriate antidiuretic hormone hypersecretion, precocious puberty, hypogonadism, hyperprolactinemia, hyperthyroidism and decreased growth hormone secretion can also be present. It develops after the first years of life.

This last two entities are rare and most cases arise as a consequence of medial disorders, drugs or OHS. Medical disorders associated with hypoventilation can affect the lung parenchyma, vasculature or the muscular or neurologic system. In most cases, increased mechanical load to breathing and decreased ventilatory drive/response combine to produce the overall result. It is important to distinguish hypoventilation from OSA, although they share pathophysiological mechanisms and co-exist frequently [5].

42.4.4 Neuromuscular Disorders

Many neuromuscular diseases (NMD) can cause hypoventilation such as amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy, myotonic dystrophy and acid maltase deficiency. In the case of ALS, apart from riluzol, Non-invasive ventilation (NIV) is the only therapy that increases life expectancy. In DMD it also improves life expectancy and quality of life [5, 6].

42.4.5 Kyphoscoliosis

Studies regarding sleep structure in kyphoscoliosis reveal that hypoventilation occurs mainly in REM sleep and that there is decreased sleep efficiency with increased stage 1 and reduced slow-wave sleep. Although treatment with NIV is first choice and effective in improving daytime symptoms and gas exchange, it doesn't seem to improve sleep structure [6].

42.4.6 Medication

Drugs are also a cause of hypoventilation. This can happen through central sleep apnea (CSA), in this case drugs like sodium oxybate may promote CSA, while acetazolamide and hypnotics like zolpidem and triazolam may attenuate the breathing

disorder. Opioids are widely used drugs, with the so-called "opioid crisis" being a more frequently discusses topic in the US and the rest of the world. This drugs are used both for pain management and in methadone programs for opioid addiction. CSA with mixed apnea or ataxic breathing was reported in approximately 14–60% of patients in methadone programs, with similar numbers in patients using opioids for chronic pain management. Benzodiazepines may potentiate the effect of opioids on ventilation. Adaptive servoventilation (ASV) and Bi-level positive airway pressure seem to be superior to conventional CPAP in reducing CSA in this patients [6].

42.4.7 Heart Failure

Heart failure can lead to hypoventilation and respiratory failure through many mechanisms. CSA is an important contribution and studies reveal that ASV normalizes the AHI in patients with CHF and CSA more effectively compared to CPAP therapy and nocturnal oxygen. If LVEF is inferior to 45%, ASV is contra-indicated, according to the results of a large RCT SERVE-ASV, which revealed a high all-cause and cardiovascular mortality in this group [7, 8].

There are many diseases in which he prognosis and influence of NIV is not yet stated, such as after stroke or in Interstitial Lung diseases.

42.5 Treatment

As in general diseases, it is first necessary to correct any causative factor. Surgical resolution can be successful in kyphoscoliosis, weight reduction in OSA and OHS and electrical diaphragmatic stimulation in individual cases. On the other hand, drugs that affect breathing regulation, neural transmission and muscular tone have to be discontinued.

In most cases, however NIV becomes necessary. It is important to correctly titrate EPAP under polygraphic and phonographic supervision in order to minimize apneas, hypopneas and optimizing oxygen saturation. The IPAP is not the primary target, but the difference between IPAP-EPAP—the pressure support that can, in addition to breathing frequency, control CO_2 elimination. A back-up frequency is essential to overcome central apneas and/or bradypneas.

The ventilatory mode used may depend on the underlying disorder. Controlled ventilation strategies aim to unload respiratory muscles during the night, restoring energy for spontaneous respiration. However, studies reveal that assisted ventilation improve synchronicity and make less muscle fiber damage. Pressure support ventilation has gradually become the most used ventilation method for this patients. Newer modes like Average volume assured pressure support (AVAPS) are useful—in this case it automatically adjusts EPAP in order to overcome upper airway obstruction during the night but adjusting the support pressure to a predetermined target.

The indications for starting NIV vary according to the underlying condition. In most cases after daily hypercapnia develops, however in NMD and Thoraco-Skeletal disorders, it can be indicated despite daytime hypercapnia when there is symptomatic nocturnal hypoventilation. In COPD, NIV is usually started when patients develop daytime hypercapnia > 52, particularly for patients with recent hospitalization. High intensity ventilation, aimed a normalization of CO_2, was shown to have better compliance and control of nocturnal hypoventilation. In OHS, PAP and weight loss are the preferred initial approach [9].

Despite from improvements in quality of life, sleep quality, oxygen nocturnal saturation, daytime $PaCO_2$, in some cases NIV lead to improvements in survival. This is the case of ALS, COPD, OHS. The classic example of survival benefit is evident in Duchenne Muscle Dystrophy, in which medium age of death raised from 18–20 to 30 years after establishment of NIV as a treatment for this patients [3, 5, 6].

42.6 Discussion of Case

In the case presented initially, alcohol consumption seemed to be a factor not permitting a total control of nocturnal hypoventilation, even despite NIV treatment. Therefore, drugs and substances can be one of the causes of hypoventilation, and have to be stopped in order to proceed to the correct treatment. Opioids are a classical example of this association. Treatment of hypoventilation, such as in this case of OHS, can lead to improvements in daytime hypercapnia, sleep quality, quality of life and sometimes survival.

Key Teaching Points

- Chronic hypoventilation can be a consequence of disorders on any level of the respiratory system.
- Sleep-related hypoventilation may be an early stage of chronic hypoventilation.
- Treatment of modifiable factors is mandatory, but most cases develop necessity of NIV.
- Long-term efficacy of PAP therapy differs according to the underlying disorder.

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Chapter 43
Non Invasive Ventilation: Nocturnal Hypoventilation and Sleep Breathing Disorders

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Abbreviations

AASM	American Academy of Sleep Medicine
ABGs	Arterial blood gases
AF	Atrial fibrillation
AHI	Apnea-hypopnea index
AVAPS	Average volume assured pressure support
BiPAP	Bi-level positive pressure ventilation
BiPAP-S	Bi-PAP spontaneous mode
BiPAP-ST-mode	BiPAP spontaneous timed mode
BiPAP-T-mode	BiPAP timed-mode
BMI	Body mass index
BP	Blood pressure
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
ESS	Epworth sleepiness scale
FEV_1	Forced expiratory volume in the first second
FRC	Functional residual capacity

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FVC	Forced vital capacity
HCO_3	Bicarbonate
HR	Heart rate
ICSD-3	International classification of sleep disorders
IPAP	Inspiratory positive airway pressure
LA	Left atrial
LV	Left ventricle
NPPV	Noninvasive positive pressure ventilation
NREM	Non rapid eye movement
OD	Oxygen desaturation
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PAP	Auto-titrating positive airway pressure
PAP	Positive airway pressure
PH	Pulmonary hypertension
PS	Pressure support
PSG	Polysomnography
REM	Rapid eye movement
RR	Respiratory rate
RV	Right ventricle
SaO_2	Arterial oxygen saturation
SDB	Sleep breathing disorders
SpO_2	Peripheral capillary oxygen saturation
SRBDs	Sleep-related breathing disorders
SrH	Sleep-related hypoventilation
SrHDs	Sleep-related hypoventilation disorders
TLC	Total lung capacity

43.1 Introduction

Alveolar hypoventilation is defined as inadequate alveolar ventilation to maintain normal gas exchange, leading in hypoxemia and hypercapnia. A variety of medical conditions, such as respiratory, neurologic and neuromuscular diseases, as well as environmental and genetic factors are associated with the development of Sleep-related Hypoventilation (SrH) [1]. According to the ICSD-3 there are six different entities of Sleep-related Hypoventilation disorders (SrHDs) [2]:

- Obesity hypoventilation syndrome
- Congenital central alveolar hypoventilation syndrome
- Late-onset central hypoventilation with hypothalamic dysfunction
- Idiopathic central alveolar hypoventilation

- Sleep-related hypoventilation due to a medication or substance
- Sleep-related hypoventilation due to a medical disorder

In the early stages of these disorders, alveolar hypoventilation manifest during sleep due to the worsening of the normally reduced ventilation in sleep, but eventually awake hypercapnic respiratory failure occurs [3]. SrH may coexist with other Sleep Breathing Disorders (SBDs) such as sleep apnea, requiring careful consideration regarding the treatment approach [1].

Apart from the etiological treatment of the underlying disorder (when possible), symptomatic treatment of SrHDs usually involves nocturnal ventilator support with Noninvasive Positive Pressure Ventilation (NPPV) [1, 4]. In most cases, nocturnal NPPV is the primary treatment option that is effective by reversing even partially the consequences of nocturnal hypoventilation and well tolerated [1]. Clinical evaluation of symptoms in association with the results of Polysomnography (PSG) is essential in diagnosis and determination of the need for NPPV therapy [1]. Initiation and titration of positive airway pressure (PAP) devices as well as long-term follow-up may be difficult and challenging, especially in patients with multiple comorbidities [5].

43.2 Clinical Case of OHS Coexisting with OSA

A 74-years old female morbidly obese patient with a history of COPD, Arterial Hypertension for more than 10 years and Chronic Atrial Fibrillation, referred to our Sleep Unit with suspected Obstructive Sleep Apnea (OSA) syndrome. She was diagnosed having Chronic Obstructive Pulmonary Disease (COPD) a year ago by her primary care physician and she was under inhaled bronchodilator therapy.

The patient complained for loud snoring for almost 5 years, observed apneas during sleep, morning headaches and daytime sleepiness for almost 2 years (Epworth sleepiness scale-ESS score of 16). She had also dyspnea on exertion.

A detailed clinical history and a physical examination were performed. The patient had never smoked and she was refused any use of respiratory depressants (e.g. alcohol, sedative drugs or narcotics). Her weight was 110 kg, height 154 cm and BMI = 48.8 kg/m^2. She gained 30 kg weight over the past 2 years after a fracture of her right leg due to a car accident. The clinical examination showed BP of 140/80 mmHg, HR of 80/min, RR of 18/min, Oxygen saturation (detected via finger pulse oximetry-SpO_2) was 92–93% on room air, in the sitting position.

Upper airway examination (nose, oropharynx, hypo pharynx, and larynx) did not show any anatomical alterations predisposing to obstruction. On auscultation there were distant but clear breath sounds especially at the lower lobes without the presence of additional breath sounds. Additionally, there was mild peripheral edema in both lower extremities.

Lung function testing consisted of spirometry after bronchodilation revealed a restrictive pattern-syndrome. The Forced Expiratory Volume in the first second

(FEV_1) was 63.8% and the Forced Vital Capacity (FVC) was 63.6% of predicted values. The FEV_1/FVC ratio (81.5%) was, slightly above the predicted normal range (Total lung capacity—TLC was decreased, indicating true restriction). Arterial blood gases (ABGs) analysis showed: pH = 7.38, $PaCO_2$ = 53 mmHg, PaO_2 = 59 mmHg, HCO_3 = 31 mEq/L, and SaO_2 = 92% (with FiO_2 = 21% in the sitting position). On chest-X-ray there was elevation of both hemidiaphragms. A High-resolution Computed Tomography of the chest was normal. Transthoracic echocardiography showed dilated left atrium (43 mm), normal left ventricular (LV) systolic function and diastolic LV dysfunction (A > E). There was mild dilatation of the right ventricle (RV) with a systolic pressure of 41 mmHg. The patient had normal thyroid function tests and serum chemistry and complete blood count.

43.2.1 What Is the Diagnosis?

In conclusion, we have a morbidly obese patient, with Arterial Hypertension, dilated LA, AF, LV diastolic dysfunction, Pulmonary Hypertension (PH), restrictive lung syndrome, OHS and clinical suspicion of OSA.

What do we know? The current definition of OHS includes [1, 2]: Daytime hypercapnia ($PaCO_2$ >45 mmHg) in obese people with Body Mass Index (BMI) >30 kg/m^2 without any other etiologies of hypoventilation (such as COPD, interstitial lung disease, chest wall disorders, neuromuscular disease, severe hypothyroidism or sedative use).

OHS is a serious respiratory complication of obesity. The pathophysiology of OHS is complex leading to the development of chronic hypercapnia. The main pathogenetic mechanisms seem to contribute to the development of hypoventilation in obese patients are associated with: (1) alterations in respiratory mechanics due to obesity leading to increased work of breathing, (2) decreased ventilatory drive and (3) other associated SBD (usually obstructive sleep apnea) [3, 4].

According to a recent European Respiratory Society task force there are four stages of Hypoventilation in obesity [1]. Stage I and stage II are characterized by the presence of normocapnia during the day (while awake) and hypercapnia during sleep with or without the appearance of increased bicarbonate levels during the day (stage II and stage I, respectively). The other two stages are referred to OHS, characterized by daytime hypercapnia with or without cardiometabolic comorbidities (stage IV and stage III, respectively) [1].

The incidence of OHS is increasing (in parallel with the increasing prevalence of obesity) with an estimated prevalence of about 0.3–0.4% in the general adult population and 10–20% in obese patients with OSA [3]. The symptoms and sighs of OHS are nonspecific and usually are associated with coexisting OSA or complications due to OHS (e.g. pulmonary hypertension). For these reasons, OHS is an under-diagnosed pathological condition and usually the diagnosis delay until the fifth or sixth decade of life [1, 3]. Although in most cases there are no evidence of obstructive lung disease, usually these patients are misdiagnosed and treated for

obstructive lung disease, particularly COPD, especially in the presence of daytime hypercapnia as in our patient that was misdiagnosed having COPD by the primary care physician [3]. Untreated or mistreated OHS is associated with increased morbidity and mortality [1, 3].

A thorough history and clinical examination are of great importance for the clinical suspicion for OHS. Additionally, a variety of laboratory tests such as pulmonary function tests, chest imaging, echocardiography and blood test analysis should be performed to exclude other causes of hypoventilation, to confirm the co-existence of obesity related hypoventilation with other disorders that may contribute to the development of hypoventilation and hypercapnic respiratory failure or to confirm the presence of OHS-related complications [3, 6].

Arterial blood gas analysis is the gold standard for the diagnosis of hypoventilation and usually reveals compensated respiratory acidosis and hypoxemia (Fig. 43.1). Although nonspecific, increased serum bicarbonate concentration (>27 mEq/L) caused by metabolic compensation to chronic hypercapnia is suggested as a useful screening test for obesity related hypoventilation patients with nocturnal hypercapnia and daytime normocapnia, as well as for OHS patients [3, 6, 7]. As in our case, the presence of unexplained dyspnea, unexplained awake SpO_2 <94% with (or without) signs of pulmonary hypertension in obese non-smoker (especially in patients with central obesity and BMI >30 kg/m^2) should trigger suspicion for OHS leading to further investigation [4, 7]. In our opinion, ABG sampling should be performed in all severely obese patients having a daytime SaO_2 <94% to confirm daytime hypercapnia or suspect nocturnal hypercapnia based on high bicarbonate values (Fig. 43.1).

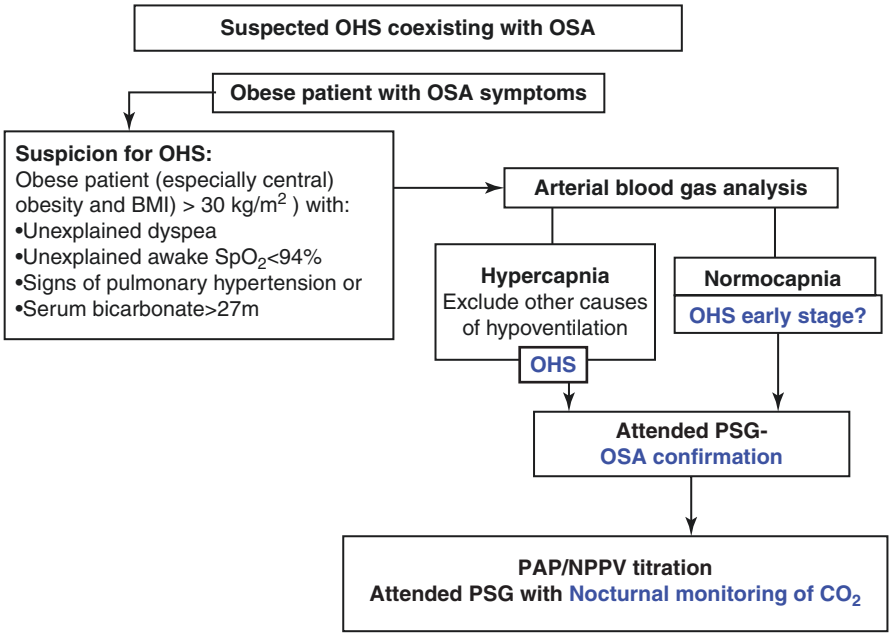

Fig. 43.1 Suggested algorithm for the management of patients with suspected OHS

43.2.2 What Is the Next Step?

Attended Polysomnography was performed in our sleep laboratory and revealed severe OSA (Fig. 43.2) with Apnea/Hypopnea Index (AHI): 70.5/h at almost 2 h of sleep, associated with episodes of oxygen desaturation, snoring and sleep fragmentation. There were 146 respiratory events consisting of 101 Obstructive Apneas (48.8/h), 1 Mixed Apnea (0.5/h), 0 Central Apnea, 44 Hypopneas (21.2/h) and 151 Oxygen Desaturation Events (OD) 72.9/h with Average desaturation of 9.6% and lowest Oxygen Saturation 74%. Mean Oxygen Saturation during wake was 90%. Average Oxygen Saturation during NREM and REM was 88% and 86%, respectively. Oxygen Saturation was below 90% for 92.7 min (57%).

According to PSG findings, the diagnosis of Obesity Hypoventilation Syndrome with coexisting severe OSA was confirmed and a Split-night study for PAP titration was performed.

What do we know? Obesity is a major risk factor for upper airway obstruction during sleep. Therefore, in most patients with OHS, almost 90%, coexist with OSA. PSG is necessary for both diagnostic and therapeutic approach of OHS patients with respiratory failure due to high incidence of coexisting OSAS [1, 3, 7].

According to the American Academy of Sleep Medicine (AASM), Sleep Hypoventilation in adults is characterized by the following criteria: an increase in

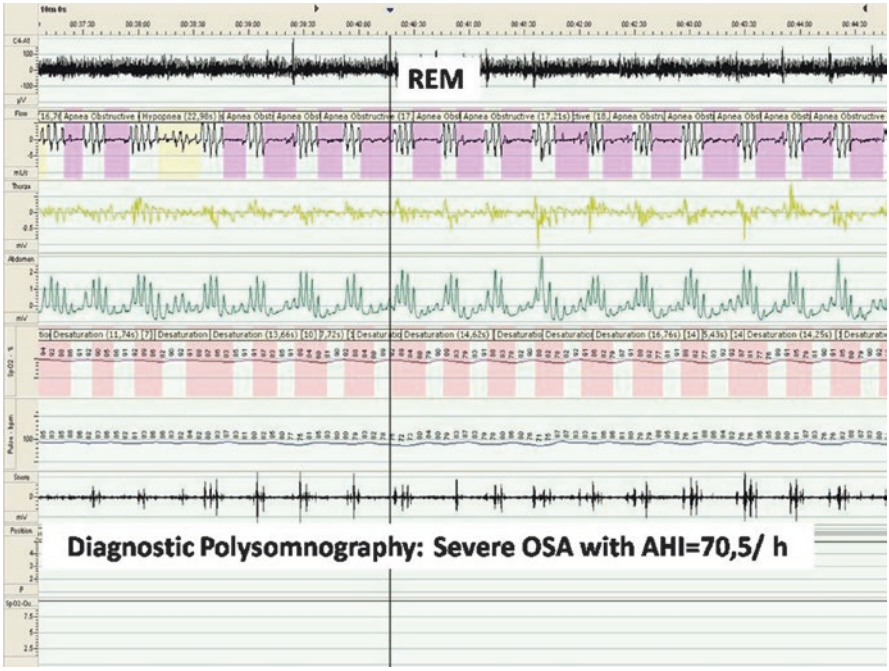

Fig. 43.2 Apneas and hypopneas during REM stage of sleep. (Data from our sleep laboratory). *REM* rapid eye movement, *OSA* obstructive sleep apnea, *AHI* apnea-hypopnea index

$PaCO_2$ to a value >55 mmHg (or surrogate such as end-tidal carbon dioxide tension or transcutaneous carbon dioxide) for at least 10 min or an increase in $PaCO_2$ (or surrogate such as end-tidal carbon dioxide tension (or transcutaneous carbon dioxide) of at least 10 mmHg increase from baseline during sleep (in comparison to awake supine values) to a value >50 mmHg for at least 10 min [7]. Hypoventilation is usually accompanied by sustained hypoxemia. A decrease of SaO_2 <90% for more than 5 min (with a nadir of 85%) may also indirectly indicate the presence of hypercapnia [4, 5]. Monitoring of $PaCO_2$ is not mandatory for the diagnosis of OHS but is very helpful for PAP/NPPV therapy titration [5].

43.2.3 Which Is Better Therapy Option: CPAP or NPPV?

Based on the findings of diagnostic PSG, a Split-night study for CPAP titration was performed (according to the AASM Clinical Guidelines for PAP Titration in Patients with Obstructive Sleep Apnea). During Split-night titration study, a CPAP device was initially applied via a nasal mask and at continuous pressure of 16 cmH_2O elimination of apneas was observed but this pressure was inadequate to correct hypopneas and hypoxemia. Oxyhemoglobin saturation remained below 90% for more than 40% of total sleep time. ABGs analysis at this point-time was performed indicating persisting hypoventilation despite CPAP use (Fig. 43.3).

A switch from CPAP to BiPAP-S (spontaneous mode) was decided with pressure titration goals to eliminate obstructive events and reverse nocturnal hypoxemia (SpO_2 >90%) and hypercapnia ($PaCO_2$ at least those observed during awake) by determining the effective level of nocturnal support pressure (IPAP-EPAP). Due to the fact that a noninvasive method for $PaCO_2$ monitoring was not available, arterial $PaCO_2$ values were used. Thus, a new attended Polysomnography trial was conducted for NPPV pressure titration. These above mentioned goals were achieved at BiPAP pressures of 18/10 cmH_2O. Next morning arterial blood gas concentrations were: pH = 7.39, $PaCO_2$ = 50 mmHg, PaO_2 = 68 mmHg HCO_3 = 31 mEq/L, and SaO_2 93% (with FiO_2 = 21%). BiPAP-S and mask use were well tolerated by the patient.

What do we know? NPPV during sleep together with lifestyle counseling is the first-choice therapy for patients with OHS [1, 3, 7]. According to the American Academy of Sleep Medicine an attended NPPV titration with PSG is the recommended method to identify optimal treatment pressure settings for patients with OHS [5]. In patients with chronic hypoventilation syndrome, apart from PSG, oximetry and arterial blood gases, transcutaneous CO_2—adequately calibrated or end-tidal $PaCO_2$ is recommended to be used for nocturnal NPPV titration [5].

Regardless of the modality, the goals of PAP titration therapy are the normalization of gas exchange (correction of hypercapnia and hypoxemia) and the elimination of obstructive events during sleep. Treatment with the application of PAP improves quality of life and also decreases morbidity and mortality in OHS patients [1, 3, 5, 7]. There are published clinical guidelines regarding CPAP and BiPAP

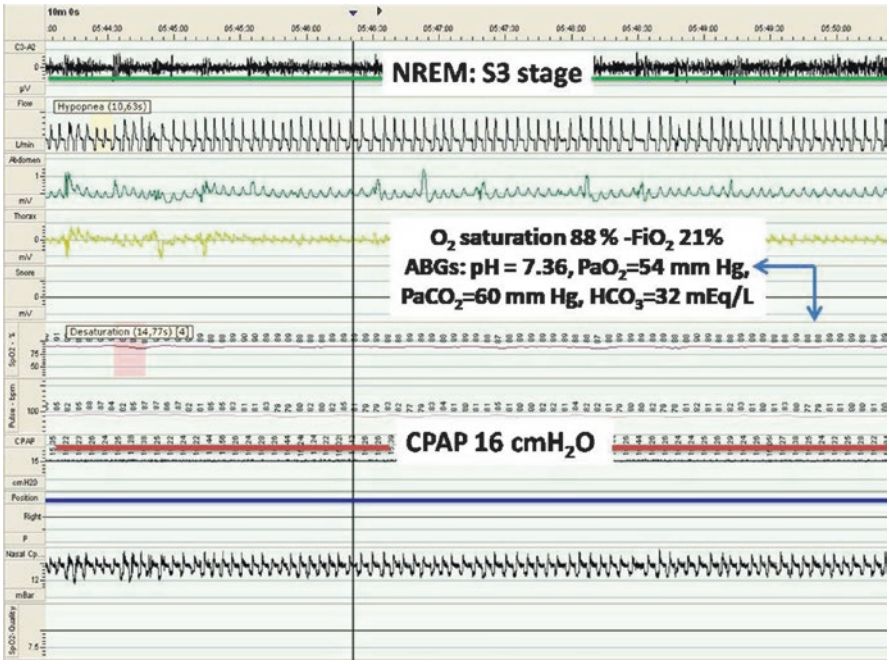

Fig. 43.3 Hypercapnia was assumed due to persistent oxygen desaturation during sleep in the absence of obstructive respiratory events for >10 min. (Data from our sleep laboratory). *NREM* non rapid eye movement, *ABGs* arterial blood gases, *CPAP* continuous positive airway pressure, PaO_2 partial pressure of oxygen, $PaCO_2$ partial pressure of carbon dioxide

titration in patients with OSAs [8], as well as recommendations for NPPV titration for patients with Central Alveolar Hypoventilation Syndromes [5], during PSG in sleep-laboratory (Table 43.1).

According to the literature, there is no proven superiority of either mode of PAP therapy (CPAP or NPPV) [1, 3, 5, 7]. Therefore, in clinical practice, the selection of the most appropriate modality of PAP treatment is individualized, depending on OHS patient's phenotype, especially the predominance of obstructive events or hypoventilation [1, 3, 7].

CPAP is the first line therapy for the majority of spontaneously breathing patients with OSA [1, 3, 7]. CPAP devices deliver a fixed (preset) continuous pressure in the airways during the whole respiration via a mask interface to prevent obstructive events during sleep. Thus, the CPAP therapy is the initial approach for patients with OHS and accompanying OSAs without serious comorbidities [3, 7, 9]. CPAP is efficient in the majority of OHS patients with OSA by stabilizing the upper airway and increasing lung volumes. CPAP increases the FRC (Functional Residual Capacity) and augments the opening of collapsed alveoli. Although CPAP does not affect significantly the ventilation, it can indirectly improve tidal volume and minute ventilation. Additionally, CPAP increases central response to hypercapnia and

Table 43.1 PAP therapy algorithm for patients with OHS coexisting with OSA [5, 8]

PAP therapy options for obese patients with OHS coexisting with OSA: Titration & follow up
1. *CPAP*: First line therapy for the majority of patients
1a. Attended CPAP titration with PSG
A. Limits of CPAP: • Minimum CPAP: 4 cmH_2O • Maximum CPAP: 20 cmH_2O
B. Adjustment of CPAP: ↑ Pressure: When: • 2 obstructive apneas or • 3 hypopneas or • 5 RERAs or • 3 minutes of loud snoring ↑ Pressure: Minimum of 1 mmHg (with an interval of ≥5 min)
C. Optimal CPAP titration • RDI (respiratory disturbance index) <5/h for at least 15 min • SpO_2 >90% • $PaCO_2$ <55 mmHg (or surrogate such as end-tidal carbon dioxide tension or transcutaneous carbon dioxide)-acceptable $PaCO_2$ goal ≤awake PCO_2) Supine REM sleep with no spontaneous arousals or awakening
2. *NPPV* in patients with: • Significant hypercapnia or severe comorbidities • No improvement in gas exchange under adequate CPAP therapy for obstructive events of breathing—non responders • OHS and OSA who do not tolerate high CPAP
2a. Attended NPPV titration with PSG
BPAP-S (spontaneous mode)
A. Limits of IPAP, EPAP, and PS • Minimum starting IPAP and EPAP: 8 and 4 cmH_2O, respectively • Maximum IPAP: 30 cmH_2O • Minimum and maximum PS: 4 and 20 cmH_2O, respectively • Incremental changes in PS: Minimum 1 cmH_2O and maximum 2 cmH_2O
B. Adjustment of IPAP, EPAP, and PS 1. IPAP/EPAP: As titration of PAP for OSA: ↑ IPAP & ↑ EPAP: By a minimum of 1 mmHg (with an interval of ≥5 min) when: • 2 obstructive apneas ↑ IPAP: By a minimum of 1 mmHg (with an interval of ≥5 min) when: • 3 hypopneas or • 5 RERAs (*Respiratory* effort-related arousal) or • 3 minutes of loud snoring 2. ↑ PS: • Every 5 min if tidal volume <6–8 mL/kg IBW (ideal body weight) • If $PaCO_2$ remains 10 mmHg ≥$PaCO_2$ goal for ≥10 min ($PaCO_2$ goal ≤awake PCO_2) • If SPO_2 <90% for ≥5 min and tidal volume <6–8 mL/kg

(continued)

Table 43.1 (continued)

BPAP-ST (spontaneous timed mode) with a back up rate: If the problem remains
C. Adjustment of the Back-up rate • Indications: Persistent sleep hypoventilation • ST mode: If maximum PS in the spontaneous mode is unsuccessful • Initial Back-up rate ≤spontaneous RR during sleep (minimum of 10 bpm) • ↑ Back-up rate: 1–2 bpm/10 min • Inspiratory time (IPAP time): 30–40% of the cycle time • Timed mode: If ST mode is unsuccessful
D. Supplemental oxygen • Indications: Awake SpO_2 <88% or SpO_2 <90% for ≥5 min (after PS and RR optimization) • Minimum initial Suppl. O_2 rate: 1 L/min • ↑ Suppl. O_2 rate: 1 L/min every 5 min until SpO_2 >90%
3. *Follow up*
• Monitoring of the efficacy and usage data of the device • Monitoring of NPPV: At 1, 3, and 6 months for titration • Re-evaluate after a significant weight reduction

hypoxemia [1, 3, 7]. In most cases CPAP improves AHI and gas exchange (hypoxemia/hypercapnia) in an adequate level [1, 3, 7].

NPPV is indicated in patients with significant hypercapnia or severe comorbidities as well as in patients with no improvement under adequate CPAP therapy—non responders [3, 7]. Patients with OHS and OSA who do not tolerate high CPAP are also candidates for NPPV therapy [3, 7]. The most common form used for NPPV is the Bi-level positive pressure ventilation (BiPAP). BiPAP devices provide different levels of pressure during inspiration and expiration. The pressure during inspiration (IPAP-inspiratory positive airway pressure) is higher than during expiration (EPAP-expiratory positive airway pressure) and the difference between them (IPAP-EPAP) provides pressure support (PS) to increase tidal volume and minute ventilation [5, 8, 9]. The EPAP maintains the patency of the upper airway, eliminating obstructive apnea–hypopnea events and allowing the delivery of pressure to lower airways. According to the American Academy of Sleep Medicine, the PS should be increased if the arterial $PaCO_2$ remains 10 mmHg or more above the $PaCO_2$ goal at the current settings for 10 min or more [5]. An acceptable goal for $PaCO_2$ is a value less than or equal to the awake $PaCO_2$ [5]. Bi-level PAP is the most common method used for ventilatory support in patients with hypoventilation disorders [5]. Thus, in patients with persistent sleep hypoventilation (and thus hypercapnia/hypoxemia), despite adequate CPAP therapy regarding obstructive airway events, a BiPAP-S (Spontaneous mode) trial is indicated [5, 6, 9]. If the problem remains, BiPAP-ST (Spontaneous Timed mode) with a back up rate is recommended [5, 9]. The adjustments for minute ventilation should be based on ABGs or transcutaneous CO_2 or both during PSG study [5]. If the BiPAP-ST mode is not successful then the BiPAP-Timed mode can be tried. AVAPS is another acceptable therapeutic option for these patients [5, 9]. Although it is as effective and safe as BiPAP, it is not superior to BiPAP in the management of these patients. Monitoring of the efficacy and usage

data of the device is needed to follow PAP therapy initiation for the evaluation of patient adherence to treatment [5].

43.2.4 What to Expect after Short-Term PAP Therapy Initiation?

Six weeks after treatment initiation with BiPAP-S, the patient was satisfied having adequate tolerance of the device. She reported a substantial improvement in sleep quality, night snoring, nocturia, morning headaches and daytime sleepiness with nightly use of BiPAP for at least 5 h. To the contrary, dyspnea on exertion was persisted.

A new full-night Polysomnography was performed applying BiPAP-S using the same settings of pressures (18/10 cmH_2O) that confirmed the resolution of obstructive breathing events (AHI = 7/h) without requiring any pressure changes. This study confirmed that initial pressure titration was appropriate. Average SpO_2 was 94% and SpO_2 duration below 90% was 4 min (2%). Before this study, ABG analysis showed: pH = 7.39, $PaCO_2$ = 47 mmHg, PaO_2 = 70 mmHg, HCO_3 = 28 mEq/L, and SaO_2 = 94% (with FiO_2 = 21%). Next morning $PaCO_2$ was 50 mmHg. BiPAP-S and mask use were well tolerated by the patient.

At the same time, the patient after our encouragement and support decided to change lifestyle and diet (under the supervision of a dietician) and exercise habits participating in a rehabilitation program. Daily PAP usage was downloaded from the device at 3 and 6 months confirming the patient adherence to treatment.

What do we know? Noctural NPPV therapy is associated with significant improvement in gas exchange, restoration of respiratory insufficiency (during sleep and in awake) and improvement in lung function in OHS patients [1, 3, 7, 9]. According to the literature, NPPV may be more effective in reducing pulmonary pressure than CPAP, due to better control of hypoventilation during sleep than CPAP. Treatment with the application of PAP improves quality of life and also decreases morbidity and mortality in OHS patients [3, 7, 9]. Major success contributor of NPPV therapy in OHS patients is adequate patient adherence to treatment. Monitoring of the efficacy and usage data is needed to follow PAP therapy initiation for the evaluation of patient adherence to treatment. Close monitoring is recommended for the first 1–3 months after the initiation of PAP therapy [3, 5].

43.2.5 Lifestyle Changes—Weight Loss: Does it Matter?

Twelve months after BiPAP-S implementation, the patient lost 20 kg (Weight = 90 kg, Height = 1.50 m, BMI = 40.0 kg/m^2). The patient reported significant improvement in daytime and nocturnal symptoms. ABG analysis showed pH = 7.41,

$PaCO_2$ = 47 mmHg, PaO_2 = 72 mmHg HCO_3 = 28 mEq/L, SaO_2 = 94% in room air. A repeated spirometry indicated an improved but still pulmonary restrictive syndrome. Re-evaluation with Polysomnography revealed severe OSA with a mild decrease in AHI 43/h [Obstructive Apnea: 36 (6.1/h), Central Apnea: 1 (0.2/h), Mixed Apnea: 0, Hypopnea: 219 (37.0/h)] with Oxygen Desaturation Events 40.8/h, while Oxygen Desaturation during sleep was still prolonged [Oxygen Saturation <90% for 205.2 min (52.3%)], requiring a mild decrease in BiPAP pressures of 16/9 cmH_2O.

Two years after treatment application with BiPAP-S, the patient has succeeded in significantly reducing her weight combining a gradual increase in physical activity and appropriate diet, while she was under well tolerated BiPAP-S therapy. She totally lost 40 kg, falling from 110 to 70 kg but she was still obese (Table 43.1). At this time, the patient reported remarkable improvement in daytime and nocturnal symptoms. She reported dyspnea only during stairs elevation to third floor. She was eucapnic with SaO_2 = 95% in room air. ABG analysis showed pH = 7.40, $PaCO_2$ = 42 mmHg, PaO_2 = 75 mmHg, HCO_3 = 25 mEq/L (with FiO_2 = 21%). There was a significant improvement in spirometric values and transthoracic echocardiography showed Right Ventricular Systolic Pressure decreased (from 41 to 25 mmHg) indicating mild PH.

A new full-night Polysomnography revealed a significant improvement that is mild OSA and AHI: 13/h (totally 69 events: 10 Obstructive Apneas and 59 Hypopneas) and 61 Oxygen Desaturation Events (OD) 12.5/h. Mean Oxygen Saturation during sleep was 95%. Oxyhemoglobin saturation was below 90% for almost 4 min. Thus, the application of PAP therapy and the significant weight loss resulted in a significant improvement of the patient.

Based on new PSG findings, PAP therapy decided to be continued. However, due to the significant improvement a switch from BiPAP-S to CPAP was selected. An optimal pressure of 8 cmH_2O was adequate in eliminating residual apneas/hypopneas and in maintaining adequate gas exchange (Mean Oxygen Saturation was 97%). Next morning ABG analysis showed pH = 7.40, $PaCO_2$ = 43 mmHg, PaO_2 = 76 mmHg, HCO_3 = 26 mEq/L.

Additionally, the patient was advised to continue the efforts for further reducing body weight and increasing (or at least maintaining) the physical activity until the next follow-up along with mild exercise and reevaluation within a year (Table 43.2).

What do we know? Although, treatment with nocturnal PAP therapy has been shown to improve gas exchange and to resolve the obstructive breathing disorders

Table 43.2 Evolution of weight, BMI and AHI over 2 years period

	Body weight (kg)	% Decrease	BMI (kg/m^2)	% Decrease	AHI (per h)	% Decrease	$PaCO_2$ (mmHg)	% Decrease
Baseline	110		48.9		70.5		53	
1 year	90	18.2	40.0	18.2	43	39	47	11.3
2 years	70	34.4	31.1	34.4	13	81.6	42	20.8

during sleep, excessive weight loss is the cornerstone of the long-term management of patients with OHS [3, 6, 7]. Weight decrease (of at least 10 kg) improves pulmonary function (as evidenced by increased VC and FEV_1) [3, 6, 7]. In OHS patients with OSA, weight loss is associated with an improvement in gas exchange and a decrease in obstructive respiratory events during sleep (decreased AHI), although in many cases a residual OSA can persist [3, 6, 7]. Therefore, re-evaluation of these patients with OHS and OSA (after a significant weight loss) is necessary before choosing to stop PAP therapy. In most cases dietary weight loss is difficult to achieve or to maintain weight, while there is always risks of weight regain [3, 6, 7].

Key Teaching Points

- OHS may coexist with OSA.
- Use of ABGs for determining hypercapnia either for daytime or during sleep based on bicarbonate levels.
- PSG with nocturnal monitoring of CO_2 is the gold standard for the recognition and evaluation of patients with sleep-related hypoventilation disorders in early stages.
- C-PAP may resolve apneas but maybe inadequate to restore hypoventilation and hypoxemia/hypercapnia. BiPAP is more efficient and suggested for these cases.
- Nocturnal NPPV is the primary treatment option in OHS patients with significant hypercapnia or severe comorbidities as well as in patients with no improvement under adequate CPAP therapy.
- Monitoring of NPPV is suggested at 1, 3, and 6 months for titration.
- Lifestyle changes and weight loss is strongly suggested.

Questions and Answers

1. The current definition of OHS includes the following criteria:

   (a) Daytime hypercapnia ($PaCO_2$ >45 mmHg)
   (b) Obesity-Body Mass Index (BMI) >30 kg/m^2
   (c) Non other etiologies of hypoventilation
   (d) All the above
   (e) a + b

   Answer: (d) All the above

2. In patients with OHS with coexisting OSA which of the following is recommended to be used for noctural NPPV titration:

   (a) Attended PSG
   (b) Oximetry
   (c) Arterial blood gases
   (d) Transcutaneous CO_2 ($TcCO_2$)—adequately calibrated or end-tidal PCO_2
   (e) All the above

   Answer: (e) All the above

3. In patients with OSA and coexisting OHS, which is the most effective treatment for reversing the hypercapnia associated with OHS:

   (a) Bilevel positive airway pressure
   (b) Continuous positive airway pressure (CPAP)
   (c) Oxygen therapy
   (d) Respiratory stimulants
   (e) Bariatric surgery

   Answer: (a) Bilevel positive airway pressure
4. NIMV is indicated in patients with OHS in association with OSA when there is:

   (a) Significant hypercapnia
   (b) Severe OSA
   (c) Severe comorbidities
   (d) No improvement under adequate CPAP therapy
   (e) a + c + d

   Answer: (e) a + c + d
5. Monitoring of PAP/NPPV is suggested in patients with OSA and coexisting OHS:

   (a) At 1, 3, and 6 months for titration.
   (b) At 3 and 6 months for titration
   (c) After a significant weight reduction
   (d) a + c
   (e) b + c

   Answer: (d) a + c

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Part VIII
Clinical Conditions: Chronic Hypercapnic Respiratory Failure

Chapter 44
Noninvasive Ventilation in Chronic Obstructive Pulmonary Disease: Ventilating the Patient with Severe Respiratory Acidosis

Biljana Joves

Abbreviations

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
FiO_2	Fraction of inspired oxygen
HDU	High Dependency Unit
HES	Hypercapnic encefalopathy
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
KMS	Kelly Matthay scale
NIV	Noninvasive ventilation
PEEP	Positive end expiratory pressure
PSV	Pressure support ventilation
RCT	Randomized controlled trial
SPN-CPAP/PS	Spontaneous-Continuous positive airway pressure or Pressure support ventilation
Ti	Inspiratory time
Vt	Tidal volume

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44.1 Introduction

As stated in the current guidelines, bilevel NIV is ventilatory support of choice in patients with moderate-to-severe acute exacerbation of chronic obstructive lung disease (AECOPD), provided they have no absolute contraindications for NIV [1, 2]. Randomised controlled trials (RCT) have confirmed that the use of NIV reduces mortality and the cost of treatment, and also helped define criteria for adequate choice of patients. As the confidence in NIV implementation grows, previously listed contraindications are being questioned. While the patients with severe acidosis and reduced level of consciousness used to be considered candidates for immediate endotracheal intubation, today it is considered appropriate to start a NIV trial in adequately monitored clinical setting—High Dependency Unit (HDU) or Intensive Care Unit (ICU). Current guidelines state that, in the above described clinical settings, there is "no lower limit of pH below which a trial of NIV is inappropriate" Clinical teams with extensive NIV experience may increase the success rate of NIV. It is important to choose and adjust the right interface, readjust the ventilator settings to ensure patient-ventilator synchrony; and also, to timely recognize early signs of NIV failure and enable quick transition to invasive mechanical ventilation, if necessary.

Case Presentation
The patient was a 64 year old man with the known history of COPD. He was unconscious upon admission, so all the information was obtained from the emergency medical team that provided initial therapy and transport to our hospital. Previous hospital records showed seven hospitalizations due to AECOPD—the first one 5 years ago, and the last one 3 months ago. Blood gas analysis at the last discharge from the hospital showed compensated chronic type 2 respiratory failure. No comorbidities or allergies were listed. The emergency medical team explained that he was increasingly breathless for 3 days prior to the transport, without signs of infection, or cardiac failure. He was first treated as an out-patient with intravenous aminophylline, methylprednisolone, and inhaled bronchodilators. On the day of admission he was found unconscious and cyanotic, with initial SpO_2 of 50% and was urgently transferred to our hospital on oxygen therapy.

The patient's Glasgow Coma Score upon admission was 8. Although widely used, GCS is the tool that was initially developed for head trauma patients. On the other hand, Kelly Matthay scale (KMS) is a six-level scale that was designed to evaluate neurological status of patients on mechanical ventilation and has even proven to be a possible prognostic factor in patients with hypercapnic encephalopathy (HES) on NIV. Our patient was grade 4 on KMS. Given the patient's medical history and initial presentation, we attributed his level of consciousness to HES—"heterogeneous and potentially reversible neurological alterations occurring in the presence of acute respiratory failure with severe decompensated respiratory acidosis" [3]. Since CO_2 can pass haemato-encephalic barrier due to its liposolubility, respiratory acidosis has profound effect on neurological status. It is important to exclude alternative causes of depressed consciousness before starting the patient on

NIV. However, if hypercapnia is considered the primary cause, NIV can be initiated in the appropriate clinical setting. Diaz conducted a large prospective trial, in which comatose patients even had slightly better success rate on NIV than the patients with higher GCS upon admission. However, inability to improve GCS after 1 h on NIV was a predictor of failure, along with severity of multi-organ dysfunction [4].

Physical findings upon admission included barrel chest appearance, almost silent lungs, prolonged expiration, and slight hypotension. Arterial blood gas analysis showed severe hypercapnia with $PaCO_2$ of 12.3 kPa and resulting pH of 7.15. Since the most frequent causes of COPD exacerbation include respiratory infections, cardiac decompensation and thromboembolism, the laboratory work-up included markers of inflammation, pro-BNP and D-dimer—all values were within normal range. The patient was treated as AECOPD due to bronchospasm with parenteral magnesium-sulfate, inhaled bronchodilators (nebulized combination of short-acting beta 2 agonist and anticholinergic), intravenous steroids, along with stress-ulcer prophylaxis.

Oxygen therapy was reduced to 0.24 FiO_2 until chest radiograph was performed in order to exclude pneumothorax prior to NIV initiation. Chest radiograph only showed signs of hyperinflation and minimal pleural adhesions. It is important to remind ourselves that uncontrolled oxygen therapy and sedative use (often given due to agitation in hypercapnic patients) are among the most frequent causes of further worsening hypercapnia in patients with COPD. Early institution of NIV also increases the chance of success and, in this case, it would have prevented negative effects of liberal oxygen therapy on the existing hypercapnia. However, early institution of NIV has so far been studied as a predictor of NIV success mostly in hospital setting, given the technical issues linked with pre-hospital use [5].

The patient had the right indications for NIV: severe hypercapnia and resulting respiratory acidosis due to AECOPD. However, his GCS of 8 prompted careful clinical decision making whether to use invasive or noninvasive ventilatory support. There are several issues to consider before deciding on NIV in patients with HES. Firstly, in patients with HES whose initial presentation is agitation, it is very hard to achieve necessary compliance. Light sedation is a possible option, but the results are varied [3]. Our patient was unconscious, so this was not an obstacle. Another issue is gastric distension and possible associated aspiration pneumonia. One way to prevent this complication is to keep maximum pressure below 20 cm H_2O—cut-off associated with opening of upper esophageal sphincter [4]. Leading concern is how to protect the airway and ensure adequate clearance of secretions. Patients with low GCS have depressed cough reflex. In the expert NIV setting, one study showed good results with fiberoptic broncho-aspiration prior to NIV in patient with HES and copious secretions, but it remains questionable how does this translate to regular clinical practice [3]. If our patient had pneumonia, immediate intubation would have likely been a safer option and probably our choice. However, the patients did not exhibit any signs of respiratory infection, so the trial of NIV was started.

The choice of NIV location was based on patient's neurological impairment—he was admitted to high dependency unit. Initial interface was chosen according to his

facial shape and size—oronasal mask that was strapped tightly enough to minimize the leakage, yet loose enough to try to prevent facial decubitus. The patient was elevated in a semi-sitting position with the head of the bed elevated 45° and then treated with noninvasive ventilation (SPONT—NIV; eVent Medical Inc.; San Clemente, CA). Most ICU ventilators have software for noninvasive ventilation—NIV option needs to be confirmed on the initial screen to allow better leak compensation. The patient was ventilated with EPAP of 6 cm H_2O and pressure support (PS) of 8 cm H_2O that was quickly titrated towards 14 cm H_2O—due to mental status, there was no need for gradual titration. Listed values resulted in the total inspiratory positive airway pressure (IPAP) of 20 cm H_2O (14 cm H_2O of PS above 6 cm H_2O of EPAP).

Initially, the tidal volume (Vt) of 6 ml/kg was obtained, but the final goal was 8 ml/kg, as recommended for patients with obstructive disorders. PS was not further increased, pending neurological improvement, and due to gastric distension and aspiration pneumonia concerns. The actually delivered Vt was visible on the monitor as expiratory tidal volume measured by the designated sensor on the expiratory valve—it is of importance to notice the difference between the inspiratory Vt and expiratory Vt. The difference between the two indicates the magnitude of leaks. Inspiratory trigger was set to the lowest value.

Patient was closely monitored and control blood gas analysis was performed after 30, instead of the usual 60, min. Attempts to define early predictors of NIV outcome in patients with HES identified correction of GCS and rise of pH within first hour of NIV initiation. Timely transition to invasive ventilation, when necessary, relies on conclusions drawn from close monitoring of vital parameters and early recognition of NIV failure. One of the findings in a large study performed by Chandra was increased mortality in the group of patients requiring invasive mechanical ventilation after NIV failure. Blood gas analysis after 30 min in our patient showed initial improvement in pH and $PaCO_2$ values, along with the rise in PaO_2. The patient started to open his eyes spontaneously. However, the manifestation of HES then changed to agitation, which was another challenge to overcome in order to maintain compliance. Staff had to constantly reassure the patient and explain the necessity of further application of NIV. Head straps were readjusted. Since the patient complained of nasal bridge pressure, oronasal mask was replaced by total face mask, as shown in Fig. 44.1.

Sedation was avoided, although there are findings that allow the use of light sedation in agitated patients with HES during NIV [3]. After about 2 h, attending physician noticed that the patient was not in synchrony with the ventilator—clinical observations indicated that not every patient's inspiratory effort resulted in matching breath delivery by the ventilator. This clinical observation was backed by the subtle changes in respiratory waveforms on ventilator monitor that implied patient-ventilator dyssynchrony classified as missed inspiratory efforts. In studies by Di Marco and Tassaux, it was concluded that adjustment of ventilator settings based on respiratory waveforms analysis led to improvement of pH, $PaCO_2$, and better compliance [6, 7]. The waveforms attending physician recorded were similar to the one shown in Fig. 44.2.

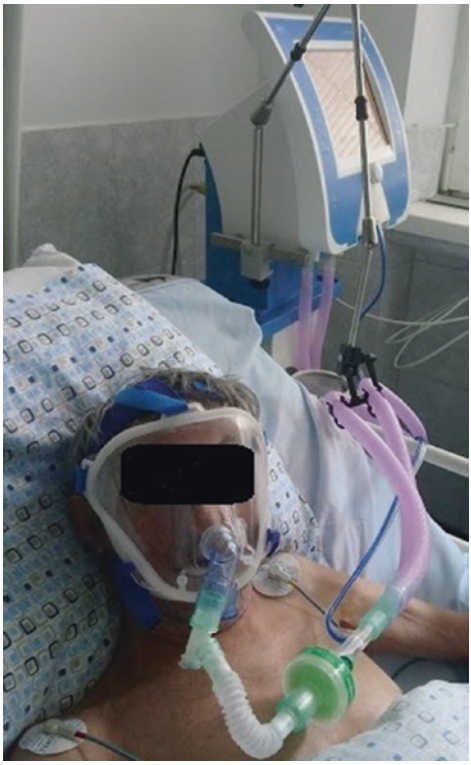

Fig. 44.1 Total face mask used on a patient with acute exacerbation of chronic obstructive lung disease

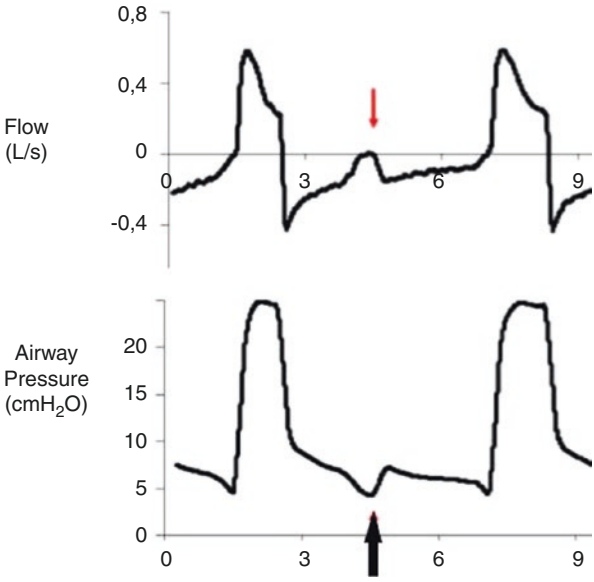

Fig. 44.2 Missed inspiratory efforts: black arrow marks a drop in pressure below baseline and red arrow marks a decrease in expiratory flow

This type of trigger asynchrony is not simply corrected by lowering the sensitivity of inspiratory trigger. The first thing attending physician did is to check for delivered tidal volume reflected in the expiratory tidal volume value on the monitor. In attempt to correct hypercapnia faster, the physician previously titrated PS after 1 h up to 20 cm of H_2O, which resulted in tidal volumes of 10 ml/kg. It is assumed that this increase in tidal volume of over 8 ml/kg generated additional hyperinflation and possibly increased the patient's intrinsic PEEP. So the first step was to decrease the pressure support in order to reduce delivered tidal volumes in the range of 7–8 ml/kg. Smaller tidal volumes are quicker to exhale, which helps reduce hyperinflation and intrinsic PEEP. Second step was to allow the patient longer time to exhale by changing the cycling criteria, and allowing expiration to start earlier. Longer expiration and reduction of Vt led to reduction of intrinsic PEEP, which enabled more effective triggering of the ventilator. It is important to remember that resulting increase in respiratory rate was not sign of deterioration but just unmasking of the missed inspiratory efforts.

After ventilator settings readjustments, patient-ventilator synchrony was improved. Vital parameters, patient's compliance and blood gas values were rechecked every hour on day one and every 4 h after the patient was initially stabilized. Each unit is advised to make its own check-lists based on the level of staffing and severity of illness of each individual patient [8]. Our patient tolerated NIV for 16 h during the first day. Once acidosis started resolving, NIV was gradually withdrawn: it was used 12 h on second day and 8 h during the third night. Stepwise manner that meant withdrawal of NIV during the day and, finally, during the night on day four was used, although there is not enough literature to confirm that this method is superior to immediate withdrawal.

The patient was fully stabilized by day four. Blood gas analysis 24 h after the last episode of NIV showed compensated type II respiratory insufficiency, with SO_2 of 88% and pH above 7.35, which was a pre-condition for a safe transfer to general ward. He was discharged from the hospital on day 9.

Key Teaching Points

- Perform a chest radiogram before NIV initiation, in order to exclude pneumothorax in patients with AECOPD.
- Hypercapnic encephalopathy is not an absolute contraindication for NIV in the appropriate clinical setting—high dependency or intensive care units.
- When deciding on invasive vs noninvasive ventilation in patients with HES, consider the issues of protected airway, risk of aspiration pneumonia and compliance based on the patient's level of agitation.
- Failure to improve GCS within **1** h should prompt transition to invasive ventilation.
- Observing respiratory waveforms in real time may lead to optimized ventilation and improved outcome.

Questions and Answers

1. Is it appropriate to avoid immediate intubation and attempt NIV, in patients with AECOPD who have severe respiratory acidosis and reduced level of consciousness

   (a) Yes, in an adequately monitored clinical setting such as ICU or HDU
   (b) No, immediate intubation is obligatory

   Answer: (a) Yes, in an adequately monitored clinical setting such as ICU or HDU
2. Why do we use external PEEP when ventilating a patient with COPD?

   (a) To reduce inspiratory effort due to intrinsic-PEEP
   (b) To avoid the atelectasis
   (c) To avoid air trapping

   Answer: (a) To reduce inspiratory effort due to intrinsic-PEEP
3. Desired tidal volume delivered to COPD patient on NIV is

   (a) 10 ml/kg
   (b) 5 ml/kg
   (c) 7–8 ml/kg

   Answer: (c) 7–8 ml/kg
4. Transition to invasive ventilation is advisable if GCS does not improve within 1 h

   (a) Yes
   (b) No

   Answer: (a) Yes
5. How can one try to avoid "missed inspiratory efforts" dyssynchrony
   (a) Lower the sensitivity of inspiratory trigger
   (b) Gradually increase extrinsic PEEP to overcome intrinsic PEEP
   (c) Reduce tidal volumes by decreasing pressure support
   (d) All of the above

   Answer: (d) All of the above

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Chapter 45
Noninvasive Ventilation in Chronic Obstructive Pulmonary Disease

Maria Joana Pereira and Maria João Matos

Abbreviations

AECOPD	Acute chronic obstructive pulmonary disease exacerbation
COPD	Chronic obstructive pulmonary disease
CV	Vital capacity
EPAP	Expiratory positive airway pressure
FEV1	Forced expiratory volume in the first second
FVC	Forced vital capacity
HINPPV	High-intensity non-invasive positive pressure ventilation
IC	Inspiratory capacity
ICS	Inhaled corticosteroid
IT	Inspiratory time
IPAP	Inspiratory positive airway pressure
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonist
NIV	Non-invasive ventilation

45.1 Introduction

The use of bilevel non-invasive ventilation (NIV) in patients suffering from an acute exacerbation of chronic obstructive pulmonary disease (COPD) complicated by hypercapnic respiratory failure is widespread, supported by a strong scientific evidence and from clinician consensus on its value and benefits [1]. Concerning to chronic hypercapnic respiratory failure, long-term NIV to treat stable severe COPD patients is still controversial. However, with the introduction of HINPPV, important

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benefits from this therapy have been shown in COPD [2]. In this chapter, the authors present a case report of a patient with severe COPD previously under chronic home NIV who comes to the emergency department with acute COPD exacerbation (AECOPD), in the context of respiratory infection.

Clinical Case

A 72-years-old female patient is being followed at Pulmonology Department due to COPD and panlobular pulmonary emphysema with about 10 years of disease progression. The patient is a former smoker with a smoking load of 80 unit pack-years. Her medical history includes obesity, hypertension and type 2 diabetes mellitus. She was previously medicated with long-acting muscarinic antagonist (LAMA) glycopyrronium, long-acting β2-agonist (LABA) indacaterol, inhaled corticosteroid (ICS) and oxygen therapy 1 L/min at rest and 3 L/min for walking and exercise. The last respiratory functional test (Fig. 45.1 and Table 45.1) revealed severe fixed obstruction (grade 4) and daytime blood gases revealed type 2 respiratory failure with 50 mmHg pCO_2 and 65 mmHg pO_2 under 1 L/min of oxygen. Despite being treated with triple bronchodilation (LABA/LAMA/ICS), the patient had about two episodes of AECOPD without hospitalization in the last year. Due to chronic respiratory failure and history of exacerbations, it was decided to initiate home NIV.

The patient was admitted to the ward for NIV titration with a bi-level positive airway pressure ventilator (Stellar 150, ResMed) with cardio-respiratory monitorization. The starting level of inspiratory positive airway pressure (IPAP) was 16 cmH_2O and an expiratory positive airway pressure (EPAP) of 6 cmH_2O. Plateau (rise time) was adjusted according to comfort, which tended to be the shortest rise time possible. Expiratory trigger was again altered according to patient comfort, and was usually 40% (i.e. inspiratory flow had to fall to 40% of peak flow in order to cycle into expiration). IPAP was then altered in increments of 1–2 cmH_2O, limited by patient tolerance and until $PaCO_2$ normalization was reached. In this patient was necessary to use a high backup rate (18 cpm) to maintain adequate minute

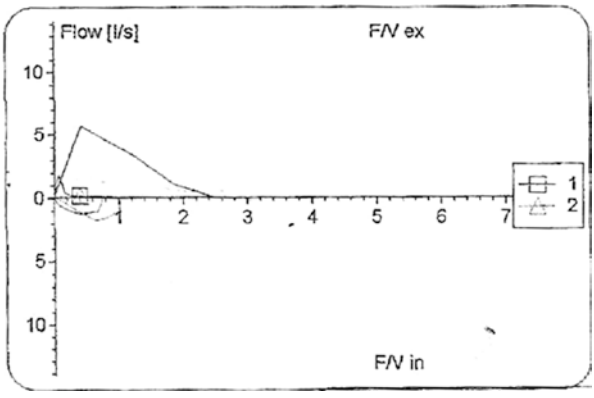

Fig. 45.1 Flow-volume curve—severe chronic obstructive pulmonary disease (see Table 45.1)

Table 45.1 Ventilatory parameters

	Unit	Theoretical value	Actual value	%Act./Th.	After BD
VC MAX	[L]	2.61	0.89	34.2	1.01
VC IN	[L]	2.61	0.74	28.2	1.01
FVC	[L]	2.48	0.80	32.4	0.89
FEV1	[L]	2.05	0.40	19.2	0.38
FEV1 % FVC	[%]	–	49.25	–	42.76

VC vital capacity, *FVC* forced vital capacity, *FEV1* forced expiratory volume in the first second

ventilation and gas exchange. Moreover, it was also necessary to ensure optimal mask fit with minimal leak in order to decrease asynchronies. The inspiratory time (IT) was 0.8 s. Flow and pressure values were recorded for monitoring as well as apnea-hypopnea index. The patient was discharged with an indication to comply with NIV during night and for periods during the day with the following ventilatory parameters: IPAP 20 cmH_2O, EPAP 6 cmH_2O, respiratory rate 18, IT 0.8 s and oxygen 1 L/min with controlled leaks, no registration of apneas and a tidal volume of 500 mL. The blood gases analysis under NIV revealed: pH 7.39, pO_2 80 mmHg, pCO_2 46 mmHg, HCO_3^- 30.0 mEq/L.

The patient had a good adaptation to the ventilator, complied every night and for 2 years had no further episodes of acute COPD exacerbation. However, during the last winter she presented to the emergency department with persistent cough with purulent sputum, dyspnea at rest and fever. The arterial blood gases analysis revealed a severe respiratory acidosis: pH 7.26, pCO_2 83.0 mmHg, pO_2 70 mmHg, HCO_3^- 32 mEq/L and the thoracic X-ray showed an image of pulmonary consolidation in the left lower lobe, compatible with pneumonia. In order to correct acute respiratory failure, the patient started NIV at the emergency department. The patient was treated with bilevel positive pressure through facial mask, spontaneous/time mode with IPAP 26 cmH_2O, EPAP 6 cmH_2O, respiratory rate 18, IT 0.8 s. She was admitted to the pulmonology department and started antibiotherapy with levofloxacin. Clinical and analytical progressive improvement was observed during hospitalization and ventilatory weaning was possible. This weaning was performed by reducing the number of hours and reducing the pressure support. The patient was clinical stable without respiratory failure under the same ventilatory parameters that fulfilled at home. The patient had a good recovery and at the last year, she continued to fulfil NIV with very good clinical day and night results with no ventilator asynchronies (Fig. 45.2).

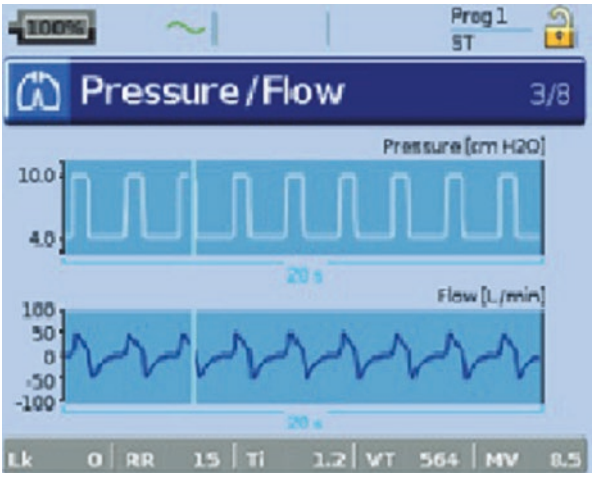

Fig. 45.2 Pressure/flow waveform with no ventilator asynchronies and controlled leaks

45.2 Discussion

The utility of NIV in acute hypercapnic respiratory failure in COPD is well-established. Currently, it is a standard component of the management of these patients and is included in the most recent international guidelines. Established criteria for patient selection include persistent acidosis (pH <7.35), hypercapnia (pCO_2 >45 mmHg) and/or tachypnoea (respiratory rate >22 breaths/min) despite optimal bronchodilator and controlled oxygen therapy to a saturation target of 88–92% [3]. When compared with invasive mechanical ventilation in randomised clinical trials, observational cohorts or meta-analyses, NIV has been shown to have better outcomes (reduced inpatient mortality and length of stay at hospital) in acute exacerbation of COPD [4]. This can be explained by a higher complication rate in the group treated with invasive mechanical ventilation.

We described a clinical case of a patient with severe COPD (GOLD grade 4, group D) with acute worsening of respiratory symptoms needing additional therapy. Those are the hallmarks to define acute exacerbation of COPD and we concluded that it was precipitated by a respiratory infection. Despite intensive bronchodilator therapy, antibiotics, mucolytic drugs and systemic corticosteroids administration, the patient persisted with respiratory acidosis. NIV was essential for the correction of acute respiratory failure. The patient was ventilated through spontaneous/time mode with high pressure support and adjusted according to the values of arterial blood gases.

It is not only important to know the indication for NIV in acute exacerbation of CODP but is also important to recognize the indicators for NIV failure. It is crucial

to have markers to predict NIV failure, in order to provide more intensive treatment in the form of invasive mechanical ventilation or allow a more conservative approach, if palliation is the most appropriate strategy [1]. Some of those criteria are: persistent tachycardia and severe acidosis despite intensive NIV treatment, persisting vomiting, deterioration of mental status under NIV or agitation inadequality controlled with sedation, persistent inability to remove respiratory secretions, severe hemodynamic instability or severe ventricular or supraventricular arrhythmias [1].

Regarding long-term NIV, it was controversial to use in severe COPD patients. However, with the introduction of HINPPV and the randomised controlled trials showing positive effects with this mode of ventilation, it is currently indicated to treat chronic respiratory COPD patients and it is described by the most recent guidelines [5]. Until now, three larger randomised controlled studies have been published that show important benefits of HINPPV in severe COPD. Of particular note is the fact that these studies were performed under different circumstances [6].

The concept of HINPPV is using higher IPAP levels in addition to controlled ventilation aiming for maximal $PaCO_2$ reduction and showed that compliance and sleep quality were not worse with HINPPV and could even be better when compared to low-intensity NIV [6]. Initiating and following patients on chronic NIV at home may be a very attractive option both for patients and the healthcare system. Rapidly evolving techniques of telemedicine assist in the transfer of more care from the hospital to the home. However, the introduction of NIV should be at the hospital and can take up to 2 weeks because it is necessary to perform pressure escalation until normocapnia or maximum tolerance is reached and to control potential ventilator asynchronies.

The indication criteria to start long term NIV in COPD, according to the guidelines of the German Society for Pulmonology, are the symptoms that indicate chronic respiratory failure and reduced quality of life in COPD patients as well as one of these criteria (at least 1 criterion must be fulfilled): chronic daytime hypercapnia with $PaCO_2 \geq 50$ mmHg; nocturnal hypercapnia with $PaCO_2 \geq 55$ mmHg; stable daytime hypercapnia with 46–50 mmHg and a rise in $PTcCO_2$ to ≥ 10 mmHg during sleep; stable daytime hypercapnia with $PaCO_2$ 46–50 mmHg and at least 2 acute exacerbations accompanied by respiratory acidosis that required hospitalization within the last 12 months [7, 8].

Standing in opposition to the positive physiological and clinical effects of long-term mechanical ventilation are the side effects induced through either the ventilation interface or the ventilation therapy itself (Table 45.2). Poor compliance with medication intake are relative contraindications for home NIV.

Table 45.2 NIV side effects

Side effects	After 1 month (%)	After 12 months (%)
Dry throat	37	26
Facial pain	33	25
Fragmented sleep	27	20
Impaired nasal breathing	22	24
Abdominal bloating	22	13
Flatulence	19	17
Sleep impairment	13	16
Eye irritation	12	11
Nasal bleeding	7	2
Nausea	1	2
Facial pressure sores	1	0
Vomiting	0	0

Adapted from Winisch et al., Eur Respir J 2008

Key Teaching Points

- NIV is the primary treatment option for acute exacerbation of COPD with respiratory failure.
- Chronic domiciliary NIV treatment should be used in patients with severe and stable COPD with chronic respiratory failure.
- The most important criteria for the advent of long-term NIV are the presence of hypercapnia in combination with the typical symptoms of ventilatory failure, recurring exacerbations and the reduction in quality of life.
- The aim of the ventilation is to normalize $PaCO_2$; sufficiently high ventilation pressures are required to achieve this.

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Chapter 46
Non-invasive Ventilation in Adults with Cystic Fibrosis

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Abbreviations

ABG	Arterial blood gas
AHI	Apnoea hypopnoea index
CF	Cystic fibrosis
CPT	Chest physiotherapy
FEV_1	Forced expiratory volume in 1 s
FiO_2	Fraction of inspired oxygen
IMV	Invasive mechanical ventilation
IV	Intravenous
MDT	Multidisciplinary team
NIV	Non-invasive ventilation
ODI	Oxygen desaturation index
$tcCO_2$	Transcutaneous CO_2

46.1 Introduction

This review will present two typical scenarios in cystic fibrosis (CF). These representative cases will be used to discuss the practical aspects of using NIV, and will focus on the indications and risks of this technique when applied to patients with CF.

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Case 1

A 29-year old woman with cystic fibrosis presented to the outpatient clinic for a routine appointment. Respiratory symptoms were stable, but she complained of fragmented sleep due to waking up with severe headaches, not associated with signs of acute or chronic sinus disease.

She had moderate to severe lung disease (FEV_1 35–45%), was known for chronic colonisation with MRSA and for recurrent pulmonary exacerbations requiring intravenous (IV) antibiotics every 2 months. Upon examination, chest was clear and oxygen saturation at rest was 95% on room air. An arterial blood gas (ABG) confirmed mild hypoxaemia and normocapnia (pO_2 8.9 kPa, pCO_2 5.04 kPa). An outpatient overnight oximetry on room air showed an oxygen desaturation index (ODI) of 4 and mean SpO_2 at 81%.

In view of these results, urgent admission for oxygen titration was arranged. Nocturnal oxygen was started via a Venturi mask with a FiO_2 0.24 aiming to achieve a target SpO_2 higher than 94%. During oxygen titration, an assessment with transcutaneous CO_2 monitoring was performed (Sentec Digital Monitoring, Sentec, Switzerland). This highlighted an increased carbon dioxide overnight (mean $tcCO_2$ 7.19 kPa), with a pattern suggestive of REM-related hypoventilation. Morning ABG continued to show normocapnia and was in keeping with the CO_2 recorded on the transcutaneous monitoring.

Following a multi-disciplinary discussion involving the sleep medicine team, non-invasive ventilation was initiated via a domiciliary bilevel ventilator (Lumis VPAP 150 ST, Resmed) using an oro-nasal mask. Pressures were slowly up-titrated to ensure adequate volumes, symptoms resolution and control of nocturnal CO_2.

Eighteen months after this admission, the patient continues to be on nocturnal NIV, showing excellent compliance (average use 7 h/night). Despite deterioration of her overall clinical condition, leading to referral to lung transplantation, she is now symptoms-free during the night, reports good sleep with no headaches during sleep or upon waking. Morning arterial blood gas remains within normal limits. Recording from the ventilator show an AHI of 0 event/h and minimal leaks.

Case 2

A 28-year old woman with CF on the lung transplant waiting list due to severe lung disease (FEV_1 0.45 L, 15%) was urgently admitted to the hospital due to hypoxia secondary to a pulmonary exacerbation (SpO_2 79% on room air). She was known for chronic colonisation with *P. aeruginosa*, was on long-term domiciliary IV antibiotics and on ambulatory and nocturnal oxygen therapy. The patient was also on enteral nutrition via PEG over-night.

Blood gas on admission revealed mild acidosis (pH 7.34), and the patient was started on controlled oxygen therapy with target SpO_2 between 88% and 92%. Intravenous antibiotics were changed to broaden antibacterial cover, and nebulised bronchodilator therapy was started, leading to a reduction in symptoms. A repeated blood gas confirmed a raised level of CO_2, with a normalised pH (pH 7.38, pCO_2 7.08, pO_2 9.18 on 1 L/min oxygen therapy). Transcutaneous CO_2 monitoring

overnight showed persistently raised CO_2 at night-time (mean $tcCO_2$ 8.05 kPa, max $tcCO_2$ 9.45 kPa, mean SpO_2 91% on 1 L/min).

A multidisciplinary team meeting suggested a trial of NIV, followed by overnight use at home. A discussion with the patient revealed severe distress at the prospect of her requiring long-term oxygen therapy and NIV. To put this in context, NIV would have been added to an already significant burden of care including multiple oral medications, four nebulisers per day, two inhalers, three doses of IV antibiotics, chest physiotherapy (CPT), exercise and nocturnal feeding via PEG. The addition of NIV was perceived by the patient as a sign of further and rapid deterioration in her general health, and as a further reduction of the time available to her beyond her daily treatments. After long discussions focusing on the rationale, potential complications and expectations of NIV, including prolonging her lung transplant window, the patient accepted a trial.

NIV as bi-level ventilation was started during the daytime. The ventilator was set in S/T mode and a full-face mask was chosen. Due to her initial difficulty in tolerating NIV, a decision was made to start with low pressures (IPAP 10 cmH_2O and EPAP 3 cmH_2O), to be increased on the following days based on tolerance. After a few days of tolerating NIV, but never for the whole night, a morning ABG was repeated showing increased carbon dioxide at 8.18 kPa (pH 7.39, HCO_3^- 33.3).

The team worked closely with the patient to understand her difficulties in using the ventilator through the night. She reported that, on multiple occasions, she felt that the time for inspiration was not sufficient and that not enough volume of air was provided. Other times, she did not feel she was able to breath out. The trigger and expiratory cycling setting were changed, as well as the rise time. By adjusting the trigger sensitivity and shortening the rise time, the patient managed to better tolerate NIV, and pressure were also increased to IPAP 16 and EPAP 4. As a result, the patient could use the NIV the whole night while sleeping, and a significant improvement was noted in the repeated TOSCA (mean $tcCO_2$ 7.7 kPa) and morning blood gas (pH 7.43, pCO_2 6.4 kPa, pO_2 8.15 kPa, HCO_3^- 30.4 on 0.5 L). On discharge, she was advised to continue using NIV during sleep with 0.5 L O_2 entraining in the system.

Two months after discharge, a clinical review recorded a 3 kg weight loss over the period of 1 month, bringing her weight below what required for transplantation (weight 44 kg, BMI 16.6). Further discussion with the patient revealed a reduction in her overnight feeding via PEG due to the bloating caused by the NIV.

An admission was arranged to review the NIV and optimise the nutritional plan. Repeated TOSCA confirmed good control of CO_2 overnight (mean $tcCO_2$ 5.85) and morning ABG showed a compensated type 2 respiratory failure (pH 7.39, pCO_2 6.7 kPa, pO_2 8.12, HCO_3^- 28.5). The patient had good compliance to NIV, using it every night approximately 6–7 h. The analysis of NIV data showed an increase in air leaks from the mask. Upon discussion, it emerged that the patient had to tighten the mask significantly to avoid air leaks and this was causing head pain. Reviewing the mask, a replacement of head gear and cushions were provided, as they proved to be quite degraded despite the short time use. This was a consequence of applying face cream immediately before sleep. Dietetic review suggested intermittently

venting some air out of the PEG, to reduce the feeling of gastric fullness, continue feeding while on NIV, and to add some bolus feeding during daytime when napping. In addition, a trial of more compact feed was suggested to reduce the volume without affecting the calorie intake. This was well tolerated and led to weight gain.

After 6 months from initiation of NIV, the patient continues on treatment and tolerates NIV well. She is now able to sleep and feed while on NIV. She reports feeling more rested and refreshed in the morning.

46.2 Discussion

Cystic fibrosis is the most common autosomic recessive life-limiting genetic condition in the Caucasian population and affects approximately 80,000 individuals in the world. It is caused by the absence or diminished activity of CFTR, an apical epithelial anion channel, which leads to secretions to be viscous. This affects the function of multiple organs, making CF a multi-systemic condition; this notwithstanding, morbidity and mortality and the large majority of hospitalisations are due to lung involvement. Respiratory disease in CF is characterised by chronic endobronchial infection, recurrent pulmonary exacerbations and progressive lung damage with small- and large-airways disease (air trapping, hyperinflation and bronchiectasis).

Over the last few decades, there have been significant improvements in the treatment of CF, leading to prolonged survival. Treatment now includes oral and nebulised antibiotics and regular chest physiotherapy (CPT) for airways clearance, associated with IV antibiotics for pulmonary exacerbations, and CFTR modulators for specific genotypes. Nonetheless, many patients with CF still develop respiratory failure. With disease progressing, patients with CF develop resting hypoxemia, which can be associated with increased work of breathing and hypercapnia. Despite gas exchange abnormalities being a common feature among patients with CF and advanced lung disease, it has been shown that patients with CF can experience significant nocturnal hypoxemia and REM-related hypoventilation at any age, and when lung function and weight are still relatively preserved [1].

In the context of hypoxaemia in CF, oxygen therapy is often utilised, with recommendations and practice being extrapolated from other chronic lung diseases such as COPD. However, oxygen therapy, including long-term oxygen therapy (LTOT), has not been shown to improve the survival rate of patients with CF. The use of low-flow oxygen therapy overnight can improve hypoxaemia, but can lead to a marginal, and only occasionally clinically significant, increase in carbon dioxide levels [2]. In these cases, as well as in other scenarios, noninvasive ventilation is often used in clinical practice, despite the paucity of available evidence recommending its use. Only a limited number of studies have, in fact, assessed the impact of NIV in patients with CF [3], and it is plausible that physicians are behaving overly cautiously in applying this technique, in view of its potential contraindications in CF.

As with every other clinical situation, no approach is "one size fits all" when treating patients with CF. A careful patient selection is essential for ensuring the success of NIV treatment, and a patient-centred approach based on tailoring the level of respiratory support according to the severity of the respiratory failure and background patients' condition is of extreme importance. Whilst patients with hypoxaemia can receive supplemental oxygen alone, those with signs of increased work of breathing or frank hypercapnia will benefit from increased support with NIV.

46.2.1 Indications

Analyses performed on the UK CF registry [4] as well as a survey performed in France [5] have shown that 5–10% of patients with CF have received NIV at least once in their lifetime.

NIV is commenced for different reasons, including:

- Chest physiotherapy
- Hypoxemia with or without increased work of breathing
- Nocturnal hypoventilation
- Acute hypercapnic respiratory failure
- Chronic ventilatory failure

46.2.1.1 Chest Physiotherapy

Airways clearance is a key component of the essential treatments in CF. An effective technique is often tiring, and challenging to be performed, especially by individuals with severe lung disease who might have increased work of breathing and dyspnoea.

In these circumstances, NIV can be a valuable adjunct to CPT. A number of small studies have compared NIV to positive expiratory pressure (PEP) devices in patients with CF and demonstrated that NIV can reduce fatigue and respiratory rate and improve oxygenation. The use of NIV, however, does not lead to any change in the volume of sputum cleared. In addition, no data are available on the effects of using NIV on the exacerbation rate [3]. Therefore, while NIV cannot be recommended as first choice as an adjunct to airways clearance, the individual circumstances of each patients, including their own preferences, should always be taken into account.

46.2.1.2 Hypoxia

The most recent ATS/ERS guidelines on the use of NIV in the acute setting do not recommend the routine use of NIV in acute hypoxemic respiratory failure, in view of the conflicting results on its efficacy and the poor outcomes that can be associated

with this treatment. The range of respiratory support available for patients with acute hypoxemic respiratory failure includes conventional oxygen therapy, nasal high flow (NHF) and invasive mechanical ventilation. The ATS/ERS guidelines recommend that NIV can be trialed in selected cases, but delivered under close monitoring in the ICU.

No data are available on the use of NHF in CF to recommend the use of this treatment in patients who are hypoxemic but not responding to conventional oxygen therapy. The use of endotracheal intubation and IMV in severe acute hypoxemic respiratory failure in CF is historically associated with extremely poor outcomes. Patients with CF and advanced lung disease are in fact difficult to ventilate invasively due to severe airflow obstruction and the high burden of secretions. Due to the underlying physiology, individuals with CF are prone to progressive air trapping and intrinsic PEEP which can lead to ventilatory asynchrony, barotrauma and haemodynamic compromise [6]. As such, in clinical practice there is a tendency to avoid, if possible, IMV in CF by starting NIV early on in the development of hypoxemic failure.

Several reports suggest that—in clinical practice—NIV is used in patients with CF and hypoxia [7], as it can effectively improve hypoxemia by increasing alveolar ventilation and reducing the work of breathing by unloading respiratory muscles.

46.2.1.3 Nocturnal Desaturation and Hypoventilation

Poor-quality sleep is very common in CF, and can be a consequence of abnormal gas exchange, increased work of breathing and cough. Rarely, patients with CF experience frank sleep-disordered breathing in the form of central or obstructive sleep apnoea. On the other hand, individual with CF can present with nocturnal hypoxaemia and hypercapnia at various stages of disease progression [1].

As in the first case presented in this chapter, oxygen desaturation during sleep, whether persistent or intermittent, is often the first sign of respiratory failure in patients with CF. This might become apparent before daytime respiratory failure develops. In fact, REM related hypoventilation are a frequent occurrence in patients with CF at different stages of their disease [1].

Nocturnal oxygen therapy is used routinely in individuals with desaturation during sleep, but does not confer any significant clinical benefit [2]. Conversely, small RCTs have shown that NIV can improve sleep efficiency and alveolar ventilation. In addition, it has been suggested that overcoming REM-related hypoventilation might delay the onset of ventilatory failure during daytime [3]. Therefore, starting NIV in the context of nocturnal hypercapnia when daytime CO_2 retention is not yet apparent might be appropriate.

Routinely, patients with CF are monitored with overnight oximetry. A careful analysis of the oxygen level patterns could provide some indications on whether one suffers with hypoventilation. However, overnight oximetry is not a reliable tool to identify nocturnal hypoventilation. As nocturnal hypoventilation in conditions other than CF is associated with raised morning CO_2, pairing of evening and morning blood gases (arterial or capillary) has been suggested as a possible tool for

assessment. However, in CF daytime CO_2 can be within normal limit when patients have significant nocturnal hypoventilation, therefore transcutaneous monitoring systems of carbon dioxide should be used. In clinical practice, these are currently reserved to symptomatic patients only. Further studies are required to determine whether a routine use of this technique would provide any advantage over the use of overnight oximetry.

Individuals who have nocturnal hypoventilation, especially if symptomatic with headaches, fragmented sleep, etc., should be offered a trial of NIV. By providing assistance during the respiratory effort, NIV increases the tidal volume and reduce the work of breathing. This helps in controlling both oxygenation and CO_2 retention, and improving symptoms and quality of life.

46.2.1.4 Acute and Chronic Hypercapnic Respiratory Failure

NIV is a cornerstone therapy for acute hypercapnic respiratory failure, but only limited data are available on its use in this context in CF, and most indications are extrapolated from other respiratory conditions. Patients with CF who develop severe pulmonary exacerbation especially on a background of advanced lung disease can present with acute hypercapnic respiratory failure. To maximise the chances of success, NIV should be commenced early on in the course of acute hypercapnia and patients should be monitored closely. In such cases NIV will help stabilising patients and result in reduced CO_2, respiratory rate and improved symptoms.

It is important to note that many patients with severe lung disease who present with decompensated respiratory failure, might actually have acute on chronic ventilatory failure on the background of previously undiagnosed chronic hypercapnia (as in Case 2). It is therefore important to periodically monitor patients with severe lung disease secondary to CF with arterial blood gases to ensure early diagnosis of chronic ventilatory failure and initiation of NIV even in the long-term and domiciliary setting.

NIV is, in fact, used in patients with chronic respiratory failure to reduce symptoms of hypercapnia, to improve quality of life and in those waiting for lung transplant as a “bridge to lung transplantation”. In these cases of chronic ventilatory failure in patients with CF and on the transplant waiting list, NIV often does not reduce significantly the levels of carbon dioxide, but controls it and allows patients who are severely ill to spend time outside of hospital and lengthen their lung transplant window [8].

46.2.2 Contraindications and Complications of NIV in CF

Some situations pose a contraindication, either absolute or relative, to the use of NIV. These include agitation, being uncooperative, recent thoracic or upper abdomen surgery, facial trauma or severe upper airways disease, pneumothorax, haemoptysis and excessive secretions that are difficult to manage.

High secretion burden is a known characteristic of CF. Whilst the presence of excessive secretions is usually considered a relative contraindication to NIV, in CF this technique is often used to aid airway clearance as part of CPT, especially in the context of atelectasis. In addition, by adding active humidification to NIV the risk of mucus dehydration is reduced.

Spontaneous pneumothorax is a common complication in CF, especially among individuals with FEV_1 <40%. It has an annual incidence of 0.64%, affecting 1 patient in 167 every year, and 3.5% of individuals with CF will have at least one pneumothorax in their lifetime. More than half of those who have a pneumothorax will have a recurrence, which often leads to the need of talc pleurodesis. While an untreated acute pneumothorax is a contraindication to NIV, patients who have a chest drain in situ or have a history of pneumothorax can be treated with NIV. Similarly, up to 9% of patients with CF will have haemoptysis once in their life, with only a minority having massive episodes. Recent data from our Centre have shown a prevalence of 6% of both pneumothorax and moderate-massive haemoptysis among patients treated with NIV, and half of those who presented these complications were known for previous history [7].

46.2.3 Starting NIV in CF

46.2.3.1 General Considerations

While the decision to start NIV as an adjunct to CPT is mainly driven and suggested by the physiotherapist, the use of NIV due to acute or chronic respiratory failure should follow a MDT discussion. Physiotherapists, but also dieticians and psychologists need to be involved in the decision making from an early stage. NIV can in fact impact significantly on one's overall perception of their health, and can affect the patient's ability to continue with adequate calorie intake (as in Case 2).

NIV should be commenced during a hospital admission, to ensure the team and the patient have time to work together to titrate the NIV settings, find the best fitting mask and instruct the patient and family member on how to use the ventilator.

Before starting NIV, irrespective of the underlying reason to start the treatment, time should be spent with the patient to explain the rationale behind this treatment and its potential complications, in order to gain consent from the patient and reduce anxiety (as in Case 2). This is of the utmost importance, especially considering that patients with CF might be at increased risk of pneumothorax, haemoptysis and sinus disease exacerbations. Patients should have a chest-X-ray to rule out the presence of an untreated pneumothorax and to identify if any large bulla is present. Finally, for those individuals who are started on NIV due to acute or chronic respiratory failure, a clear discussion on the ceiling of treatment should take place.

46.2.3.2 Chest Physiotherapy

NIV as an adjunct to physiotherapy is usually started in hospital when patients are unwell or struggle to clear secretions due to increased work of breathing or severely compromised lung function. NIV is usually set in pressure-cycled modes. It can be delivered as IPPB (inspiratory positive pressure breathing—inspiratory pressure only), or bilevel ventilation. Bilevel ventilation would combine the advantage of reducing the risk of dynamic airway collapse by providing positive expiratory pressure with the unload of inspiratory muscle and increased tidal volume.

The goal of using NIV during airway clearance is to unload the respiratory muscles. It is therefore suggested to increase the inspiratory pressure or pressure support as tolerated. Back-up rate should not be used, as, together with high expiratory pressure, it could in fact interfere with forced expiration, coughing and expectoration. The choice of interface should be performed with the patient: while some might prefer a mouth-piece or a nasal mask for the ease of expectoration without the need of removing the mask, other might prefer an oro-nasal mask.

46.2.3.3 Hypoventilation and Respiratory Failure

NIV in patients with raised nocturnal CO_2 for acute respiratory failure is usually commenced following evidence that strategies aiming at delivering controlled oxygen therapy to target oxygen saturation between 88% and 92% have not been effective.

Studies have looked at the preferred way to start NIV in patients with CF, in terms of mode, settings, interfaces, but have provided no unequivocal results [3]. Bilevel ventilation in pressure cycled mode is usually commenced with positive expiratory pressure (PEEP or EPAP) at 4 or 5 cmH_2O and a pressure support as high as tolerated, to offload respiratory muscles and provide adequate alveolar ventilation.

Patients with CF do not have respiratory drive problems, therefore spontaneous or spontaneous/timed mode of ventilation are appropriate in this setting. Particular attention should be taken when setting the thresholds for the inspiratory triggering and the expiratory cycling. The inspiratory triggering should be sensitive enough to avoid these patients, who often have very low lung function, to feel suffocated at the beginning inspiration, but not too sensitive to cause auto-triggering in the event of coughing or leaks. Some ventilators allow to set the rise time, consisting in the interval time it takes to reach the inspiratory pressure at the beginning of inspiration. This should be carefully assessed based on patients' comfort and needs: a fast rise delivers more air by getting to the inspiratory pressure quickly, but it is often uncomfortable; on the other hand, a longer rise time might reduce the volume of air per cycle.

Whenever clinically possible, a gentle up-titration of the pressures and adjustment of the settings should be done, to allow sufficient time for patients to get used to the ventilator. In order to facilitate the use of NIV, patients who are not acutely unwell might be advised to start using the ventilator initially during the day for short periods of time. When starting to feel comfortable on NIV, appropriate treatment should be started by using the ventilator over-night. Clearly, such a slow process to adapt to NIV cannot be used in the context of acute respiratory acidosis.

NIV delivers air at high flow and with low relative humidity. Therefore, it is of the utmost importance to add an active humidification system as soon as the patient is being established on treatment. Humidification does in fact reduce the risks of drying of secretions and sputum retention.

The choice of interface should also be performed very carefully. While a French survey showed that some CF centres use custom-made masks [5], the vast majority of patients worldwide are started on treatment with commercially-available interfaces. The selection of the mask needs to be done together with the patient, finding the most suitable for each individual based on their facial characteristics, and way of breathing (mouth or nose breather). Patients should be adequately trained in position the mask to avoid having it on too tight, which can cause pressure ulcers, or too loose as it could cause leaks.

Finally, airway clearance remains a priority in patients with CF, especially when they are acutely unwell. Individuals who use NIV in the chronic setting might continue with their habitual CPT techniques rather than using NIV as an adjunct to physiotherapy. However, in those patients who are acutely unwell with respiratory acidosis or who in later stages of disease progression are NIV-dependent, airways clearance can be performed under NIV. In such cases, a change of setting might be required during CPT sessions. Similarly, inhaled treatment is often administered in patients with CF. While some drugs can be delivered via NIV using appropriate connectors for metered dose inhaler or T-piece for nebulisation, some nebulised antibiotics cannot be delivered via NIV. Therefore, in NIV-dependent patients a reassessment of treatment is needed if patients are not sufficiently stable to have breaks from NIV.

46.3 Conclusion

The use of NIV in patients with cystic fibrosis is supported by a physiological rationale, and is part of routine clinical practice in many scenarios. Due to the lack of robust evidence on the use of NIV in CF, there are no clinically-validated criteria to initiate treatment or strong recommendations on its preferred settings and modes. However, surveys and retrospective analyses on the use of NIV in patients with CF indicate that the vast majority of patients across the world are treated similarly, with NIV being started following MDT discussions and significant involvement of respiratory physiotherapists.

Further studies are needed to establish the appropriate timing to start NIV and its potential long-term care applications, and to investigate its impact on the rate of exacerbations and on disease progression.

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Chapter 47
Non Invasive Mechanical Ventilation in Idiopathic Pulmonary Fibrosis: A Clinical Case

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Abbreviations

%pred	Percent of predicted value
AE-IPF	Acute exacerbation of IPF
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
DLCO	Carbon monoxyde diffusion capacity
DNR	Do not resuscitate
ETI	Endotracheal intubation
FBS	Fiberoptic bronchoscopy
FEV1	Forced expiratory volume in the first second

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FiO_2	Inspired oxygen fraction
FM	Face-mask
FVC	Forced vital capacity
GCS	Glasgow Coma score
GORD	Gastro-oesophageal reflux disease
HRCT	High resolution computed tomography
ICU	Intensive care unit
ILD	Interstitial lung disease
IMV	Invasive mechanical ventilation
IPF	Idiopathic pulmonary fibrosis
MV	Mechanical ventilation
NIV	Noninvasive mechanical ventilation
O_2-LT	Oxygen long-term therapy
P/F	PaO_2/FiO_2: ratio of PaO_2 to fraction of inspired oxygen
$PaCO_2$	Carbon dioxide arterial pressure
PaO_2	Oxygen arterial pressure
PBW	Predicted body weight
PFTs	Pulmonary function tests
PSV	Pressure support ventilation
pts	Patient/s
RR	Respiratory rate
SaO_2	Arterial oxygen saturation
SB	Spontaneous breathing
TLC	Total lung capacity
UIP	Usual interstitial pneumonia
VAP	Ventilator-associated pneumonia
VILI	Ventilator-induced lung injury
Vt	Tidal volume
WOB	Work of breathing

47.1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe, progressive, chronic disease of unknown cause, seen primarily in older adults, with high mortality and morbidity. The median overall survival of IPF patients varies from 2 to 7 years in different studies, which is comparable to many malignant disorders [1]. Reductions in lung compliance occur early in IPF, and may be tightly correlated with the degree of lung fibrosis [2]. Although most IPF patients display a gradually progressive course, some subjects follow a relatively rapid decline. In this subset of subjects, mechanical ventilation (MV) may be required, in order to improve oxygenation, when high flow oxygen-therapy is not enough, and/or an increase in $PaCO_2$ levels and a pH shifting towards acidosis are also observed, and, as a palliative therapeutic option, to reduce patient discomfort, avoiding more aggressive approaches.

Clinical Case

A 70-year-old retired male (Body Mass Index: BMI = 28), was referred to our outpatient respiratory Unit for persistent chronic cough substantially not responsive to antibiotics and exertional shortness of breath, with, on examination, minimal bibasal, fine, end-expiratory crackles during auscultation. The patient was an exsmoker with a 25 pack-year smoking history and his past medical history included: chronic obstructive pulmonary disease (COPD), arterial hypertension, hypothyroidism and gastro-oesophageal reflux disease (GORD). He received an IPF diagnosis after initial pulmonary function tests (PFTs) (FVC 58%pred, FEV1 59%pred, TLC 59%pred, DLCO 45%pred), and a chest radiograph followed by a High Resolution Computed Tomography (HRCT) scan (Fig. 47.1). Serology testing was negative. The therapeutic plan involved initiation of pharmacological treatment with pirfenidone, a proton-pump inhibitor for GORD and diurnal (on exercise) and nocturnal oxygen-therapy. The patient was also vaccinated for influenza and pneumococci and referred to an outpatient rehabilitation centre. After less than 3 years of substantial stability of periodical clinical, radiological and functional examinations, patient underwent a progressive decline in lung function with worsening PFTs and HRCT scans. Subsequently to an upper respiratory tract infection, patient's dyspnoea suddenly worsened and he was hospitalized with a severe acute on chronic respiratory failure with critical hypoxemia: the ratio of oxygen arterial pressure (PaO_2) to fraction of inspired oxygen (PaO_2/FiO_2 = P/F) <150; mild hypercapnia (carbon dioxide arterial pressure: $PaCO_2$ = 57.4 mmHg) (Table 47.1). At a new HRCT the typical signs of IPF were confirmed (reticular pattern more prominent at the lungs bases, traction bronchiectasis and areas of honeycombing); in addition progressive bilateral shadowing of lung parenchyma was observed, with diffuse areas of ground-glass attenuation (Fig. 47.2). Because of his progressive dyspnoea and hypoxemia, in the three following days the patient was treated with an increasing

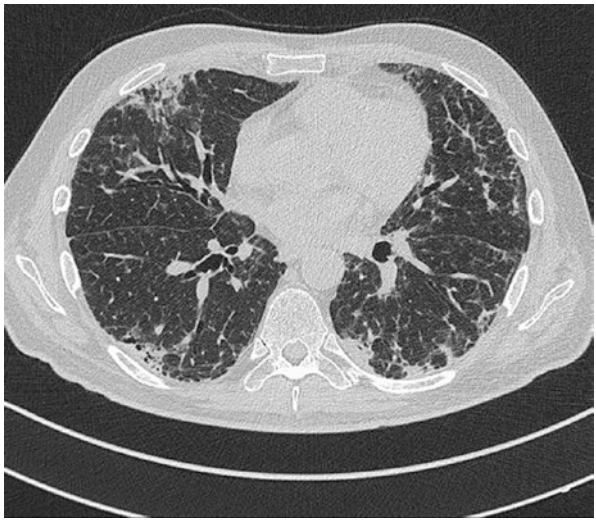

Fig. 47.1 Patient's baseline HRCT images, showing reduced lung volumes, diffuse fibrosis, architectural distortion with bronchiectasis juxtapleural honeycombing

Table 47.1 Evolution of pH, $PaCO_2$, PaO_2, RR, PaO_2/FiO_2, FiO_2, GCS during hospital day stay in a IPF patient treated with Non-Invasive Ventilation through Face Mask (NIV-FM) and Helmet (NIV-Helmet)

	pH	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	RR (b/min)	PaO_2/FiO_2	FiO_2 (%)	GCS
Admission	7.34	57.4	51	37	102	50	15
Day 2 (S.B.)	7.28	67	106	35	152	70	13
Day 3 (S.B.)	7.19	85.8	145	15	182	80	11
Day 4 (NIV-FM)	7.30	64.5	61.6	16	154	40	15
Day 5 (NIV-Helmet)	7.38	65.6	69.2	28	115	60	15
Day 10[a]	7.39	73	71	25	142	50	15
Day 20 (discharged)	7.39	70	74	25	148	50	15

[a]NIV stopped

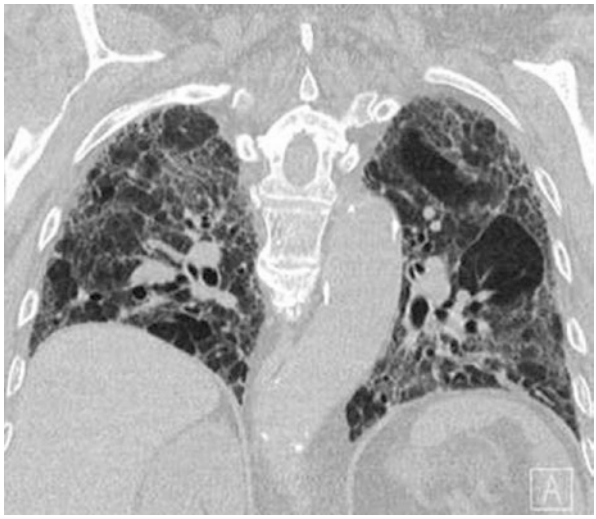

Fig. 47.2 Patient's HRCT during an acute exacerbation and worsening of the underlying disease, showing progressive fibrosis and honeycombing, bronchiectasis and widespread ground-glass opacities

oxygen-therapy flow: inspired oxygen fraction (FiO_2) up to 80%, high doses of methylprednisolone (240 mg/day for 3 days and then 120 mg/day), and antibiotics (Imipenem 1 g twice/day, Gentamicin 1 mg/kg three times a day). Fiberoptic bronchoscopy (FBS) was not performed due to critical clinical conditions. This oxygen therapy ameliorated P/F, but caused progressive hypercapnia and acidosis, with a light deterioration of mental status: Glasgow Coma score (GCS: 11) (Table 47.1); so that it was necessary to apply MV which started after discussing with the patient and his own caregivers, besides a short briefing among medical and nursing staff. Invasive mechanical ventilation (IMV) by means of endotracheal intubation (ETI) was excluded both due to a do not resuscitate (DNR) request previously made by the patient, and because of the poor prognosis. Delay in starting MV is to be ascribed to the above-mentioned circumstances. Therefore, in order to reduce respiratory muscles' fatigue, a first attempt of non-invasive ventilation (NIV) through a face-mask

(PerforMax Face Mask ©, Philips Respironics, Monza, Italy) was performed in assist/controlled mode: Tidal Volume (Vt) 450 cc (about 6.5 mL/kg predicted body weight (PBW), respiratory rate (RR) 16/m, positive end-expiratory pressure (PEEP) 5 cmH_2O, with a FiO_2 necessary to obtain an arterial oxygen saturation (SaO_2) > 90% through a ventilator (MonnalT75 © Air Liquide Medical Systems, Antony, France). About 6 h later, despite the improving in gas exchange, the face mask was replaced with a helmet (Castar-R Next ©; Starmed, Mirandola, Italy) in pressure support mode (PS 18 cmH_2O, PEEP 7 cmH_2O)—with a mean expired Tidal Volume (Vte) about 460 cc—because of bad patients' compliance. Pressure support, PEEP, and FiO_2 values were adjusted in order to obtain the best oxygenation and to reduce RR and were modified on the basis of blood gas data. After about 72 h of continuous ventilation, the patient was temporarily disconnected and NIV performed in 2/3 h periods alternated with about 1 h spontaneous breathing (SB) phase. In the following days SB phases became more and more prolonged; however several attempts to reduce FiO_2 without increasing dyspnoea failed. Ten days later NIV was definitively suspended, and, in about one further week, patient was discharged in long-term oxygen therapy (FiO_2 50% 24/24 h). He underwent two follow up visits after 15 and 45 days, than he missed the third evaluation due to a new episode of acute on chronic respiratory failure, refused a new hospitalization, and died at home in a few days.

47.2 Discussion

Acute exacerbation of IPF (AE-IPF)—often associated with prior smoking status, as in our case—is an acute worsening or development of dyspnoea, typically <1 month in duration, characterized by evidence of low P/F or a decrease in PaO_2, that may lead to severe hypoxemia requiring MV; evidence of new bilateral ground-glass opacity and/or consolidation on an usual interstitial pneumonia (UIP) pattern is present; clinical and physiological status deterioration is not explained by infection, cardiac failure, fluid overload, or pulmonary embolism [1].

47.3 Non-invasive Mechanical Ventilation in IPF

Current IPF guidelines recommend that the majority of patients with respiratory failure should not receive MV [1]. The reason of these indications lies in the fact that both the structural lung disease and the precipitating condition causing Acute Respiratory Failure (ARF) are irreversible and progressive [1]. Nevertheless "*Noninvasive positive pressure ventilation may be appropriate in some patients. In rare circumstances, mechanical ventilation may be appropriate as a bridge to lung transplantation*" [1]. In pts with *hypoxaemic respiratory failure* (*) NIV is used with the aims of improving oxygenation, facilitating ventilation, decreasing the work of breathing and dyspnoea, avoiding intubation, and reducing the complications associated with invasive mechanical ventilation [3]. A few studies have

evaluated the *outcome* of patients (pts) with AE-IPF receiving NIV in the intensive care unit (ICU) with important limitations: significant variation in disease severity; ventilatory pattern and setting; limited number of patients; single-centered and retrospective analysis; and use of heterogeneous drugs. Overall, the available data are consistent in stating that MV (neither IMV, nor NIV) can significantly modify the poor prognosis of these patients (high hospital mortality rate) [4].

(*) *Usually defined as significant hypoxaemia (arterial oxygen tension/inspiratory oxygen fraction ratio* (PaO_2/FiO_2) ≤ *200), tachypnoea (respiratory rate > 30–35 breaths/min) and a non-COPD diagnosis.*

47.4 Indication to Start MV in IPF

The American Thoracic Society guidelines on IPF, before the extensive use of protective mechanical ventilation to prevent ventilator-induced lung injury (VILI), recommended the use of MV only in a few selected patients developing severe AE-IPF [1]. Main indications to apply MV are: persistent hypoxemia although high flow oxygen rate in spontaneous breathing (SB) is applied; respiratory fatigue and hypoventilation with hypercapnic acidosis. The indication to begin NIV in IPF pts is generally based on the occurrence of moderate-to-severe dyspnoea, respiratory rate above 30 breaths/min, signs of increased work of breathing (WOB), and/or P/F < 200 not responding to the oxygen and pharmacological therapy [3].

The presence of "refractory" hypoxemia (PaO_2 < 50 mmHg under FiO_2: 50%) and tachypnea characterizes the end stages of the disease and causes ARF in about 40% of patients. Alveolar hypoventilation and hypercapnia is not a common finding in the first stage of ARF, probably due to respiratory muscle adaptation to the increased respiratory workload associated with lung stiffness [2]. In the late stage, the onset of respiratory fatigue may lead to CO_2 retention, as well as it occurs to IPF pts with associated COPD when a high flow oxygen-therapy in SB is administered (as in our case) [2].

47.5 Modes of MV

Different modes of ventilation (IMV or NIV) can be effective for treating hypoxemia with tachypnea (CPAP), hypoxemia with hypercapnia and hypoventilation (PSV) and respiratory fatigue (assisted/controlled ventilation).

NIV application, either by pressure support ventilation (PSV) or continuous positive airway pressure (CPAP), has been recognized as a mean to avoid ETI, reducing ventilator-associated pneumonia (VAP), and improving prognosis in selected cases of ARF. Antonelli et al. reported that when NIV was applied as first-line intervention in acute respiratory distress syndrome (ARDS), ETI could be avoided in 54% of treated patients in skilled centers, with less VAP and lower ICU mortality rate [5]. In most studies, the early NIV mode generally was CPAP; CPAP level was gradually increased with a range 8–10 cmH_2O. The onset of hypercapnia and respiratory

acidosis or high respiratory rate oblige to perform PSV. In the presence of acute alteration of consciousness (GCS <8), cardiac arrest, poor mask compliance, inability to clear secretions, or haemodynamic instability, IMV must be performed, unless the patient had previously declared a wish not to be resuscitated [3]. Criteria for the end of NIV use were defined by P/F > 200, respiratory rate < 20/min, and clinical improvement of radiological findings [3].

47.6 Interfaces: Helmet vs. Facial Mask

Several studies have evaluated the effectiveness of mask and helmet interfaces to deliver MV in IPF. The *helmet* is a transparent hood that covers the entire head of the patient and a soft collar adheres to the neck and ensures a sealed connection once the helmet is inflated. The *helmet* offers important advantages over the mask when used in CPAP mode: it is well tolerated, with a satisfactory environmental interaction for the patients; it can be applied to any patient regardless of differences in facial contour and its fixation system has low risks of cutaneous lesions This is important specially in hypoxemic patients, who need prolonged MV [6]. The use of helmet to provide NIV, allowing the patients to drink and expectorate, communicate, improving cooperation among caregivers and clearance of the airways, and reducing pressure ulcers, can improve patient compliance [6]. Conversely, helmet interface is less effective than *facial-masks* to deliver noninvasive PSV and to remove CO_2 [7]. High internal volume (12–15 L) interferes with circuit pressurization, trigger sensitivity, and WOB, thus facilitating rebreathing [8]. Note that an increasing in $PaCO_2$ is described while using single-limb-circuit bi-level ventilators, which do not have efficient exhalation systems [9]. In addition, the higher compliance of the helmet could delay ventilatory assistance and promote patient-ventilator asynchrony [10]. On the other hand, in patients with AE-IPF, there is a significant hyperactivation of the respiratory drive that cause an increase in RR and effort; this may be reduced by increasing the PS values [11]. Chiumello et al. evaluated the breathing pattern and WOB with helmet and face-masks during CPAP and PSV. During CPAP, there was no difference in breathing pattern and WOB; on the contrary, during PSV, the face-mask significantly reduced the WOB compared to the helmet [12]. As a matter of fact the helmet requires high PS values in the early phase of inspiration in order to pressurize his inner volume, as in our case [11]. This does cause a longer time to reach the required level of pressure support and can result in pt's less assistance, and asynchrony for a significantly longer inspiratory trigger delay [10]. Racca et al. also compared the helmet and face-mask during PSV with normal and high respiratory muscle load to simulate dyspnoeic patients. With normal muscle load, the breathing pattern and inspiratory effort was not different, but with high respiratory muscle load the inspiratory effort was significantly higher while applying the helmet than with the face-mask [8]. The need for high PS values leads to large transpulmonary pressures, reaching −30 to −40 cmH_2O, that may exacerbate lung injury if prolonged over time and can cause pneumothorax onset [13]. Furthermore the high pressures increase air leaks, gastric inflation and patient

intolerance [14]. Thus spontaneous breathing in patients with high respiratory drive could be more injurious [15]. These evidences define the recommendation to use helmet in CPAP mode and face-mask in PSV [8].

47.7 Predictors of MV Failure in IPF

In subjects who receive NIV, an APACHE II scores <20 and a non-continuous demand for NIV, show an higher survival compared to older subjects receiving IMV [16]. The presence of diffuse ILD ("widespread opacification") [17], a SAPS II >34 [18], and the inability to improve P/F after 1 h of NIV, later requiring to switch to IMV, have shown to correlate with a higher mortality [19, 20]. Also an early start of NIV during AE-IPF is associated with a better 30-day survival, improving patients' management and short-term outcomes [4, 21].As regard to MV setting in ILDs patients, since high PEEP has no effect on fibrotic, unrecruitable areas, thus promoting VILI, an high in-hospital mortality rate is referred when high levels of PEEP (>10 cmH_2O), and high Vt (>8 mL/kg) are applied [22].

47.8 Conclusions

Whereas IMV shows a high mortality, NIV may be an option in less severely ill patients with an APACHE II score <20. Since the extremely poor prognosis of IPF, NIV can be a viable option for the respiratory management of AE, although it seems not to be the only therapeutic strategy for AE-IPF pts [23].

Key Teaching Points

- MV should be performed early in IPF pts, as soon as no improvement in oxygenation is observed (P/F < 200), despite of high flow rate oxygen therapy.
- Do not wait for the onset of hypercapnia ($PaCO_2 \geq 50$ mmHg) to start MV.
- In the presence of hypercapnia use face-mask with low tidal volume and low PEEP.
- In pts who do not tolerate face-mask or when a prolonged ventilation period is expected, use helmet in CPAP mode, OR in PSV; use high level of PS and PEEP, only in the presence of hypercapnia.
- If NIV fails do not start invasive mechanical ventilation if the patient had previously declared a wish not to be resuscitated.
- Invasive mechanical ventilation should be performed at low tidal volume and low PEEP and be avoided in patients with advanced IPF.
- In patients with advanced IPF, NIV should be performed as a compassionate mean of an integrated palliative care.

Questions and Answers

1. Why in idiopathic pulmonary fibrosis (IPF) pts MV should be performed?

   (a) To improve the outcome
   (b) To treat the end-stage IPF
   (c) To improve oxygenation and to reduce dyspnoea
   (d) All of the above

   Answer: (c) To improve oxygenation and to reduce dyspnoea

2. When in IPF pts MV should be performed?

   (a) At the appearance of the symptoms (mainly dyspnoea), regardless of an improvement in oxygenation is waiting for.
   (b) At the onset of hypercapnia.
   (c) As soon as no improvement in oxygenation is observed, although oxygen therapy is administered at high flow rate.
   (d) Never, because MV does not improve the outcome.

   Answer: (c) As soon as no improvement in oxygenation is observed, although oxygen therapy is administered at high flow rate.

3. How in IPF pts MV should be performed?

   (a) By invasive mechanical ventilation (iMV) if non-invasive ventilation (NIV) fails.
   (b) By NIV-face-mask in the presence of hypercapnia (at least at the beginning of ventilator treatment).
   (c) By iMV at high tidal volume and high PEEP level particularly in patients with advanced IPF.
   (d) All of the above.

   Answer: (b) By NIV-face-mask in the presence of hypercapnia (at least at the beginning of ventilator treatment).

4. Which interface in IPF pts MV should be chosen?

   (a) Always face-mask, regardless of the patient compliance, even when a prolonged ventilation period is expected.
   (b) Always helmet, even if in the presence of hypercapnia, at the lowest pressure support and PEEP level.
   (c) Helmet in pts who do not tolerate face-mask or when a prolonged ventilation period is expected.
   (d) None of the above.

   Answer: (c) Helmet in pts who do not tolerate face-mask or when a prolonged ventilation period is expected.

5. Which of the following is correct?

   (a) Early NIV trial may facilitate the recognition of NIV-responders with a better short-term clinical outcome.

(b) NIV improves oxygenation in patients with pneumonia, but not in those with acute exacerbation (AE) IPF.
(c) NIV may be appropriate in some patients. In rare circumstances, mechanical ventilation may be appropriate as a bridge to lung transplantation.
(d) All of the above.

Answer: (d) All of the above.

6. In the end-of-life of IPF patients which of the following is correct?

(a) MV should only be used after discussion with patients and their caregivers regarding goals of care.
(b) Early integrated palliative care with advance care plan can improve the end-of-life care of IPF patients.
(c) NIV treatment during the last weeks of life can relieve dyspnoea as a palliative treatment.
(d) All of the above.

Answer: (d) All of the above.

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Chapter 48
Non Invasive Ventilation, Pulmonary Rehabilitation and Chest Physiotherapy-1

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Abbreviations

ABGA	Arterial blood gas analysis
ACBT	Active cycle of breathing technique
ALS	Amyotrophic lateral sclerosis
GPB	Glossopharyngeal breathing
HRQoL	Health Related Quality of Life
IC	Inspiratory capacity
ICU	Intensive care unit
IPPB	Intermittent positive pressure breathing
LTMV	Long term mechanical ventilation
LVR	Lung volume recruitment
MAC	Manual assisted cough
MI	Mechanical insufflations
MI-E	Mechanical insufflation-exsufflation

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NIV	Noninvasive ventilation
NMD	Neuromuscular disease
PCF	Peak cough flow
PR	Pulmonary rehabilitation
RF	Respiratory failure
ROM	Range of motion
RR	Respiratory rate
SMA	Spinal muscular atrophy
VC	Vital capacity

48.1 Introduction

Pulmonary rehabilitation (PR) is defined as a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of patients with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors. A multidisciplinary pulmonary rehabilitation program has become an important part of the treatment of both neuromuscular diseases (NMD) and chronic respiratory diseases. PR covers a wide range of multidisciplinary services designed to manage patients with respiratory problems and to cover other needs such as muscle changes, and emotional or social problems [1].

Most NMD are characterized by progressive muscle weakness, and it may affect respiratory muscles as well, leading to respiratory failure (RF). RF is one of the leading cause of mortality and morbidity in these patients, and it is not attributed to problems in the lung parenchyma but to the weakened, inspiratory and expiratory muscles both. This muscle weakness with related ineffective alveolar ventilation and difficult airway secretion clearance, lead to chronic respiratory insufficiency, as well as to potentially life-threatening problems [2]. The key factor in respiratory care of NMD, is managing the respiratory muscle fatigue. One of the main therapeutic intervention to support the respiratory muscle function and to increase life expectancy and health related quality of life (HRQoL) is long term mechanical ventilation (LTMV), delivered either invasively or noninvasively (non invasive mechanical ventilation-NIV). Today data clearly show that NIV improves survival and HRQoL in patients with NMD. Special attention should be focus on therapies that maintain and enhance chest wall mobility and aid in clearing secretions, both in the hospital and at home. Techniques in airway clearance are classified in two groups: the techniques to clear the proximal airways, which can improve pre-cough inspiration, expiratory flow or both, and peripheral airway clearance techniques, which improves mobilization of secretions towards the central airways from the periphery. PR in these patients is also one of the “everyday action”. This program must be focus both on skeletal and respiratory muscles. The most frequently NMD included

in PR programs are: Amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy, Becker muscular dystrophy, Myotonic muscular dystrophy [3].

48.2 Discussion

A 26 year-old woman with an underlying diagnosis of ALS, was hospitalized in intensive care unit (ICU)—Institute for pulmonary disease of Vojvodina due to respiratory failure. It was her first hospitalization in our Institute (June 2013).

Two years earlier, in 2011 she gave birth to a healthy child. Soon after that, she had first problems with muscle strength and mobilization. In 2012 at the Clinic for neurology, Clinical Centre of Vojvodina, she was diagnosed ALS. ALS is rapidly progressive NMD, and it is characterized by muscle impairment which worsens over months, results in death within a few years.

Our patient didn't has respiratory symptoms during the first year of her illness.

A 1 week history of general deterioration was described at presentation, with increased work of breathing, limited upper limb function and morning headaches. On the day of admission, she had SpO_2 about 30%, respiratory rate (RR) 28/min. Arterial blood gas analysis (ABGA) showed hypercapnic respiratory failure, PCO_2-10, 87; pH < 7.206. She was put on invasive mechanical ventilation.

After 48 h she was successfully weaned, and further ventilation support was given via NIV. NIV was administered via device VIVO 50 (Breas Medical AB, Sweden) with full face mask. According to BTS guidelines [4] the initial parameters were set on IPAP: 10 cmH_2O, EPAP: 5 cmH_2O; and I:E ratio 1:1. The values of IPAP and ERAR should be started low, and titrated gently. During the first 24 h, patient was on NIV for as much time as possible. Patient tolerated NIV very well, so we didn't change these parameters during first few days.

Data about ALS and NIV shows that patients who tolerate NIV has a longer survival than those who were unable to tolerate it, and tolerance was better in the group with a higher vital capacity (VC) and fewer bulbar symptoms, which has been seen in our patient [5].

ALS is the NMD for which NIV is more frequently prescribed than in the other NMD. NIV improves HRQoL of these patients and increases survival, especially in cases without bulbar involvement. Despite these advantages NIV cannot be performed in all NMD patients. In patients with cognitive impairment and patients with severe bulbar muscle palsy, NIV is contraindicated. At this stage of the disease, our patient had a mild bulbar dysfunction [6].

NIV via tracheostomy is a necessary consideration in situation of recurrent aspiration, inability to control arterial blood gas tensions or if there is severe problem like laryngospasm.

Today, there is still uncertainty about the right time for starting ventilation in these patients. Starting ventilation early could be beneficial for survival, although the evidence for that is not strong. However, lack of evidence is not evidence of the absence of effect [2].

Thanks to NIV, the number of patients with NMD who can participate in PR program is bigger day by day. We can divide them in two groups: (1) Patients on elective ventilation that will starts during a stable phase, and these are patients who have had no episodes of acute respiratory failure. In this group of patients NIV is performed at night, and patients may participate in conventional PR program. (2) Patients on ventilation that is started during an episode of acute respiratory failure. These patients are mostly referred from ICU, and a large part of them are ventilated via tracheotomy. The aim of PR in such cases is to prepare them to return to the community and participate in recreational and social activities. The last but not the least is to instruct patients caregivers on how to provide care [3].

During these first few days, early rehabilitation program was conducted, twice a day. At this point, one of the main goal of physical therapy for NMD patients is mobilization and prevention of skeletal muscle stiffness and spasticity through passive mobilization of all joints and muscles. The other goals of this program are to ensure proper functioning of the diaphragm and to facilitate the elimination of secretions. Diaphragmatic breathing is used to optimize the function of the diaphragm, because its task is to generate enough power to overcome airway resistance and the elastic recoil of the lungs and chest wall [6]. Breathing exercise can be used as well, to increase secretion removal. The most common exercise that is used is active cycle of breathing technique (ACBT) or an autogenic drainage. ACBT consists of three parts: breathing (diaphragmatic) control, thoracic expansion exercises and the forced expiration technique. Every cycle must end with forced expiration technique or “huff”. “Huff” starts with medium sized breath in, which is followed by a fast breath out through an open glottis, using the thoracic and abdomen muscles in order to force the breath out. However this is only possible in patients who have preserved respiratory muscle function. In patients with weak respiratory muscles or who are ventilator depend, we have to modify ACBT [7].

In most NMD, with the exception of spinal muscular atrophy (SMA), both inspiratory and expiratory muscle strength deteriorates in parallel. Such weakened respiratory muscles can neither expand them to its maximal capacity nor collapse the lung to its minimal residual volume. These changes in compliance can cause serious problems by reducing the capacity to cough and clear secretions. It can also results in reduced inspiratory capacity (IC), and over the time, breathing at lower lung volumes is hypothesized to be the main reason that stiffen chest wall and lung tissue as well, because the respiratory system is not expanded through its full range of movement [8].

Coughing is the one of the most protective mechanisms in our body that clears out airway secretions to prevent further complications such as pneumonia and atelectasis. Assessment of cough in patients with NMD has traditionally centred on the measurement of peak cough flow (PCF). Coughing capacity—PCF can be measured by instructing the person to cough as forcefully as possible through the peak flow

meter. Techniques that are used for augmenting both cough and IC beyond the value that is achievable with spontaneous breathing, we can categorize as lung volume recruitment (LVR), glossopharyngeal breathing (GPB), manual assisted cough (MAC), intermittent positive pressure breathing (IPPB), mechanical insufflations (MI) delivered via NIV or the insufflations component of an MI-exsufflation device (MI-E). All of these techniques are called *assisted inflation techniques*. Which of these techniques will be used to stimulate coughing and the elimination of secretions will depend on the type and the stage of disease [8]. The most common techniques that are used in these patients are: glossopharyngeal breathing, manually assisted coughing techniques and mechanical in-exsufflation. The greatest improvement in PCF, however, is seen when a combination of these techniques is used. Cough augmentation techniques will be effective in patients who have reduced PCF. When PCF drops below 270 L/min mechanical and manual assisted coughing are recommended. If the value of PCF is below 160 L/min patients are more likely to benefit from a combination of techniques or a mechanical insufflations-exsufflation device (cough assist) (Fig. 48.1) [5].

One recent study of 48 patients with ALS/NMD found a PCF cut-off value of 166 L/min to be the best predictor of an ineffective cough, defined as inability to clear secretions. There is consensus among the many studies that have examined immediate effect of interventions on PCF in NMD, that both inspiratory and expiratory interventions can augment cough compared to a spontaneous, unassisted effort [8].

The first measurement of PCF in our patient was on the third day of hospitalization. PCF was 145 L/min. Because of this low value we decided to start pulmonary rehabilitation, precisely chest physiotherapy, with using MI-E device (cough assist).

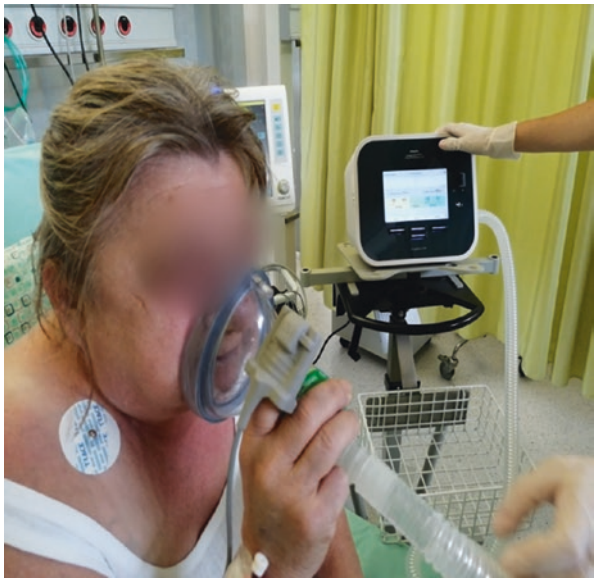

Fig. 48.1 The technique of mechanical in-exsufflation

Besides the value of PCF below 160 L/min, another indication for using this device is situation when manually assisted coughing is not enough. In this case, we used the combination of MI-E with an abdominal thrust, which is called *mechanically assisted cough*. Cough assist device delivers deep insufflations followed immediately by deep exsufflations. Inspiratory-expiratory pressures of 40 to -40 cmH_2O, delivered via oronasal interface or adult tracheotomy with the cuff inflated are the most common and most effective modules. We use Cough assist E 70 (Philips Respironics, Pittsburgh, PA, USA).

In this situation, when patient is already on NIV, we start with the insufflations/exsufflation pressure 5–10 cmH_2O greater than the same parameters on NIV device. These pressures were delivered via an oronasal mask. The initial values of positive and negative pressures were 15 cmH_2O for insufflation, and 10 cmH_2O for exsufflation pressure. After 2 days we increase expiratory pressure for 5 cmH_2O, and patient started to expectorate better, so we decided not to change parameters in next 5 days.

There has always been debate about what settings to use. We think that patients who are extremely weak with a low and even with an unrecordable PCF, required high pressures. Moreover, when patients are actually unwell and weaker, it is likely that the pressures on the device will should be increased, or combined with MAC. We should be aware that use of cough assist cannot help in avoiding tracheotomy, if bulbar innervations is inadequate, as in advanced bulbar ALS [5].

During these 5 days our patient had every day rehabilitation, which included exercises for skeletal muscles (active mobilization, strength and stretch exercise), cough assist, breathing exercises-ACBT, postural drainage (gravity assisted positioning), vibrations and percussions (Fig. 48.2).

Skeletal muscle weakness is the ultimate cause of most clinical problems associated with NMD. In slowly progressive NMD, a 12-week moderate-resistance training (training at 30% of maximum isometric force) showed improvements in muscle strength, without any notable deleterious effects. A 12-week high-resistance training (training at the maximum weight a patient could lift 12 times) showed no benefit

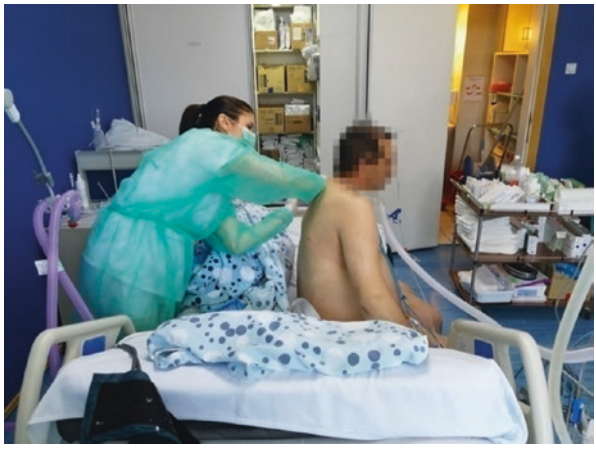

Fig. 48.2 Technique of chest physiotherapy; percussions

over the moderate-resistance program, but some evidence of overwork weakness was found in some patients. In rapidly progressive NMD, the risk of overwork weakness and exercise-induced muscle injury is much greater. In these patients, exercise should be prescribed with caution.

Last three actions are part of the conventional airway clearance techniques, and they may be effective in clearing secretions in non-cooperative patients. These techniques can easily be performed in combination with NIV. Airway clearance should be performed in NMD patients when their SpO_2 is <95% on room air [5].

Although, chest percussions and vibrations can help us to mobilize airway secretions, remember they cannot substitute coughing.

As she got better day by day, after that period of first 10 days, we repeated PCF, and its value showed improvement, 180 L/min. Peak cough flow with lung-volume recruitment >180 L/min is associated with a longer survival. That was the reason why we stopped with cough assist and start with glossopharyngeal breathing (GPB) and manual assisted coughing (MAC). GPB is the act of the glottis taking air and propelling it into the lungs. One breath usually consists of six to nine gulps of 60–100 mL each. This technique can be used by patients to accumulate consecutive volumes of air for lung volume recruitment, and to increase their VC to achieve a higher PCF. MAC increases expiratory airflow by either compression of the chest wall or abdomen. Synchronous compression of abdomen with the patient's own cough effort causes a sudden increase in abdominal pressure. This action further causes the abdominal contents to push the diaphragm upwards increasing expiratory airflow, which assist in moving airway secretions towards the mouth. MAC requires a cooperative patient and good coordination between the patient and caregiver [2].

All of these techniques (including previously mentioned), we delivered to our patient twice to three times a day, every day until she was discharged from the hospital. Our patient was very cooperative, she improved range of motion (ROM) in upper limbs, her mobilization, muscle strength in all limbs and ROM of chest wall, as well. On the last day of hospitalization her ABGA has shown a reduction in PCO_2-7.01; pH value was 7.37; and RR was 14.

Her family purchased the new NIV device for home use. She got this device on the 12th day of hospitalization. It was Vivo 40 (Breas Medical, AB, Sweden). The parameters on this device was set on-IPAP 12 cmH_2O, and EPAP 5 cmH_2O.

Patient was instigated to continue with nocturnal use of NIV, for next 1-month period, till the first follow-up visit. She was also adviced to perform every day strength and stretch exercise, and breathing exercise as well.

She was discharged after 16 days of hospitalization.

Latest data shows that active implementation of a pulmonary rehabilitation program and NIV can help in relieving patients' respiratory symptoms, preventing possible complications and improving HRQoL [8]. Patients with NMD are considered as those in greater need of pulmonary rehabilitation, and they are often overlooked due to preoccupation with the nature of their disease. People, and even doctors, think that these patients are untreatable. That is so wrong, because their disease is difficult, and yes, their disease is incurable but their symptoms are treatable.

At the end, we have to admit that the recent advanced in respiratory care of NMD, which leads to prolonged survival by many years and improved HRQoL in a

Key Teaching Points
The following clinical implications should be noted:

- NIV improves the quality of life in patients with NMD, including ALS.
- NIV increases survival in patients with ALS, especially in cases without bulbar involvement.
- NIV and pulmonary rehabilitation can improve symptoms caused by respiratory muscles, symptoms are treatable although their disease is incurable.
- The management of secretions is crucial in the care of patients with ALS.

previously lethal condition, should be considered as a major success in medicine. Certainly, all of that could not be possible without the sacrifice of the patient's family and caregivers as well. All of them have changed from traditional non interventional to a more aggressive and supportive approach.

Questions and Answers

1. For which neuromuscular disease is NIV the most frequently prescribed:

   (a) Myotonic muscular dystrophy
   (b) Becker muscular dystrophy
   (c) Amyotrophic lateral sclerosis
   (d) Parkinson's disease
   (e) Duchenne muscular dystrophy

   Answer: (c) Amyotrophic lateral sclerosis
2. Peak cough flow (PCF) below 160 L/min is the start point for using:

   (a) Glossopharyngeal breathing (GPB)
   (b) Forced expiration technique ("huff")
   (c) Postural drainage (gravity assisted positioning)
   (d) Active cycle of breathing technique (ACBT)
   (e) Mechanical insufflations-exsufflation device (cough assist)

   Answer: (e) Mechanical insufflations-exsufflation device (cough assist)
3. When patients is already on NIV, starting parameters (the most common values) for insufflations/exsufflations pressures are:

   (a) The same as the pressures settings on NIV device
   (b) 20 cmH_2O greater than pressures settings on NIV device
   (c) 5–10 cmH_2O lower than pressures settings on NIV device
   (d) 5–10 cm greater than pressures settings on NIV device
   (e) 40 cmH_2O greater than pressures settings on NIV device

   Answer: (d) 5–10 cm greater than pressures settings on NIV device

4. What techniques of pulmonary rehabilitation for clearing secretion can be used in non-cooperative patients:
   (a) Mechanical insufflations-exsufflation device (cough assist)
   (b) Postural drainage, vibrations and percussion
   (c) Breathing exercise and cough assist
   (d) Active mobilisation and cough assist
   (e) Glossopharyngeal breathing and postural drainage

   Answer: (b) Postural drainage, vibrations and percussion

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Chapter 49
Non Invasive Ventilation, Pulmonary Rehabilitation and Chest Physiotherapy-2

Laura D. Ciobanu

Abbreviations

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
APCV	Assist pressure control ventilation
BiPAP	Bi-level positive airway pressure
CHRF	Chronic hypercapnic respiratory failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
FEV1	Forced expiratory volume in 1 s
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	Health-related quality of life
LTOT	Long-term oxygen therapy
NIOV	Noninvasive "open" ventilation
NIV	Noninvasive ventilation
NPPV	Noninvasive positive pressure ventilation
NPV	Negative pressure ventilation
PAP	Positive airway pressure
PAV	Proportional assist ventilation
pNIV	Portable noninvasive ventilation
PR	Pulmonary rehabilitation
SpO_2	Pulsoximetric arterial oxygen saturation

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49.1 Brief Introduction to the Concept of Pulmonary Rehabilitation

Pulmonary rehabilitation is described as a "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease, and to promote the long-term adherence to health-enhancing behaviours" [1]. The main goal for PR programmes is to enhance physical activity towards normal levels, to return the patient to the highest possible capacity in order to achieve the maximum level of independence and functioning in the community [2]. Despite being a cost-beneficial intervention, only approximately two-fifth of chronic respiratory patients have been informed by their health care provider about PR and its positive results. This might be an explanation why <2% of the patients are referred to one of the available PR programmes.

The main body of evidences comes from COPD patients, but PR is effective in many others obstructive and restrictive conditions. COPD patients are referred to PR due to persistent respiratory symptoms and/or limited activities of daily living and an unsatisfactory response to the medical treatment offered in primary care. It is recommended to all symptomatic patients, regardless the severity of disease, but recommendations are stronger in moderate-to-severe COPD. PR is addressed to stable patients, after an acute exacerbation, in intensive care unit, in the perioperative period after a lung transplantation, before and after lung cancer surgery, and before endobronchial lung volume reduction [3]. It can be offered in a hospital-based outpatient setting, in an inpatient setting (Fig. 49.1), a community-based setting and at the patient home [1].

Exercise training is the cornerstone in PR programmes and the best approach for increasing muscle strength, decreasing symptoms, reducing mood abnormalities, improving cardiovascular function and the motivation for physical activity [3].

Fig. 49.1 The gym hall for inpatients in our hospital

Fig. 49.2 Devices for inspiratory muscle training, improving muscle endurance and strength

Exercise training (upper and lower limb endurance aerobic exercise, resistance training, flexibility training, inspiratory muscle training—Fig. 49.2) should be completed by education (information about disease, bronchial hygiene and mobilization of secretions by cough managing, breathing techniques, relaxation, energy conservation, stress management, coping techniques and education of relatives), psychological and nutritional support [3, 4]. Typical modes of aerobic exercise are walking or cycling. In stable COPD patients, a combination of endurance and resistance training should be performed to maximize improvement in limb muscle function and whole-body exercise capacity [1].

Breathing training consists of purse-lipped, controlled and diaphragmatic breathing [5]. Airway clearance during chest infections through intensive physiotherapy consists in a modified active cycle of breathing technique accompanied by physical procedures such as percussions and shaking, and manually assisted cough; however, standard or intensive physiotherapy might be tiring for the patients and can precipitate episodic oxygen desaturation [6]. There are some cough augmentation techniques like: cough after inspiration supported by a NIV ventilator type bi-level positive airway pressure (BiPAP); exsufflation-assisted cough with delivery of negative pressure initiated manually at the end of inspiration; insufflation (given manually during inspiratory phase) and exsufflation-assisted cough with delivery of the negative pressure immediately preceding the cough effort via a facial mask [6].

49.2 Noninvasive Ventilation: Why to Think About It?

In advanced stages of respiratory diseases, patients frequently develop chronic hypercapnic respiratory failure (CHRF). NIV is the standard treatment for patients with CHRF due to COPD and restrictive lung disease, and a major indication for home mechanical ventilation (HMV) in Europe [7]. COPD patients benefit from

NIV once they have COPD GOLD stage III or IV and CHRF (arterial partial pressure for carbon dioxide >6.0 kPa) in a stable clinical condition. In patients with CHRF, long-term noninvasive positive pressure ventilation (NPPV) improves important physiological variables such as blood gases and lung hyperinflation. Results from clinical studies have shown that NPPV improves exercise capacity, exercise-related dyspnoea, pulmonary cachexia, sleep quality and health-related quality of life (QRQoL). Moreover, NPPV treatment might be associated with fewer hospital admission and lower overall treatment costs [8]. The best results with long-term NPPV have been noted in studies using more intensive forms of NPPV, with higher inspiratory pressures and high back-up frequencies that have improved or even normalised hypercapnia [7]. They have been reported two disadvantages of high-intensity NPPV: patients need more days in hospital to acclimatise and there is an increased expiratory leakage comparing to low-intensity NPPV. In high-pressure NIV may develop a haemodynamic compromise due to reduced venous return from high intra-thoracic pressures. These factors may affect results of NIV in NIV-naïve patients or in those with compromised cardiac performance.

It was hypothesized that a substantial reduction in hypercapnia may lead to the benefits of NIV, including survival, but this is not entirely true. A survival benefit was shown without a change in daytime hypercapnia, and not all studies showing a reduction in hypercapnia could demonstrate improvements in survival [7]; consecutively, chronic NIV may lead to above mentioned benefits through different mechanisms [7] like resting the respiratory muscles at night [3]. Moreover, NIV might prevent exacerbations in a subgroup of frail severe persistent hypercapnic patients, an effect that might also affect survival [7]. Nevertheless, it is still unclear how and why chronic NIV improves survival [7]. Recent pulmonary rehabilitation BTS guidelines suggest that NIV during exercise training should be offered to patients who already receive domiciliary NIV [4]. With increased use of high-pressure NIV for home therapy, the use of NIV during PR would become more feasible.

Köhnlein et al. have conducted a study in 2014 with the intention to assess survival in chronic hypercapnic COPD patients using NPPV (ResMed, Martinsried, Germany; Weinmann, Hamburg, Germany; and Tyco Healthcare, Neuburg, Germany ventilators) in addition to standard treatment for at least 6 h at night and anytime during daytime. The results provided evidence that NPPV addition in a group of stable COPD patients reduces hypercapnia, improves overall survival, exercise capacity and HRQoL over 1 year when comparing with guideline-oriented COPD treatment without NPPV [8]. In the study conducted by Raveling et al. in 2018, NIV was initiated in COPD patients in a stable condition and after an episode of acute respiratory failure using BiPAP (Synchrony and A30 Respironics, Murrysville, PA, USA) [7]. After 3 months results have shown that a higher body mass index and forced expiratory volume in 1 s, a lower bicarbonate before NIV initiation, younger age and NIV initiated in stable conditions were independently associated with better survival [7]. A higher level of bicarbonate before NIV initiation, the use of higher inspiratory ventilatory pressures, the presence of anxiety

symptoms, and NIV initiated after an exacerbation compared with NIV initiated in stable disease were associated with a better reduction in arterial partial pressure of carbon dioxide, as NPPV improves respiratory centre's sensitivity to carbon dioxide.

49.3 Types of NIV Useful in Association with Pulmonary Rehabilitation

49.3.1 Negative Airway Pressure Devices

Techniques to deliver ventilatory support have developed in nineteenth century and became popular during the polio epidemic in early twentieth century [9]. There are two types of negative pressure ventilation (NPV). One is tank ventilation that provides intermittent sub-atmospheric pressure around the whole body. The other one is cuirass ventilator that provides negative pressure around the chest only and creates a gradient pressure between thorax and lower body, which may increase intrathoracic venous return, right cardiac output and lung perfusion [5]. Breathing pattern undergoing cuirass ventilator is a real approximation of the normal physiological breathing, with more natural distribution of air in the lungs. Hence, NPV does not restrict the patients' activities and they can be more comfortable [5].

49.3.2 Positive Airway Pressure Devices

Positive airway pressure (PAP) devices offer today a consistent solution; they unload respiratory system and increase its capacity, with a consecutive reduction in neural respiratory drive and breathlessness [9]. Limitations of negative pressure devices promoted development of PAP devices to deliver continuous positive airway pressure (CPAP) and bi-level pressure support. CPAP delivers a fixed level of positive airway pressure during the whole respiratory cycle [9].

Bi-level pressure support, known as NIV, delivers a positive pressure during expiration and a higher positive pressure during inspiration to support inspiratory effort. PAP devices deliver respiratory support through oronasal or nasal mask interfaces, and not through endotracheal tube or tracheostomy, thus being considered as non-invasive devices [9]. PAP devices have well established benefits in acute and chronic respiratory failure in a large range of conditions, including COPD, obstructive sleep apnoea, obesity-related respiratory failure, progressive neuromuscular disease and cardiogenic pulmonary oedema, through restoring respiratory muscles load-capacity balance, promoting alveolar ventilation and improving gas exchange [9].

49.3.3 Non-invasive Ventilation as an Adjunct to Pulmonary Rehabilitation

NIV may be used as an adjunctive therapy to PR that unloads the respiratory muscles with the aim to increase the intensity of exercise training in selected patients with severe chronic respiratory diseases who have a suboptimal response to exercise [1]. The benefits appear to be more marked in patients with severe COPD, and higher tolerated positive pressure may lead to greater improvements, with improved exercise performance and reduced breathlessness [1]. COPD is characterized by recurrent exacerbations leading to episodes of severe clinical deterioration requiring hospitalization and ventilatory support. Persistent hypercapnia after an episode of acute exacerbation of COPD (AECOPD) is associated with excess mortality and early hospitalization. That means extra costs for caring same patients; therefore, it is an urgent need for measures to prevent readmissions in this area. Non-invasive PAP interventions applied during exercise, at rest and in the end-of-life setting, can be used to restore the balance of respiratory muscle load and capacity, with reducing neural respiratory drive and dyspnoea [9]. Table 49.1 summarises the use of NIV and chest physiotherapy along to PR in different stages of COPD.

Long-term oxygen therapy (LTOT) and non-invasive ventilation (NIV) are potentially valuable therapeutic options, especially in COPD patients with severe lung hyperinflation and exercise-induced desaturation noticed during exercise training as part of a comprehensive PR programme [1]. For patients with COPD and chronic hypoxia LTOT is crucial in terms of improving survival. In these cases, use of supplemental oxygen during exercise may be associated with reduced exertional pulsoximetric arterial oxygen saturation (SpO_2) and increased exercise performance. The addition of nasal positive pressure ventilation to LTOT in hypercapnic patients has been shown to improve arterial blood gases, dyspnoea, quality of life and survival. Oxygen supplementation in moderate to severe COPD patients can acutely increase exercise capacity, the amount of training they can undertake, and thus the benefits of PR. Alleviation at a certain extend of ventilatory limitation will allow greater cardiac and muscular stress, with further beneficial effects on stroke volume and oxygen extraction [4]. SpO_2 should be >88% during exercise; if SpO_2 is

Table 49.1 Pulmonary rehabilitation in COPD patients at different stages of disease. NIV used as an adjunct and chest physiotherapy

COPD	Pulmonary rehabilitation	Noninvasive ventilation	Chest physiotherapy
Stable COPD	Outpatients, inpatients, community-based setting, at home	CPAP, pNIV, PAV, NIOV, APCV	Airway clearance during chest infections
AECOPD	Inpatients	CPAP	Airway clearance and cough assistance
Terminal COPD	Palliative care services	CPAP	Airway clearance, palliation of dyspnoea, oxygen therapy

≤88% while breathing room air, supplemental oxygen should be used to maintain SpO_2 at >88% or >90% according to different authors [5].

49.3.4 Pulmonary Rehabilitation and Noninvasive Ventilation in Acute Exacerbation of COPD

COPD exacerbations are known to deteriorate life quality, to enhance disease progression and increase mortality [3]. Acute respiratory failure leading to acute or acute-on-chronic respiratory acidosis, develops when the respiratory muscles fall to achieve adequate alveolar ventilation despite high levels of diaphragmatic activity [10] and when appear alterations in central ventilatory control [8]. The official American Thoracic Society/European Respiratory Society clinical practice guidelines suggest to consider bi-level NIV in patients with AECOPD in three clinical settings: to prevent acute respiratory acidosis; to prevent endotracheal intubation and invasive mechanical ventilation in patients with mild to moderate acidosis and respiratory distress; and as an alternative to invasive ventilation in patients with severe acidosis and more severe respiratory distress [10]. Bi-level NIV is known to improve related symptoms, and to reduce the length of hospital stay, intubation rate and mortality rate [10]. Applying of noninvasive positive pressure ventilation in these cases will correct acute respiratory acidosis and relieve dyspnoea, will lower the rate of ventilatory associated pneumonia and extend hospital stays, that often results in mortality. NPPV is a life support intervention that does not require sedation, allowing the patients to communicate with the family and caregivers during the interruptions, to eat, to drink and to take decisions regarding their care. The outcomes were more favourable in COPD patients with strong cough and awake.

British Thoracic Society recommends the initiation of early PR within 1 month of hospital discharge after exacerbation, consisting of a minimum of twice a week supervised session, lasting between 6 and 12 weeks [4]. PR can be delivered late post-exacerbation, that is 6 months after COPD exacerbations, the majority flare ups requiring hospitalisation or hospital at home services [4]. More recently, a reliable group of experts have strongly recommended the initiation of PR during and shortly after an exacerbation-related hospitalisation, as this results in clinically relevant improvements in exercise performance, lower-limb muscle function, balance and quality of life compared to usual care [2]. The integrated peri-exacerbation PR programme must be tailored carefully to the patients' physical and psychological status, making it safe and effective for patients with a spectrum of illnesses, even in mechanically ventilated, critically ill patients [2]. NIV can improve exercise tolerance with less desaturation in patients admitted to hospital with an exacerbation of chronic respiratory disease, but participation is limited in older populations; it is more suitable in younger patients with fewer comorbidities.

Early mobilisation and exercise therapy within the intensive care unit target the goals of enhancing the functional outcome, health-related quality of life and

reducing of healthcare utilization [2]. In these cases, specifically, exercise should combine progressive muscle resistance and aerobic training [3]. Moss et al. proposed a graduate manner to increase the physical training programme, for 30 min while in intensive care unit up to 60 min when the patient was in a regular ward, in an outpatient setting or at home, with five components: techniques for proper breathing during exercise; progressive range of motion; therapeutic exercises addressed to the muscle strength; exercises designed to improve core mobility and strength; and functional mobility retraining including bed mobility, transfers, gait and balance [11]. Unfortunately, an intensive physical therapy programme did not improve long-term physical functioning compared with a standard-of-care physical therapy programme [11].

49.3.5 Pulmonary Rehabilitation and Noninvasive Ventilation in Stable COPD Patients

Exercise capacity is significantly reduced in patients with COPD and chronic hypercapnia. Reduced ventilatory capacity combined with an increased ventilatory load leads to intolerable dyspnoea at low level of exercise. However, severe COPD patients have strong recommendations to follow a PR course and to perform a specific exercise training, but these individuals have difficulties in performing exercise training at a sufficiently high training intensity to achieve physiological and clinical benefits due to severe breathlessness. Therefore, NIV was proposed has an adjunct to PR in patients with severe COPD in order to allow the patients to exercise at a higher training intensity and to obtain a greater effect compared to exercise training without NIV, with both improvement in physical functions and exercise performance [12]. In majority of studies have been used relatively low to moderate levels of inspiratory pressure during exercise, and the optimal mode and settings in a population with very severe lung disease is still unknown [12]. A Cochrane review performed in 2014 by Menadue et al. has shown that NIV during exercise training may allow COPD patients to exercise at a higher training intensity and to achieve a greater physiological training effect compared with exercise training alone or exercise training with sham NIV [12]. It is currently unknown if the demonstrated benefit of NIV during exercise training is clinically worthwhile or cost-effective [12].

NIV delivered during exercise enables patients with severe COPD to exercise at higher intensity, to increase their exercise endurance time and walking distance [8, 9]. NPPV is a feasible and beneficial tool in hospital-based PR [8], but clinical application of NIV during physical exercise is limited by time consuming NIV setup, need for specialist supervision, limited portability of devices and the ventilator model, battery duration and poor patient tolerance [9]. Another recommendation is at night in patients with chronic respiratory failure, to improve their clinical status during the exercise programme, functional capacity, HRQoL and sleep quality [8, 9]. The benefits are achieved through optimization of the respiratory muscle load-capacity-drive relationship [9].

NIV prolongs endurance during exercise in COPD, but routine use is difficult. Recently, handheld, battery operated and portable NIV (pNIV) devices, providing pressure support ventilation, require the patient to inspire and expire through a mouthpiece, are intended to be applied at the end of exercise to reduce the time to return at baseline respiratory status in COPD patients, thus acting as dyspnoea-relief tools. They provide an accessible and acceptable method to improve exercise capacity and relieve exertional breathlessness by reducing dynamic hyperinflation and leg discomfort, together with improving cardiac output, systemic oxygen delivery and exercise endurance time [9, 13]. The pNIV device (VitaBreath, Philips, Respironics, Morrisville, PA, USA) delivers 18 cmH_2O inspiratory and 8 cmH_2O expiratory pressures, and it is used only during recovery periods interspersing bouts of moderate or high-intensity physical activity [13]. The fixed pressures may be sub-optimal in some patients; therefore, the future devices should have the ability to adjust expiratory positive airway pressure, making the pressure support more desirable and potentially automated [13]. Future studies should investigate the additive effect of oxygen supplementation to intermittent NIV support during conventional PR [13].

Less practical in daily life but providing a greater improvement in exercise tolerance are the continuous positive pressure support devices like CPAP, inspiratory pressure support including proportional assist ventilation (PAV), and noninvasive "open" ventilation (NIOV) [13]. All these ventilation support strategies provide continuous unloading of the respiratory muscles and reduce the work of breathing, thus reducing dyspnoea and enhancing exercise tolerance in COPD patients [13, 14]. Portable CPAP devices, light-weighted and battery-powered, are very useful in cases with excessive dynamic airway collapse where they provide a pneumatic stent to maintain airway patency, reduce expiratory resistance and improve expiratory airflow [9]. After providing PAV to a group of patients with more severe COPD during a supervised high-intensity out-patients cycle exercise programme, mean training and peak work rate was higher in this group. PAV is a mode of ventilation that matches ventilator output to patient effort, allowing the patients to prolong exercises and to achieve greater improvements in exercise performance [14]. NIOV system (BT-V2S Breath Technologies) operating in conjunction with a portable oxygen tank was found to decrease respiratory muscle activation and dyspnoea, and to improve cycle ergometer exercise tolerance; it is a light, wearable 1-lb ventilator, practical for facilitating activities of everyday living [15].

Some centres use Assist Pressure Control Ventilation (APCV) mode with a high backup rate, intending to achieve controlled ventilation. The use of APCV mode during exercise implies to best set up a minimum mandatory backup rate along with a fixed inspiratory time for both patient and machine-triggered breaths [12]. Negative pressure ventilation (NPV), when used as an adjuvant to PR, improves lung function, increases exercise capacity, prolongs survival and reduces exacerbations in COPD patients with exercise desaturation, who have an increased mortality risk compared with non-desaturating COPD patients. The NPV group had a slower yearly decline in lung function and in 6-min walking distance, irrespective of exercise desaturation [5]. Maintenance of NPV reduces long-term mortality in COPD patients, irrespective of the presence of desaturation during the 6-min walking test.

49.3.6 Pulmonary Rehabilitation and Noninvasive Ventilation at Home

After successfully completing a course of PR, the only way to maintain the achieved improvements is to continue with a home-based exercise programme and participate to follow-up visits in the PR centre. The scope is to make chronic respiratory patients to become more active in daily living life and to preserve endurance capacity, psychological and cognitive benefits [3]. NIV can be used for long-term treatment of chronic respiratory failure at home. High-pressure NIV is addressed to the patients who have persistent hypercapnia for 2–4 weeks after resolution of respiratory acidemia that has required acute NIV. In COPD patients, long-term NIV decreases arterial partial pressure of carbon dioxide and improves mortality [2]. NIV may be initiated by using nasal, oronasal or total face masks according to the patient preference. The aim is to achieve control over nocturnal hypoventilation with a high-pressure ventilation strategy. After 12 weeks of use at home the pNIV devices, patients reported reduced anxiety and recovery time from breathlessness, as well as improvement in the speed, duration and confidence to undertake activities of daily living [13]. Another treatment option would be the use of NIV in addition to oxygen therapy in home setting, at least for 6 h per night.

Manual techniques, including postural drainage, percussion and vibration, and breathing pattern exercises can be implemented to assist airway clearance [9]. Mechanical insufflation-exsufflation technique is not an alternative for secretion clearance but can be vital for expulsing secretions from central airways for patients with weak respiratory muscles and a partially preserved bulbar (laryngeal intrinsic) muscle function [6]. This new technique of secretion management reduces airway resistance and respiratory muscle load, with increased lung volumes and improved ventilatory capacity; it produces a higher peak cough flow than a voluntary unassisted cough or a cough assisted by NIV [6, 9]. Mechanical insufflation-exsufflation technique is well tolerated and should be considered as an adjunct to manual airway clearance techniques for patients with a peak cough flow less than 160 L/min [9].

49.3.7 Pulmonary Rehabilitation and Noninvasive Ventilation in Palliative Care Services

In advanced chronic patients admitted to palliative care services, it is essential to reduce breathlessness and improve survival, quality of life and function. The use of PAP devices in end-stage hypercapnic disease is frequently implemented in clinical practise, as suggested by international guidelines. Notably, timing of its initiation remains controversial because of potential side-effects as mask discomfort and limited communication with caregivers and family [9]. NPPV is a mean of potentially ensuring the highest quality of life during the final hours, allowing to reduce the dose of morphine necessary to palliate dyspnoea, maintaining better cognitive

function and with a similar rate of acceptance by patients compared with oxygen therapy [10]. The American Thoracic Society/European Respiratory Society guidelines suggest offering NIV to dyspnoeic patients for palliation in the setting of terminal cancer or other terminal conditions [10].

49.4 Conclusions

Pulmonary rehabilitation is a unique non-pharmacological therapy addressed to symptomatic COPD and non-COPD patients with a poor HRQoL due to breathlessness and fatigue. Because of dyspnoea, patients become more socially isolated and finally housebound. PR, LTOT and NIV bring hope in this difficult and long-term fight with a chronic respiratory disease, encouraging patients to meet other people with same disability and fear from illness and death, to exercise together and to continue their lives in a better condition.

Questions and Answers

1. Pulmonary rehabilitation is a non-pharmacological intervention addressed to chronic respiratory patients that improves:

   (a) Exercise capacity
   (b) Survival
   (c) Dyspnoea
   (d) Health-related quality of life
   (e) Muscle performance

   Answers: (a), (c), (d)
2. Standard medical management in chronic respiratory conditions might be optimized through:

   (a) Thoracic taping
   (b) Pulmonary rehabilitation
   (c) Oxygen therapy
   (d) Saline therapy
   (e) Non-invasive ventilation

   Answers: (b), (c), (e)
3. Non-invasive positive pressure ventilation used in chronic hypercapnic respiratory failure conditions improves:

   (a) Blood gases
   (b) Survival
   (c) Lung hyperinflation
   (d) Cardiac fitness
   (e) Exercise capacity

   Answers: (a), (c), (e)

4. The disadvantages of using high-intensity non-invasive positive pressure ventilation are:
   (a) Face wounds
   (b) Bronchial epithelial damage
   (c) More days to stay in hospital to acclimatise
   (d) Increased expiratory leakage
   (e) Developing of a haemodynamic compromise

   Answers: (c), (d), (e)

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Chapter 50
Obesity Hypoventilation Syndrome

David Barros Coelho

Abbreviations

BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
NIV	Non-invasive ventilation
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnea
$PaCO_2$	Arterial carbon dioxide tension
PAP	Non-invasive positive ventilation
REM	Rapid-eye movement
SDB	Sleep disordered breathing
StO_2	O_2 saturation

Clinical Case

Female patient, 58 years old. History of hypertension, obesity Body Mass Index (BMI) 35 kg m^2, non-smoker. Referred to the respiratory care department after a hospital stay during 5 days due to hypercapnic respiratory failure, with necessity of NIV. One month after clinical stability, the patient referred chronic excessive daytime sleepiness (Epworth Sleepiness Scale 15), morning headaches, and non-repairing sleep. Blood gas analysis (BAG): pH: 7.38. pCO_2: 55 mmHg. pO_2: 67 mmHg. HCO_3: 34 mmol/L. stO_2: 93%. Lung function tests were normal. Type 3 Polysomnography revealed: AIH: 25/h Average Oxygen Saturation (StO_2) 89.6%, with 35% of time with StO_2 below 90%. The graph (see Fig. 50.1) reveals a pattern

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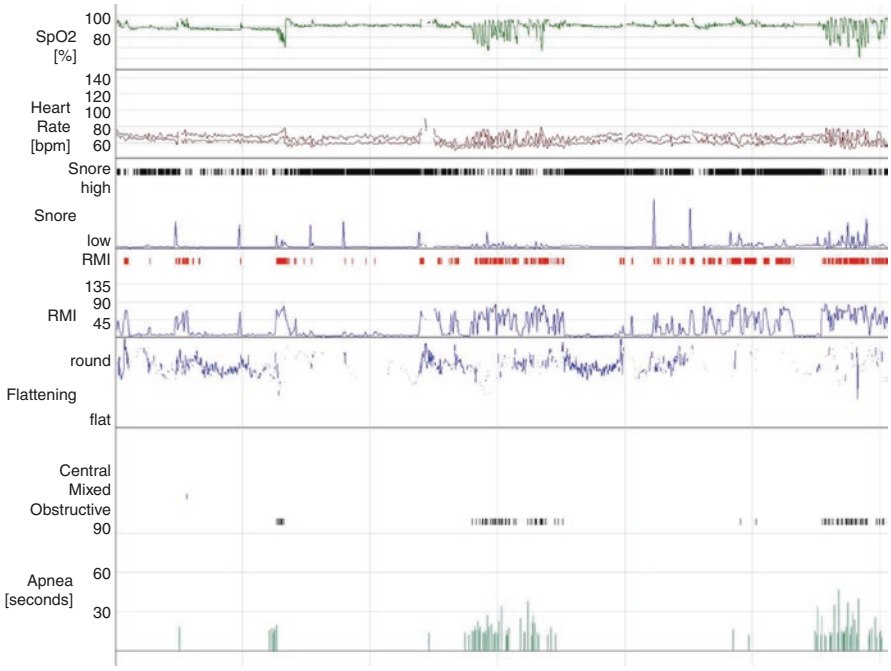

Fig. 50.1 Type 3 polygraphy report of a patient with OHS

of obstructive events and desaturation in possible relation to REM sleep (a level 1 PSG was afterwards done to confirm this findings). The patient started CPAP therapy, with Sleep Breathing Disorder (SBD) and symptoms improvement.

50.1 Definitions

OHS is defined as the combination of obesity (BMI $\geq$ 30 kg m^2), SDB and daytime hypercapnia (arterial carbon dioxide tension ($PaCO_2 \geq 45$ mmHg at sea level)) during wakefulness, occurring in the absence of an alternative neuromuscular, mechanical or metabolic explanation for hypoventilation [1].

Only 30% of patients with OHS have non-obstructive or hypoventilation with mild Obstructive sleep Apnea (OSA), therefore, OSA is very prevalent in this individuals [2].

The definition of hypoventilation according to the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine is: $PaCO_2$ (or surrogate such as end-tidal carbon dioxide tension or transcutaneous carbon dioxide) >55 mmHg for >10 min or an increase in $PaCO_2$ (or surrogate) >10 mmHg compared to an awake supine value to a value >50 mmHg for >10 min. This is the definition used to state hypoventilation in OHS patients' sleep studies, which is therefore essential for a diagnosis [3].

Table 50.1 Staging of hypoventilation in obese patients (BMI > 30 kg/m^2)

0	Obesity-associated sleep hypoventilation	No hypercapnia.
1	Obesity-associated sleep hypoventilation	Intermittent hypercapnia during sleep. Normal diurnal P_{CO2} or P_{tcCO2}. Bicarbonate <27 mmol/L.
2	Obesity-associated sleep hypoventilation	Intermittent hypercapnia during sleep. (P_{CO2} or P_{tcCO2}) morning > evening. Bicarbonate >27 during wake. Bicarbonate increased during dat.
3	Obesity hypoventilation	Sustained hypercapnia. P_{CO2} > 45 mmHg while awake.
4	Obesity hypoventilation syndrome	Sustained hypercapnia while awake, cardiometabolic comorbidities.

According to the European Respiratory Society task force from 2018, other markers of gravity should be taken into account, including bicarbonate, cardiovascular and metabolic comorbidities. Since hypoventilation precedes the development of daytime hypercapnia, milder forms of the disease (without raised pCO_2) should be evaluated. A score [4] is suggested in Table 50.1.

50.2 Epidemiology

Obesity is the most prevalent factor contributing to hypoventilation by means of increased mechanical load [5].

It is a growing public health problem, with increasing numbers particularly in developed countries. Worldwide, it is estimated that one third of adults are overweight (BMI > 25 kg m^2). In the USA, recent numbers from Centre for Disease Control (CDC) indicate that 7.6% of the population has severe obesity as defined by a BMI > 40 kg m^2.

The prevalence of OHS can be estimated as 0.4% in the general population. Between the obese population referred to sleep centers, its prevalence is between 8% and 20%. It is, however, different to state an actual number and estimates vary across studies.

OSA has a male predominance, however the male-female ratio decreases according to women's hormonal state, since OSA risk increases four times after menopause. In contrast to OSA, the prevalence of OHS is similar between men and women [4].

50.3 Pathophysiology

OHS seems to develop as a combination of many factors. According to the ERS publication, there are three main mechanisms: obesity-related changes in the respiratory system, alterations in respiratory drive and breathing abnormalities during sleep [4].

Obesity, with fat deposition in the abdomen and chest wall leads to reduced functional residual capacity and expiratory reserve volume. On the other side, diaphragmatic function is diminished and there is premature airway closure. Patients have an increased work of breathing with consequences in terms of blood gas levels [4, 5]. If the increase in respiratory drive is not sufficient to maintain normal CO_2 levels, then hypoventilation with hypercapnia develops. This mechanism is more evident during Rapid-eye movement (REM) sleep. One of the factors involved in central hypoventilation in OHS patient is leptin.

Leptin is a protein produced by adipose tissue. Leptin crosses the blood-brain barrier and is a stimulant of ventilation. It correlates positively with BMI, however in hypercapnic patients with OHS, a mechanism of central resistance to leptin seems to be involved.

Patients with OSA without OHS have a better capacity of eliminating CO_2 than those with OHS due to reduced ventilation or longer periods. On the other hand, eucapnic OSA patients have less severe night desaturation.

Pulmonary mechanics are also affected due to fat deposition on the abdomen and chest wall leading to ventilation/perfusion mismatch, reduced muscle strength (particularly in the supine position). Besides, it leads to impaired ventilatory control (reduced neural dive, reduced ventilatory responsiveness, leptin resistance and carbon dioxide overproduction).

50.4 Clinical Presentation and Diagnosis

Some patients with OHS present with acute on chronic hypercapnic respiratory failure, however some are referenced for pulmonology specialist due to chronic symptoms. It is estimated that 8% of all patients in an intensive care unit meet diagnosis criteria for OHS, however 75% of these are misdiagnosed as COPD exacerbation, despite no COPD diagnosis present.

Patients are obese, usually with severe OSA and, comparing with non-hypercapnic OSA patients, tend to present with more dyspnea and cor pulmonale [2].

A blood gas analysis is essential for diagnosis. Hypercapnia should be suspected when patients present with common symptoms of OSA and OHS, and hypoxia and raised serum bicarbonate are important clues. Serum bicarbonate <27 mEq/L has a 97% negative predictive value for excluding a diagnosis of OHS. There are other methods for measuring CO_2, as to measure carbon dioxide levels continuously during sleep by end-tidal or transcutaneous monitoring [6]. Improving technologies should greatly expand our ability to identify and quantify nocturnal hypoventilation in sleep laboratories, or even at home. SDB should be accessed by polysomnography.

OHS should be suspected in the following cases:

- Reduced lung function due to obesity
- Reduced inspiratory muscle strength

- Diurnal O_2 saturation (SpO_2) ≤94% or an overnight nadir saturation <80%
- Severe OSA (AIH > 50)
- Exertion dyspnea
- Pulmonary hypertension and/or right-sided heart failure without a recognisable reason
- Facial plethora
- Raised bicarbonate on venous blood sampling

50.5 Comorbidities

Many comorbidities of SHO are shared with OSA, such as increased cardiovascular risk. Apart from cardiovascular, the most frequent comorbidities are metabolic.

OSA is an independent risk factor for hypertension, with the risk increasing with higher Apnea-Hypopnea Index. The prevalence of hypertension in OHS varies between 55% and 88%. It is also related to Atrial Fibrillation, Heart Failure [4].

Chronic hypoventilation also leads to pulmonary hypertension. Corral et al. observed that patients treated with Non-Invasive Ventilation (NIV) rather than CPAP, showed an improvement in pulmonary hypertension, reduced left ventricular hypertrophy and exercise performance improvement. However, daytime blood pressure did not improve. There are also metabolic consequences such as insulin resistance, therefore it is important to access electrocardiogram, plasma glucose, triglycerides and cholesterol to ensure this comorbidities are being correctly managed.

OHS is a devastating complication of obesity, with 24% mortality in 1.5–2 years, if untreated [4].

Treatment of comorbidities including pharmacologic and rehabilitation interventions are essential for improving prognosis.

50.6 Treatment

CPAP and NIV are associated with clinical and polysomnographic improvements. Since most patients with OHS have concomitant OSA, it is expected that CPAP can be effective for this patients. There are some studies on the impact of CPAP on OHS, comparing it to NIV treatment with Bi-level. CPAP has a lower cost and complexity when compared to NIV.

In the first phase of the Pickwick study, Masa et al. compared 2 months of CPAP or non-invasive versus lifestyle modifications—both continuous and non-invasive ventilation improved $PaCO_2$, bicarbonate when compared with lifestyle changes, but with no difference between the two treatment methods.

Long-term follow-up results were recently published by Masa et al., with a mean follow up of 5.44 years. The trial showed no significant long-term differences between CPAP and NIV in hospitalization days, other hospital resource utilization, blood pressure, cardiovascular events, mortality, respiratory function and health-related quality of life, daytime sleepiness and related symptoms of OHS. Higher level of adherence was associated with lower hospitalization days and reduced hospital resource utilization and mortality. Most deaths occurred due to cardiovascular problems, which suggests that both treatments may reduce morbidity and mortality due to respiratory causes but with less effects on cardiovascular outcomes. Adverse effects were similar between groups. It is important to state that there is no control group, which makes it difficult to access the long-term cardiovascular effects of non-invasive and continuous positive pressure ventilation. Therefore, in patients with OHS with severe OSA, CPAP and NIV seem to have similar long-term effectiveness [7]. PAP is usually the preferred first treatment modality for patients with severe OSA, with the necessity of close follow-up in terms of clinical and gas exchange. NIV should be reserved in first line for OHS patients presenting with primarily central hypoventilation during sleep.

Despite the effectiveness of this treatments, a multimodal strategy should be used including weight loss, changes in lifestyle habits and rehabilitations programs.

NIV can be successful when treating acute exacerbations of OHS and should, therefore be the preferred mode of treatment, with the exception of severely unwell patients or those with organ dysfunctions in whom endotracheal intubation and mechanical ventilation is mandatory. Factors associated with a successful response to NIV included high $PaCO_2$ at admission and a diagnosis of idiopathic hypercapnic decompensation of OHS [8]. Another factor that influences prognosis is the previous adherence to NIV or CPAP at home. The ideal NIV mode is not yet established, however it is important to overcome upper airways obstruction and the respiratory muscle load. This is achieved with increased EPAP and inspiratory driving pressure.

50.7 Discussion of Case

OHS is responsible for chronic respiratory failure in many obese patients, mostly with OSA. It is also responsible for acute on chronic exacerbations, leading to hospital and intensive care unit. This was the case of the patient reported, in which a previous clinical suspicion could have potentially prevented an exacerbation. It should be differentiated from COPD, because these patients may not have obstructive disease and need a different follow-up and treatment strategy. Both CPAP and NIV improve gas exchange, SBD and symptoms, leading to a better quality of life. In this case, the respiratory events seemed to have a relation to REM sleep (initially only a suspicion, since no type 1 PSG was performed), so NIV could be a possible first treatment strategy. However, due to the patients' improvement both in terms of night saturation, daytime hypercapnia and symptoms, CPAP therapy was continued.

Key Teaching Points

- OHS is associated with respiratory, cardiovascular, metabolic comorbidities and increased mortality.
- CPAP has a lower cost and complexity than NIV and both treatments' role on the different OHS phenotypes is yet to be fully understood.
- In stable patients with predominant severe OSA, NIV and CPAP have similar long-term effectiveness.
- NIV should be reserved for OHS patients presenting with primarily central hypoventilation during sleep.

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Chapter 51
Elderly Non Invasive Mechanical Ventilation Applications

Fatma Çiftci

51.1 Introduction

The proportion of elderly people in the population has increased in recent years due to the increase in life expectancy in developed countries and the low birth rate. In addition, the prevalence of disability free life expectancy among the elderly is increasing and the prevalence of serious disability is decreasing. In the elderly population, these variables should be considered together and future clinical decisions should be made [1].

The reduced invasiveness of NIV therapy in selected populations of critically ill patients leads to better outcomes than endotracheal intubation. In addition, the use of NIV as a palliative treatment for respiratory failure and dyspnea has become increasingly common. NIV is also very useful in patient groups with 'do not intubate (DNI)' orders. The proportion of elderly adults among hospitalized patients, including ICU admissions, is currently increasing rapidly [2]. Many of these patients are then discharged with NIV treatment at home to reduce number of hospitalizations, maintain quality of life, and reduce dyspnea symptoms [3]. It shows that avoiding invasive procedures may help to reduce mortality, especially in the elderly. Contradictory age-related results have been observed in NIV treatment as a factor affecting mortality (Table 51.1).

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Table 51.1 Applications of NIV therapy in elderly population

Acute respiratory failure
Acute cardiogenic pulmonary edema
Immunocompromised patients
Palliative care and DNI
Weaning
Domiciliary NIV

51.2 Acute Respiratory Failure

In older patients with acute respiratory failure (ARF) treatment may be quite complex for reasons such as reduced life expectation and an increased rate of complications. The management of critical respiratory illness in the elderly is therefore of particular importance. Although NIV is an attractive technique for the management of ARF in older patients, specific data for this population are limited. The success of NIV is directly related to the number and severity of the comorbidities and also consciousness of the patient. ICU acceptance and mechanical ventilation in the elderly is not associated with an absolute poor prognosis [4]. However, most studies with the elderly have been conducted on patients without pre-existing lung diseases. However, people with chronic respiratory failure represent a large proportion of patients older than 65 years who apply to ICU. Randomized, controlled trials have shown that the use of NIV in the treatment of ARF in elderly patients reduces the need for intubation, improves survival, and produces a faster resolution of respiratory distress compared to standard medical treatment. NIV is not only a palliative measure, but also a primary treatment modality where intubation is not desired by the patient or required by the physician. NIV decreases tachypnea and dyspnea, which are the main symptoms of respiratory distress, and increases the survival rate [5]. The results of the studies show that patients who are planned for NIV for the treatment of ARF should be evaluated independently of age considering their compliance and tolerance, specific clinical findings (respiratory rate, PaO_2/FiO_2) and arterial blood gas analysis [4].

51.3 Acute Cardiogenic Pulmonary Edema

Acute respiratory failure due to congestive or ischemic heart failure is one of the indications for NIV treatment. NIV therapy increases lung compliance, activates pre-collapsed alveoli, reduces preload and afterload, leads to increased oxygenation and reduced workload of the respiratory muscles [6]. Continuous and bilevel positive airway pressure significantly reduces endotracheal intubation rates and mortality [7].

Age is not a limiting factor for the effectiveness and safety of ventilator support; similar results have been observed for various age groups.

51.4 Immunocompromised Elderly Patients

The immunocompromised are at an increased risk of disease morbidity and mortality rate. NIV is preferred in patients with immunodeficiency and respiratory failure treatment because of the high risk of severe secondary infections and complications. In addition, beneficial effects on survival have been demonstrated. Additionally, the use of guideline-concordant antibiotics in the immunocompromised with pneumonia was significantly associated with lower mortality. Similar studies have investigated and found a beneficial association between NIV use and survival in patients with hematological malignancies. Research results have reported that age alone cannot be said to be a factor affecting prognosis in this patient group [8].

51.5 Palliative Care and DNI

In fact, the DNI procedure can not be regarded as a justification for the NIV. However, the use of NIV as a palliative method rather than invasive treatments is increasing. Palliative NIV treatment includes a range of applications, from symptom based intervention concurrent with disease oriented treatment to purely palliative treatment at the end of life. In patients predicted to be impaired by advanced respiratory failure (for example, patients with terminal lung cancer, idiopathic pulmonary fibrosis not suitable for transplantation, and severe COPD patients), the administration of NIV as a potential intervention should be discussed in an outpatient setting, but routinely should not be offered. NIV has also been shown to be useful in the treatment of dyspnea in patients with advanced solid organ malignancy [9]. It was observed that oncology patients receiving NIV treatment had improved dyspnea scores despite lower narcotic doses compared to patients receiving only opiate and oxygen. Studies have indicated that, despite receiving intensive treatment at home, very old patients with DNI decision presenting with ARF should be placed in an open or semi-open place outside the ICU. Recent reviews have reported a dramatic shift towards the use of NIV for the treatment of acute respiratory exacerbations [10]. The reasons for this trend were, health care providers were more confident in using NIV and extending their practice beyond those defined in clinical trials. A number of clinical studies have consistently reported that NIV is effective in reducing the need for IMV and in hospital mortality. Very old DNI patients with ARF can be treated with NIV together with trained doctors and nurses in a semi-open geriatric ward. The presence of family members increases patient comfort and reduces anxiety levels even at the end of life. Mortality in the geriatric ward was associated with the diagnosis of admission. When NIV is administered by an experienced

doctor in a geriatric ward and patients are closely supported by family members and nurses, the mortality rate is approximately 25%. It appears that individuals with chronic respiratory failure represent a greater proportion of patients over 65 years of age who apply to ICU [11]. Patients with older hypercapnia have been shown to have poor survival rates after an exacerbation with acute hypercapnic respiratory failure. Randomized, controlled trials have shown that the use of NIV to treat ARF in elderly patients reduces the need for intubation, improves survival, and improves respiratory distress more quickly than standard medical therapy. NIV is important not only as a palliative measure, but also as a primary treatment where intubation is not desired by the patient or required by the physician. NIV increases the survival rate and also reduces tachypnea and dyspnea which are the main symptoms of respiratory distress. In addition, NIV reduces the need for sedatives by contributing more to the prevention of delirium and immobilization compared to IMV. In addition, NIV treatment in a non-ICU setting allows relatives to visit more often and longer.

51.6 Weaning

NIV is a useful tool during weaning process in the appropriate patient population. There is evidence that early administration of NIV immediately after extubation is effective in the prevention of respiratory failure after extubation in a population at risk [12]. In a systematic literature review, including randomized controlled trials comparing NIV treatment with conventional oxygen therapy after planned extubation has been shown to reduce reintubation rates in patients at high risk of extubation insufficiency. In this review, there was no difference between the elderly and the other groups [13].

51.7 Home NIV in Elderly Patients

The treatment plan becomes more complicated with the increasing age of the patients who are planned to be treated at home because of respiratory failure. Physiological parameters, social support, patient motivation, comorbidities and the natural course of the disease should be considered when starting NIV treatment in elderly patients. In fact, all of these elements are closely interrelated and should be evaluated together. However, with the development of more sophisticated interfaces, new NIV devices are being used to provide a more acceptable, safer and more comfortable ventilator support with a larger positive pressure support system. Consensus guidelines emphasize that age, by itself, is not a criteria for NIV treatment at home [14]. Recent publications have reported that NIV is effective and safe in the elderly patient population. Given the long-term home ventilation in individuals over 75 years of age with multiple comorbidities, including acute significant cognitive impairment and acute delirium with respiratory failure, early reports have

not yielded particularly positive results. This was primarily based on neuropsychological deterioration and difficulties in adapting to home NIV compared to younger individuals [3].

In the elderly population with good NIV compliance, after the onset of NIV, a significant improvement in gas exchange and a reduction in hospitalizations were observed. Compliance was also good in this elderly population; comparable to data reported in the large series of home ventilation which included patients of all ages [15].

In conclusion, the results of the researches show the efficacy of NIV in the elderly. An improvement in arterial blood gases and nocturnal desaturation, reduction in hospitalizations and a decrease in hospital stay were observed. Moreover, compatibility and tolerance in elderly patients were comparable to those in the general population. Since there is no predictive factor for NIV treatment at home and NIV should be tried in all patients who meet the criteria for indication regardless of age.

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Chapter 52
Elderly-NIV: Non-invasive Mechanical Ventilation Treatment in Elderly Patient with Usual Interstitial Pneumonia

María Pilar Martín-Fortea and Laura Anoro Abenoza

Abbreviations

BIPAP	Bilevel positive airway pressure
bpm	Breaths per minute
CRP	C-Reactive protein
EPAP	Espiratory positive airway pressure
FiO_2	Fractional inspired oxygen
HCO_3	Bicarbonate
IPAP	Inspiratory positive airway pressure
IV	Intravenous
NIMV	Non-invasive mechanical ventilation
NT-proBNP	N-Terminal pro-brain natriuretic peptide
O_2	Oxygen
pCO_2	Arterial carbon dioxide tension
pO_2	Arterial oxygen tension
UIP	Usual interstitial pneumonia

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52.1 Real Case Clinic

52.1.1 Introduction

Woman 86 years old, she's autonomous for the daily activities of life. Medical pathological history: hypertension, diabetes, heart failure, pulmonary tuberculosis and pulmonary interstitial disease type UIP (usual interstitial pneumonia), mild dementia. Chronic treatment: furosemide 60 mg/day, lormetazepam 1 mg at bedtime, escitalopram 10 mg/day, ciclesonide 160 μg 2 inhalations in 12 h, olodaterol/tiotropium 2.5/2.5 μg 2 inhalations per day.

She went to the hospital emergencies due to a progressive increase in dyspnea that lasted 48 h until, with an increase in cough but no sputum, fever, orthopnea or edema. In the physical examination she presented tachypnea at 38 breaths per minute (bpm), oxygen (O_2) saturation 80%. She needed to use accessory muscles, she had prolonged inspiration and diffuse dry crackles in both pulmonary fields with expiratory sibilants predominantly in lung bases; there is no evidence of edema in lower extremities or jugular ingurgitation.

52.1.2 Complementary Explorations

- Hemogram: Hemoglobin 11.9 g/dl, Hematocrit 37%, 24,000 leukocytes/mm^3 (neutrophils 83%), platelets 210,000/mm^3.
- Biochemistry: creatinine 1.38 mg/dl, sodium 138 mEq/l, potassium 4.3 mEq/l, C-reactive protein (CRP) 27.1 mg/l, procalcitonin 0.1 μg/l, N-terminal pro-brain natriuretic peptide (NT-proBNP) 1952 ng/l.
- Initial gasometry (with endonasal oxygen at 3 l/min): pH 7.42, pO_2 (arterial oxygen tension) 70 mmHg, pCO_2 (arterial carbon dioxide tension) 37 mmHg, bicarbonate (HCO_3) 24 mmol/l, lactate 2.6 mmol/l.
- Thorax radiography: diffuse bilateral interstitial involvement with associated alveolar edema (Fig. 52.1).
- Electrocardiogram: sinus rhythm at 90 bpm.

52.1.3 Discussion

In the hospital emergency department, treatment was initiated with furosemide 20 mg intravenous (IV), methylprednisolone 20 mg IV, ceftrixone, nebulizations with ipatropium bromide, salbutamol and oxygen at 4 l/min and fractional inspired oxygen (FiO_2) 28%.

The immediate evolution is not satisfactory because the patient maintains tachypnea at more than 30 bpm and use of the accessory musculature, with O_2 saturation of 90%. It was decided to start ventilatory support with NIMV.

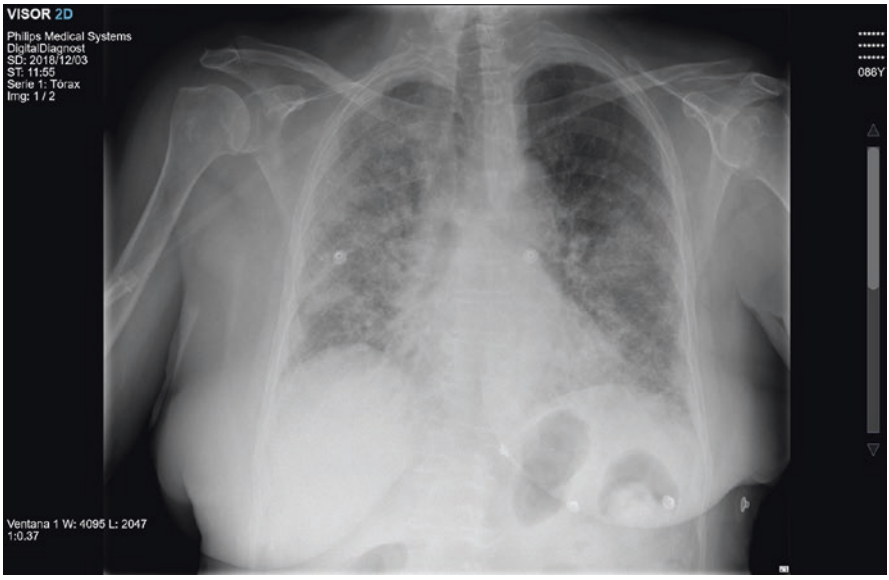

Fig. 52.1 Thorax radiography at the emergency room: diffuse bilateral interstitial involvement with associated alveolar edema

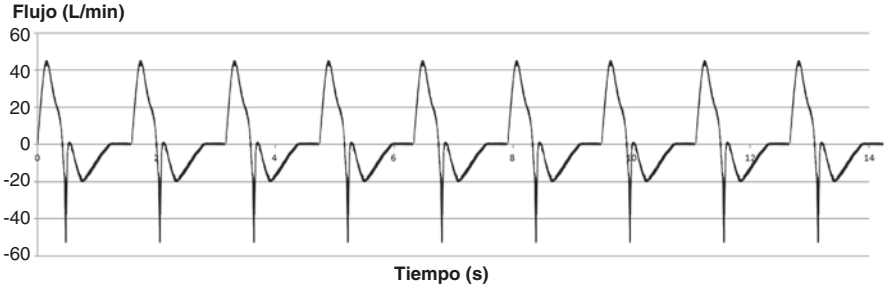

Fig. 52.2 Flow curve in ventilator monitor: expiratory asynchrony

Although arterial acidosis was not found in arterial blood gas analysis, it is a patient with pulmonary restriction due to fibrosis and impaired elasticity due to alveolar edema associated with heart failure. The muscular fatigue that the patient present, will cause metabolic complications, which will perpetuate muscle work and respiratory failure. Therefore, the objective in this case is to relieve muscle fatigue in an elderly patient with chronic respiratory disease and muscle weakness.

VMNI was started in mode bilevel positive airway pressure. (BIPAP) (VIVO 50 Breas Medical®), spontaneous/assisted mode with IPAP 10 cmH_2O (inspiratory positive airway pressure), EPAP 4 cmH_2O (espiratory positive airway pressure), and FiO_2 40%. Flow curve can be seen in monitor (Fig. 52.2).

After observing good patient tolerance to NIMV, IPAP was increased to 12 cmH_2O, with the intention of increasing support pressure and improving respiratory work.

After 6 h of uninterrupted treatment, there was no objective use of accessory musculature at the cervical level, but the use of the abdominal respiratory musculature persists, and the respiratory frequency is 28 bpm.

The ventilator registered a Tindal volume of 400–500 ml range, without significant leakage detected by the system, improves the flow curve and oxygen saturation improvement is achieved (94% with oxygen at 7 l/min associated to the BIPAP). Control arterial gasometry was performed under these conditions: pH 7.5, pO_2 72 mmHg, pCO_2 36 mmHg, sat O_2 95%, HCO_3 28.5 mmol/l, lactate 2.2 mmol/l.

After the night rest maintaining NIMV, the patient presented subjective improvement. She has a good level of consciousness and a respiratory rate is 18 bpm, does not use the respiratory accessory musculature, and maintains adequate oxygen saturation with FiO_2 of 40%. The blood gas analysis at that time is as follows: pH 7.47, pO_2 83 mmHg, pCO_2 48 mmHg, sat O_2 96%, HCO_3 33 mmol/l, lactate 2.2 mmol/l. In view of the clinical improvement but with the gasometric worsening, it was decided to start the progressive withdrawal of NIMV, which is completed 48 h after arrival at the hospital. The flow of oxygen provided also decreases progressively.

Key Teaching Points

- This clinical case shows alteration of the ventilatory function of multifactorial origin: Interstitial lung disease causes a decrease in pulmonary elasticity and an inadequate gas exchange in addition to pulmonary edema of cardiological origin. On the other hand, the patient presents a weakness of the respiratory musculature typical of patients with advanced age. The treatment with NIMV type BIPAP in our case improved muscle fatigue avoiding the appearance of hypercapnia and respiratory acidosis.
- Advanced age is not a contraindication to apply NIMV. When this treatment is justified, it has shown a decrease in morbidity and mortality in multiple studies [1] and is indicated in patients not subsidiary to orotracheal intubation [2].
- The positive pressure at the end of expiration decreases the work of the respiratory musculature, CPAP (continuous positive airway pressure) or high flow oxygen therapy could be indicated in patients with pathology similar to that of our clinical case [3]. The use of the BIPAP also provides the necessary support pressure to improve ventilation.
- The onset of NIMV early, when metabolic complications have not yet appeared, favors a faster clinical improvement, avoids complications derived from NIMV (such as pressure ulcers of the interface), and shortens the average hospital stay [4].

- NIMV is usually well tolerated by the elderly [5]. During the monitoring, an alteration in the flow curve characteristic of a short-cycle asynchrony is observed, in which the neural inspiratory time of the patient is greater than the inspiratory time of the ventilator. This asynchrony is typical of patients with very low thoraco-pulmonary compliance (pulmonary fibrosis, scoliosis, obesity…). In this situation an underventilation is possible. Some solutions of this asynchrony could be increase the support pressure or low EPAP, in addition to checking interface leaks and seating patient in the correct way.

Questions and Answers

1. Cuál es la principal indicación del uso de VMNI en este caso?

   (a) La edad
   (b) EL aumento del trabajo muscular
   (c) La contraindicación para intubación orotraqueal

2. Qué modo ventilatorio se podría usar en este caso?

   (a) CPAP y alto flujo
   (b) BiPAP y alto flujo
   (c) CPAP, BiPAP y alto flujo

3. Qué afirmación es la correcta en relación a la asincronía de ciclo corto?

   (a) Ocurre en los pacientes mayores que mala tolerancia a la mascarilla nasobucal
   (b) Aparece en las situaciones en las hay afectación de la elasticidad pulmonar
   (c) Para corregirlo hay que disminuir la presión de soporte, ya que esa disminución ayuda a acoplar el tiempo neural inspiratorio al tiempo del respirador

4. Señala contraindicaciones absolutas para aplicar VMNI tras objetivar acidosis respiratoria en ancianos:

   (a) Insuficiencia cardiaca asociada
   (b) Hipoxemia grave
   (c) Ninguna de las anteriores

5. En ancianos, antes de iniciar la VMNI, debemos ser especialmente cuidadosos:

   (a) Eligiendo la interface adecuada a las caracteristicas anatómicas del paciente dado que en muchas ocasiones existe falta de piezas dentarias lo que da lugar a deficit de ajuste y fugas.
   (b) Posicionando al paciente de forma correcta ya que las cifosis y cifoescoliosis son muy frecuentes en este rango etario.
   (c) Todas las anteriores son correctas.

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Chapter 53
Clinical Case in Non Invasive Ventilation in End of Life

Nicola Vargas, Loredana Tibullo, Andrea Fabbo, and Antonio M. Esquinas

53.1 Introduction

Palliative care includes the concept of caring patients at end-of-life. This part is an essential part of palliative medicine in which many people have an active role. First, the patients with their preferences and wishes and secondly the family members that may have specific requests, especially in the case of not competent patients. These aspects are closely related to the caring task of maintaining the quality of end-life and the quality of dying. Although the alleviation of the breathlessness is the most crucial goal of quality palliative medicine in patients with respiratory failure, the ability to communicate with their loved ones at the terminal phase is the other peculiarity of preserving the quality of dying. Invasive mechanical ventilation (IMV) is beneficial in the relief of the breathlessness but has some many other limitations. The IMV may lead to further suffering and often unneeded medical approaches, and it may often be a barrier between the family members and patients. On the other hand, the application of non-invasive ventilation (NIV) associated with the

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discomfort of the mask straps could prolong the suffering before death. Many studies have analysed the advantages and disadvantages of these two treatment options. We report a case of terminal ill patient with acute respiratory failure who choose the option of NIV.

53.2 An Ill Cancer Patient Who Has Chosen NIV

A patient of 57 years of age with a history of long chronic neurologic disease, COPD and lung cancer treated with chemotherapy and radiotherapy had a global acute respiratory failure. She stayed in the past in intensive care (ICU) for pneumothorax as a complication of a lung biopsy. This episode a year before had influenced her caring preferences. Two brothers were her unique family members. They passed all-time with her. In our half-open ward, they could assist their loved ones. They experienced admission in ICU as a limitation.

She had breathlessness and abundant secretions. The patient showed these values of blood gases at the entrance: pH 7.32; pCO_2: 92; pO_2: 52 in room air ambient; HCO_3: 46.9 Lactates: 0.9. The physicians explained her the necessity of mechanical ventilation.

She said " I know that I am dying. Two weeks ago, I refused the intubation and admission in ICU. Now I feel worse, but I have to communicate some important messages to my family members during my last days". She had advance directives (Italian DAT) [1] .

A chest Tc showed as new event three obstructive atelectasis due to mucus plug and lung cancer in an advanced stage of the disease. The physicians explained that the presence of abundant secretions might be a cause of NIV failure as well as even the necessity of bronchoscopy [2].

NIV may compromise her clinic conditions. She asked comfort only. The bronchoscopy during the NIV was the best option for the physicians.

The patient started with the support of IPAP 16 cmH_2O and PEEP of 4 cmH_2O. A FiO_2 used was at a level that provides O_2 saturation above 90%. Physicians used a FiO_2 higher than 0.5. The expiratory tidal volume (Vt) obtained was at between 8 and 10 ml/kg (between 550 and 650) and respiratory rate always below 25 min^{-1}. The patients Saturation was 92%. The bronchoscopy was performed in ICU. During the bronchoscopy, the FiO_2 increased at 100%, but her saturation decreased at 80–82% while the bronchoscopist applied a suction of secretions [3]. It was necessary to administer topical anaesthesia for a laryngeal spasm [4].

After the bronchoscopy and the bronchoalveolar lavage (BAL), the patient continued the NIV. She needed a minimal dose of morphine. After cultures of BAL, the patient begins a specific antibiotic therapy. Her brothers continued to administer meals and talk with her every day.

The patient chooses a hospice where she died after 2 weeks.

53.3 Discussion

The cancer patients are at increased risk of respiratory failure due to infection, malignant cell infiltration and treatment toxicity. For these patients and this environment, NIV has been accepted as a treatment option [5]. For cancer patients, the main goal that physicians should take in mind is that at advanced stages, they should prolong and increase the quality of life. But many authors consider the use of NIV in patients with Do not intubate order (DNI) controversial. Many ethical problems regard the use of NIV in terminal patients should be discussed. The discussion could be done only between patients, caregivers and their doctors. Valuable information assisting in formulation of a management plan may be obtained through collaboration and good communication [6]. If NIV causes discomfort such as the skin lesions, claustrophobia and other signs of intolerance for the patients, the NIV should be suspended. The physicians should consider some contraindications such as, in this case, the presence of abundant secretions. The quality of dying not excluded from the safe setting. All the manoeuvres as the bronchoscopy should be performed in an adequate environment such as ICU.

Some evidence has shown that a safe setting might be beneficial in patients with advanced solid malignancies for treatment of dyspnea [7].

53.4 Conclusion

The end of life is a very complex state associated with psychological and physical fragility. The quality of life and dying could be only reached through a multidimensional evaluation that involves the caregivers, the patients, the physicians. The use of NIV in terminal patients with respiratory failure is one of the treatment options available for the physicians. Furthermore, its use requires a correct awareness of the devices and sufficient ability in treating respiratory failure.

Questions and Answers

1. The end of the life decision-making process about the intervention should consider:

   (a) Firstly the family members' preferences and wishes
   (b) The patient's preferences and desires if competent
   (c) The physicians can decide a caring plan without a discussion with the patient and the family members
   (d) None of the above
   (e) All of the above

   Answer: (b) The patient's preferences and desires if competent

2. The dosage of the morphine in patients at the end of life are treated with NIV?

   (a) It may be increased
   (b) It may be reduced
   (c) The NIV use does not modify the dose of the morphine
   (d) None of the above
   (e) All of the above

   Answer: (b) It may be reduced
3. In patients at the end of life with solid malignancies, the treatment with NIV in a safe setting?

   (a) It is not necessary
   (b) It is not beneficial
   (c) It is helpful for the patient
   (d) There is no relation between the setting and end of life treatment with
   (e) None of the above

   Answer: (c) It is helpful for the patient
4. If NIV does not guarantee the right comfort?

   (a) It should not be suspended
   (b) It should be suspended, and the use of the HFNC should be considered
   (c) The invasive mechanical intubation is an option although the patient refused it
   (d) The physicians may decide the best intervention
   (e) All of the above

   Answer: (b) It should be suspended, and the use of the HFNC should be considered
5. At the end of life, the ventilator setting is different from the configuration of the other treatment diseases?

   (a) Yes, it necessary a different modality and setting
   (b) No, it is the same
   (c) It is essential to start with a higher level of PEEP
   (d) None of the above
   (e) All of the above

   Answer: (b) No, it is the same
6. The discussion about the ethical aspects should be?
   (a) A critical component of the caring planning
   (b) The ethical aspects are well considered in recent guidelines
   (c) The ethical elements don't refer to the possibility that the NIV prolongs the suffering
   (d) All of the above
   (e) None of the above

   Answer: (a) A critical component of the caring planning

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Chapter 54
Clinical Cases in Non Invasive Ventilation: Home Mechanical Ventilation

Fatma Çiftci

54.1 Introduction

In the treatment of respiratory failure, non-invasive positive pressure mechanical ventilation (NIV) was started to be used more frequently, as a result of home NIV therapy also increased. Home NIV is defined as NIV treatment for 3 months or more at home or in non-hospital nursing homes [1].

Noninvasive positive pressure ventilation is increasingly replacing ventilation by tracheotomy for different indications. Although there is not enough data except amyotrophic lateral sclerosis and Duchenne muscular dystrophy in the guidelines, they are used for different indications in clinical practice. Chronic obstructive pulmonary disease, obesity hypoventilation syndrome, neuromuscular diseases and chest wall diseases are the most common etiologies where home NIV treatment is used (Table 54.1).

54.2 Neuromuscular Diseases

Neuromuscular diseases constitute a heterogeneous group of diseases. In addition to respiratory failure in these patients, problems such as inadequate cough, inability to clear secretions, swallowing dysfunction due to bulbar weakness, muscle weakness, and cardiomyopathy in some patients are also the problems that need to be addressed. When we look at the use of NIV over time, we see that after the successful results of positive pressure ventilation in Polio patients, its use in musculer dystrophy patients has become widespread. Similarly good results have been observed with

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Table 54.1 Major indications of domiciliary NIV

Neuromuscular diseases (ALS, Musculer dystrophy, etc.)
Chest wall diseases
Chronic obstructive pulmonary disease (COPD)
COPD-obstructive sleep apnea overlap syndrome
Bronchiectasis
Cystic fibrosis
Obesity hypoventilation
Palliative care

NIV treatment in slow progressive dystrophies such as congenital muscular dystrophies, spinal muscular atrophy type II, and myopathies. In type I spinal muscular atrophy with onset after 3 months, NIV may prolong survival or can be used to palliate symptoms [2]. In ALS patients, there are few randomized controlled trials on ventilation support. The American Academy of Neurology Practice Parameters [3] on drug, nutritional, and respiratory therapies in ALS recommends NIV to lengthen survival and slow decline of FVC and to improve quality of life. National Institute for Clinical Evidence guidelines [4] in the UK recommend referral for assessment for NIV if daytime arterial oxygen saturation is 93% or less, FVC is less than 70% predicted, maximum inspiratory pressure is less negative than −60 cmH_2O, or marked symptoms of sleep-disordered breathing or orthopnea are present. The initiation of NIV is recommended in the presence of daytime hypercapnia, symptomatic sleep-disordered breathing, and deteriorating pulmonary function. Serial measurement of respiratory muscle strength is an accurate predictor of survival. It is not clear whether earlier initiation of NIV offers any survival advantage.

54.3 Chest Wall Diseases

Hypercapnic respiratory failure may occur in many diseases of the chest wall. Severe respiratory failure develops frequently in scoliosis and less frequently in kyphosis, which leads to severe deformity, while it develops slowly in the sequelae of tuberculosis and rarely in ankylosing spondylitis [5]. NIV is an effective treatment option for hypercapnic respiratory failure in patients with a chest wall disorder. Ventilation through tracheostomy may be more appropriate in patients with impaired bulbar function. In other cases, however, NIV may be preferred.

There are no randomized controlled trials of indications for initiating NIV therapy. However, NIV is recommended if there are symptoms of nocturnal hypoventilation, hypercapnia and right heart failure. Similarly, there are no randomized controlled trial on the outcome of NIV therapy under these circumstances. However, studies have shown a slight improvement in other physiological conditions such as increased quality of life, physical activity and hemodynamic improvement, normalization of blood gases, and vital capacity [6].

54.4 Chronic Obstructive Pulmonary Disease

Patients with chronic hypercapnic respiratory failure are the subgroup of Chronic Obstructive Pulmonary Disease (COPD) who benefit most from home NIV treatment.

Home NIV treatment in COPD patients provides relief of dyspnea symptoms, decreased number of hospitalizations and improved quality of life. The two most important reasons for NIV treatment at home are recurrent severe exacerbations requiring NIV and failed weaning from NIV [7].

The indication for Home-NIV in the subgroup of COPD patients with stable chronic hypercapnic COPD has been a controversial topic over the last two decades. In addition, when patients with chronic hypercapnic respiratory failure were given overnight NIV treatment with a multidisciplinary rehabilitation program, it was shown that there was an improvement in terms of exercise tolerance, health related quality of life and lung function compared to rehabilitation alone [8].

In response to these poor outcome data, studies were initiated to investigate whether survival could be improved with the continuation of home NIV after an exacerbation. In addition to the before mentioned criteria for prescribing home NIV, physicians involved in the provision of home-NIV in Europe suggested that one of the most important indications for long-term NIV in COPD patients is the failure to wean from acute NIV [7].

In addition, the recently published guidelines recommend home NIV treatment for COPD patients whose symptoms of hypoventilation and hypercapnia are controlled only after continuous use of NIV after separation from invasive mechanical ventilation [9].

54.5 Post-acute Exacerbation of COPD

Previous data have shown that patients with reversible acute hypercapnia and normocapnic in the recovery phase after exacerbation have a similar prognosis to those with normocapnic during acute exacerbation, and have a better prognosis than those with chronic persistent hypercapnia following recovery from an exacerbation [9]. In patients with reversible hypercapnic phenotypes, long-term NIV has less physiological and clinical effect since there is no chronic respiratory failure in these patients. As a result, the data will strongly support the assessment of COPD patients with decompensated respiratory failure requiring NIV, after 2–4 weeks after recovery of respiratory acidosis. If the patient has persistent hypercapnia at 2–4 weeks, NIV at home should be added to long term home oxygen therapy.

54.6 COPD-OSA Overlap Syndrome

It has been shown that the exacerbation frequency and severity of COPD and OSA overlap patients are also much more higher than pure OSA patients [10]. In addition, amelioration of this risk with CPAP therapy appears when compared with patients who are not compatible with CPAP therapy. Sleep efficiency and quality in COPD are associated with the degree of hyperinflation and may worsen with high-pressure CPAP as increased hyperinflation may worsen expiratory flow limitation.

Furthermore, daytime high-pressure CPAP application increases shortness of breath in patients with COPD-OSA overlap. CPAP compliance has been shown to be poor in patients COPD patients with dyspnea. The use of new comprehensive automatic titration devices (Auto-IPAP, Auto-EPAP, and Auto-backup speed) instead of devices which make flow wave analysis to detect upper airway obstruction, increases NIV comfort and compliance in patients with hypercapnic COPD-OSA, while enhancing NIV comfort and safety [11].

54.7 NIV in Bronchiectasis

COPD and bronchiectasis have many pathophysiological similarities, and NIV treatment is useful in increasing airway patency and clearence in bronchiectasis. However, early observational studies in mixed cohorts of patients with chronic respiratory failure identified, in contrast to other groups with chronic respiratory failure, NIV does not achieve the desired success in bronchiectasis patients. In addition, the number of randomized controlled trails on this subject with the bronchiectasis patient group is insufficient. Unlike data in stable hypercapnic COPD, the literature on NIV in bronchiectasis consists only of small, observational studies with no RCTs. Moving forward, there are opportunities for RCTs early in the course of disease, perhaps targeting development of overnight hypercapnia to define when respiratory support may be most useful.

54.8 NIV in Cystic Fibrosis

Unlike bronchiectasis in CF, there are a few small studies showing that NIV improves airway clearance. NIV provides advantages over invasive ventilation as it provides coughing and phlegm clearance and may prevent ICU entry. It is widely used in home treatment of NIV for bridge to transplantation and end-stage CF for palliative treatment.

54.9 NIV in Obesity Hypoventilation

NIV improves respiratory mechanics, carbondioxide sensitivity, arterial blood gas values, sleep quality and clinics of patients with obesity hypoventilation syndrome (OHS). It also provides a significant reduction in annual hospitalization rates. NIV acts by several mechanisms in the improvement of OHS outcomes. The most important is the correction of obstructive sleep apnea which is found in most patients. It also affects lung volumes, inspiratory muscle functions, and improves central respiratory impulse.

The use of NIV in this population has increased dramatically over the past 15 years, although the evidence base for the shift in respiratory support from CPAP is somewhat lacking. There is good evidence that PAP improves outcomes in OHS, but randomized controlled trials comparing CPAP and NIV have been either too short or too small to demonstrate significant differences in mortality to date [10]. Until those data become available, an individualized, patient-centered approach in provision of respiratory support, with a switch from CPAP to NIV in those patients who require high CPAP pressure, are in respiratory failure, or have residual OHS despite CPAP, seems sensible. PAP is only one aspect of supporting the obese patient; optimal lifestyle advice must be delivered in the context of an integrated bariatric service with surgical interventions available.

54.10 Palliative NIV

In many cases of severe respiratory failure, the home NIV system is used to improve survival and quality of life. Reducing dyspnea or reducing respiratory symptoms during sleep and providing optimal use of opiates may be the sole purpose. Therefore, home NIV can be used as a palliative tool in patients with ALS/motor neuron disease and has been shown to reduce dyspnea and opiate requirements in patients with end-stage cancer and respiratory failure [2–4].

54.11 Ventilator Settings and Compliance

In addition to patient selection, adequate establishment of ventilator settings are thought to play an important role in the success of home NIV treatment.

Based on this observation, one could conclude that a substantial improvement in alveolar ventilation is needed both for treatment success and a better outcome in chronic hypercapnic COPD patients.

Regarding the application of increased IPAP levels, it should be noted that mechanical ventilation can affect cardiac output. Nevertheless, cardiac output can be reduced by the application of higher IPAP levels, especially in patients with pre-existing heart failure and should therefore be applied with caution. Despite this, there has so far been no reason for withholding home NIV therapy from chronic hypercapnic COPD patients due to concerns about adverse cardiac outcome.

Home NIV vs. conventional NIV showed similar effects (e.g., improvements in gas exchange monitoring, exercise capacity, compliance, pulmonary function, and quality of life). However, one advantage of target volume NIV was that fewer titration days compared to the conventional NIV [12]. In light of this, target-volume NIV might serve as a means for faster establishment of home NIV in chronic hypercapnic COPD patients, although this remains speculative and needs to be investigated further.

54.12 Selection of Interface

The type of interface has been reported to be crucial for the success of NIV therapy in the acute and chronic settings. There is a broad variety of interfaces available, including nasal masks, oronasal masks, total face masks, or mouth pieces, depending on patient needs and ventilation strategies. However, further research is needed to elucidate the role of the interface in home NIV treatment of COPD and other subgroups of patients [13]. Materials have also progressed so that normally a silicone cushion is used, which is less irritating to the skin.

54.13 Conclusion

For patients with chronic respiratory failure, home NIV has become an important form of therapy in recent years, although there is no consensus in the relevant scientific literature. However, recent studies has demonstrated that home NIV is beneficial in long term survival as well as improvements in quality of life, gas exchange and lung function. These positive results were first observed in stable hypercapnic COPD patient subgroup. However, this indication should be considered because of lack of scientific evidence. While a treatment strategy aimed at lowering carbon dioxide levels by applying high inspiratory pressure forms the basis of therapeutic success, there is a clear trend towards the use of oronasal masksAll settings on home ventilators may affect patient compliance and tolerance. Health care providers who make the ventilator settings should be aware of the effects from each setting and the possible damages associated with settings that are not appropriate for each patient. Increasing NIV compliance in patients is crucial in reducing recurrent

hospitalizations and secondary health care costs. Recent studies in this area have been aimed to better understand the pathophysiological changes in patients using long term ventilation. It should focus on selecting the most suitable candidates for home NIV, taking into account the degree of hypercapnia.

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Chapter 55
Comorbidities Conditions Impact (Renal Failure/Liver Failure/Neurologic) in Non Invasive Mechanical Ventilation

Kamil İnci

Abbreviations

ARF	Acute respiratory failure
CKD	Chronic kidney disease
CLD	Chronic liver disease
ED	Emergency department
IMV	Invasive mechanical ventilation
NIV	Noninvasive ventilation

55.1 Introduction

The use of noninvasive ventilation (NIV) in acute respiratory failure (ARF) is increasing primarily to avoid the adverse events of invasive mechanical ventilation (IMV). As an initial treatment strategy, NIV accounts for approximately half of the total mechanically ventilated ARF patients [1]. Most of these mechanically ventilated patients with ARF are the ones with exacerbations of chronic obstructive pulmonary disease (COPD) and acute cardiogenic pulmonary edema [1]. However, the specific role of NIV in these patients with comorbidities and how comorbidities affect the outcome is not a topic that is mostly emphasized.

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Although the mechanism of relationship is not elucidated clearly yet, there are studies linking chronic kidney disease (CKD) with COPD, which possibly may be as a result of an underlying systemic inflammatory process [2]. Moreover, it is well known that patients with CKD are more prone to metabolic acidosis which was reported to be a significant predictor of NIV failure in patients with ARF [2]. This may be explained by the loss of renal compensation ability in patients with respiratory acidosis like COPD exacerbation. Additionally, positive fluid balance, which may also be a result of CKD may worsen clinical outcomes in most of the mechanically ventilated patients regardless of the mechanical ventilation type or ARF etiology.

Several pulmonary complications may occur in relation with underlying liver disease. Diaphragm elevation may be the result of ascites, diaphragmatic defects may allow ascites fluid to shift into the pleura and cause hydrothorax and these conditions may both cause loss of pulmonary functions with or without causing pulmonary atelectasis [3]. Additionally, hepatic encephalopathy may be the reason of respiratory abnormalities by itself. But, more serious respiratory complications of liver disease are hepatopulmonary syndrome and portopulmonary syndrome which are caused by pulmonary vascular abnormalities [3]. All these effects of chronic liver disease (CLD) on respiratory system are challenging issues and all of them may significantly effect the outcome of mechanical ventilation strategy. In the aspect of NIV, pleural effusion, atelectasis, hypoxemia and level of consciousness may be the primary factors that may cause treatment failure in patients with liver disease.

Noninvasive ventilation is standard practice for patients with neuromuscular respiratory failure [4]. There are studies linking NIV treatment with life prolonging in patients with Duchenne muscular dystrophy and amyotrophic lateral sclerosis [4]. Insufficient vital respiratory capacity, overnight hypoventilation and weaning from mechanical ventilation are main indications for NIV in this patient population and patients should be monitorized carefully to decide the timing of the treatment. Additionally, more frequent diseases like dementia and cerebrovascular diseases may also mediate respiratory complications in various ways like recurrent lower respiratory infections in relation with aspiration of gastric contents.

Case Presentation

A 75 year old male, a follow up case of chronic renal failure, heart failure and dementia, presented to the Emergency Department (ED) with complaints of dyspnea, acute cough and purulent sputum, followed by increasing fatigue and somnolence for 2 days. His next of kin also gave history that he had hypertension for 30 years, he was undergoing hemodialysis treatment for 4 h a day, three times a week for 10 years and he was diagnosed with dementia 2 years ago. He had complaints of forgetting locations of objects at the time of diagnosis and he is losing balance while walking and has effortful and prolonged chewing for 6 months with no additional limitations in his daily life. Presently he was on amlodipine besylate 10 mg/day, calcium acetate 1400 mg/day and donepezil 2.5 mg/day. On examination, he was somnolant with a Glasgow Coma Score (GCS) of 10, afebrile, and with

a pulse rate of 115 beats/min, blood pressure of 100/70 mmHg, respiratory rate of 34/min. Saturation of peripheral oxygen was 94% with a reservoir mask of 6 l/min. On physical examination, he was somnolent but had no lateralizing neurological sign, had bilateral diffuse rhonchi and weak respiratory sounds were heard in the lower left chest. Chest X-ray showed basal left pulmonary infiltrate and arterial blood gas results were as follows; pH: 7.17, PaO_2: 77 mmHg, SpO_2: 96%, $PaCO_2$: 62 mmHg and HCO_3: 15 mmol/l (Under a reservoir mask of 6 l/min). Than he was shifted to respiratory intensive care unit (ICU). Medications including salbutamol nebulizer (ventolin®, GlaxoSmithKline, Australia) and antibiotherapy for potential gastric aspiration related or community-acquired pneumonia (piperacillin tazobactam-Tazocin®, Wyeth Lederle S.r.L, Catania, Italy) were initiated. Laboratory tests revealed a serum C-reactive protein (CRP) level of 66 mg/dl (normal <14 mg/dl), white blood cell (WBC) count of 14,000 cells/μl, serum creatinine of 5.24 mg/dl (estimated glomerular filtration rate [CKD-EPI] < 15 ml/min) and a serum urea of 116 mg/dl (normal 17–48 mg/dl). Detailed information about admission laboratory data is in Table 55.1. After ICU admission, noninvasive ventilation (NIV) was initiated with bi-level positive airway pressure (BiPAP) at FiO_2 of 50%, inspiratory and expiratory pressures of 15 and 5 cmH_2O respectively via an oronasal mask. Then, inspiratory and expiratory pressures were titrated until reaching 6–8 ml/kg tidal volume and SpO_2 > 90% while carefully monitorizing patient-ventilator synchrony and patient tolerance. One hour after the initial treatment, the patient was still somnolant, less responsive to communication and respiratory rate was 32 with BiPAP at FiO_2 40%, inspiratory and expiratory pressures of 20 and 5 cmH_2O respectively. Arterial blood gas analysis after 1 h of initial treatment was pH: 7.16, PaO_2: 79 mmHg, SpO_2: 94%, $PaCO_2$: 46 mmHg and HCO_3: 10 mmol/l. Following nephrology consultation, hemodialysis treatment was initiated in 1 h. Following hemodialysis session, his neurological status improved (GCS: 14) and arterial blood gases showed marked improvement (2 h after hemodialysis, pH 7.36, PaO_2 79 mmHg, SpO_2 94%, $PaCO_2$ 39 mmHg and HCO_3 19 mmol/l). In second ICU day, the patient had acute onset coughing, wheezing and shortness of breath after first attempt of oral feeding. Than a nasoduodenal feeding tube was placed and respiratory symptoms did not recure thereafter. Patient improved subsequently and his ventilatory support was discontinued after 3 days. He had another 4 h hemodialysis treatment at third ICU day. Arterial blood gas analysis was normal on day 4 (room air: pH: 7.41, PaO_2: 74 mmHg, SpO_2: 95%, $PaCO_2$: 39 mmHg and HCO_3: 22 mmol/l). Videofluoroscopic swallowing examination resulted oropharyngeal swallowing dysfunction. Because swallowing dysfunction is possibly depending on dementia progression, percutaneous gastrostomy was administrated. Patient had no complication during the hospital stay, he didn't need another session of hemodialysis and his renal function tests improved spontaneously. He was discharged on levofloxacin oral tablet, appropriate enteral feeding solutions and his previous medications on seventh hospital day.

Table 55.1 Laboratory findings on ICU admission

Parameter	Result	Normal range
Hemoglobin (g/dl)	13.2	(13–17)
White blood cell count (×10E3/μl)	**14**	(4.5–11)
Platelet count (×10E3/μl)	268	(166–368)
Fasting glucose (mg/dl)	115	(105–140)
Blood urea (mg/dl)	**116**	(17–48)
Creatinine (mg/dl)	**5.24**	(0.67–1.17)
Sodium (mmol/l)	138	(136–146)
Potassium (mmol/l)	4.67	(3.5–5.1)
Calcium (mg/dl)	8	(8.8–10.6)
Phosphorus (mg/dl)	2.6	(2.5–4.5)
Chloride (mmol/l)	101.3	(101–109)
Albumin (g/dl)	**2.98**	(3.5–5.2)
Alanine aminotransferase (U/l)	20	(0–50)
Aspartate aminotransferase (U/l)	39	(0–50)
Alkaline phosphatase (U/l)	66	(30–120)
Gamma glutamyl transferase (U/l)	30	(0–55)
Total bilirubin (mg/dl)	0.64	(0.3–1.2)
Direct bilirubin (mg/dl)	0.17	(0–0.25)
C-reactive protein (mg/l)	**66**	(0–8)
Blood gas analysis		
pH	**7.17**	(7.35–7.45)
PCO_2 (mmHg)	**62**	(33–45)
PO_2 (mmHg)	77	(80–100)
HCO_3 (mmol/l)	**15**	(22–26)
Thyroid stimulating hormone (mIU/ml)	1.02	(0.38–5.33)

ICU intensive care unit, *g/dl* gram/deciliter, *μl* microliter, *mg/dl* milligram/deciliter, *mmol/l* millimol/liter, *g/dl* gram/deciliter, *U/l* Units/liter, *μg/l* microgram/liter, *mmHg* millimeter Hg, *mIU/ml* Million International Units/milliliter

55.2 Discussion

Predictors of NIV failure is an important issue because of the strong link between NIV failure and poor hospital outcomes. Even though relationship is not well defined, there are trials showing that the presence of acute or chronic comorbidities may be stronger risk factors for NIV failure than the severity indices in patients with hypoxemic respiratory failure [5].

We present a case of a 75 year old man with chronic renal, cardiovascular and neurologic comorbidities who admitted to ED with hypoxemic and hypercapnic respiratory failure caused by aspiration pneumonia and metabolic acidosis caused by acute on chronic renal failure. At the beginning, NIV treatment was initiated because the patient had hypercapnic and hypoxemic respiratory failure. Even though appropriate ventilatory settings resulted lower PCO_2 values, clinical condition was

worse and arterial blood gas showed a serious metabolic acidosis after NIV treatment. Because the patient also had an acute on chronic renal failure in addition with respiratory failure caused by aspiration pneumonia, this made things even more complicated by causing metabolic acidosis which could be corrected by emergent hemodialysis treatment. Prolonged metabolic acidosis, application of central venous catheter and hemodialysis treatment itself could easily have caused important additional complications in a 75 year old patient with multiple comorbidities. Additionally, the beginning of all these problems in our case was an aspiration pneumonia which was caused by dementia, which is not a rare neurological comorbidity for elderly population.

The patient's chronic cardiac disease was stable and didn't result decompensated heart failure during the course of the disease in this case. But we should always be careful about the patients with cardiovascular disease because decompensated heart failure is one of the most frequent conditions that may be the reason of respiratory failure in this patient population. Additionally, any kind of respiratory failure resulting need of mechanical ventilation may cause a metabolic stress which may trigger a new cardiovascular event and this also may be another challenging issue for NIV success.

As mentioned before, hepatic encephalopathy, ascites and diaphragmatic dysfunction are the main pathologies causing respiratory failure and serious complications like hepatopulmonary syndrome and portopulmonary syndrome may cause poor outcome in patients with chronic liver disease. These conditions may easily be the reason of NIV failure when decompensated liver failure is not or can not be palliated or treated appropriately.

In conclusion, underlying renal, liver and neurologic comorbidities may have an important impact on NIV success. But we should also note that these comorbidities may be the reason of respiratory failure in the first place.

Key Teaching Points

- Heart failure may both be the cause and effect of respiratory failure. Thus, acute decompensation or cardiovascular event should immediately be detected and treated effectively to prevent NIV failure.
- Patients with CKD have less or no ability to compensate respiratory acidosis and are more prone to have positive fluid balance. Thus, these patients should be monitored more carefully than patients with normal renal functions and timing of interventions to correct renal failure or metabolic acidosis may be essential for NIV success in these patients.
- Hepatic encephalopathy and complications caused by uncontrolled ascites may be the most challenging issues which may determine NIV success in patients with chronic liver failure.
- Noninvasive ventilation is standard practice for patients with neuromuscular respiratory failure.

Questions and Answers

1. Which one is a less common reason causing acute respiratory failure (ARF) in pts with chronic liver failure?

   (a) Hydrothorax
   (b) Pulmonary atelectasis
   (c) Portopulmonary syndrome
   (d) Hepatic encephalopathy

   Answer: (c) Portopulmonary syndrome

2. Which is the main mechanism of NIV failure in ARF patients with chronic kidney disease?

   (a) Frailty
   (b) Level of hypercapnia
   (c) Loss of renal compensation ability in pts with respiratory acidosis
   (d) Requirement of hemodialysis treatment

   Answer: (c) Loss of renal compensation ability in pts with respiratory acidosis

3. Which is not a main indication for NIV in pts with neuromuscular respiratory failure?

   (a) Insufficient vital respiratory capacity
   (b) Persistent hypercapnia
   (c) Overnight hypoventilation
   (d) Weaning from mechanical ventilation

   Answer: (b) Persistent hypercapnia

4. In which patient group with neuromuscular respiratory failure, NIV is a life-prolonging treatment?

   (a) Cerebrovascular disease
   (b) Dementia
   (c) Duchenne muscular dystrophy
   (d) None of the above

   Answer: (c) Duchenne muscular dystrophy

5. Which of the following is correct?

   (a) Pts with CKD have enough ability to compensate respiratory acidosis
   (b) NIV should not be a standard practice for pts with neuromuscular respiratory failure
   (c) Pts with decompensated liver failure doesn't have an increased risk for ARF
   (d) None of the above

   Answer: (d) None of the above

6. What is the main advantage of NIV over invasive mechanical ventilation in patients with multiple comorbidities?

   (a) Better hospital outcome for all cases
   (b) Safer airway management for respiratory deterioration

(c) Avoiding complications of endotracheal intubation and providing better comfort while airway defense mechanisms are preserved
(d) None of the above

Answer: (c) Avoiding complications of endotracheal intubation and providing better comfort while airway defense mechanisms are preserved

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Chapter 56
Clinical Cases in Noninvasive Ventilation: Clinical Conditions—Hypercapnic Failure—Neuromuscular Disorders

Maria Joana Pereira and Maria João Matos

Abbreviations

CV	Vital capacity
EPAP	Expiratory airway pressure
FEV1	Forced expiratory volume in the first second
FVC	Forced vital capacity
IC	Inspiratory capacity
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
NIV	Non invasive ventilation
NMD	Neuromuscular disease
PCF	Peak cough flow
PEF	Peak expiratory flow
PSG	Polysomnography
WWS	Woodhouse-Sakati syndrome

56.1 Introduction

The Woodhouse-Sakati syndrome (WSS) is a rare autosomal recessive disease, caused by mutations of the DCAF17 gene. This gene encodes a nuclear transmembrane protein that associates with cullin 4A/damaged DNA binding protein 1 ubiquitin ligase complex. This protein is found in several organs and tissues in the body, including the brain, skin, and liver. However, the function of this protein is still unknown [1].

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WSS is a disorder that primarily affects the endocrine system and the nervous system. More than half of people with this syndrome have movement abnormalities called dystonias, generally beginning in adolescence or young adulthood. Muscle weakness can lead to ineffective cough and retained secretions, which predispose to recurrent pneumonias and atelectasis [2]. This may result in decreased lung compliance, increased airway resistance, and heightened ventilatory demands, eventually leading to respiratory insufficiency, first during sleep and subsequently progressing to diurnal hypoventilation. Dyspnea and fatigue are late symptoms of nocturnal hypoventilation [3].

Thus, a thorough clinical evaluation of respiratory health is important for all neurometabolic and neuromuscular diseases. Moreover, respiratory function exams and eventually type 1 polysomnographic study are crucial and can be used to help to evaluate the respiratory status at the time of diagnosis, monitor disease and carry out informed decision-making regarding to the initiation of non invasive ventilation and ventilatory parameters.

Clinical Case

A 32-year-old woman with the diagnosis of WSS was referred to Pulmonology department because of fatigue and progressive worsening of dyspnea, as well as progressive neurologic deficits namely dysarthria, dysphagia, lower limb dystonia and spastic tetraparesis. She also presented with dysmorphic facial features, alopecia, mild intellectual disability and sensorineural hearing loss. Her symptoms started at age of 19 with primary hypothyroidism, hypergonadotrophic hypogonadism, diabetes mellitus, and progressive neurologic deficits. She was the only child of a consanguineous couple. Common genetic, metabolic and mitochondrial diseases were excluded. Sequencing of DCAF17 gene detected the homozygous variant c.1091+2T>C, confirming the diagnosis of WSS.

At the age of 31, she started with symptoms of progressive worsening of dyspnea and fatigue, as well as morning headaches and poor sleep. A spirometry in sitting and supine positions, maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), peak cough flow (PCF) and blood gases analysis were performed. The spirometry revealed a moderate restrict syndrome, with MIP of 67.4 cmH_2O and MEP of 40.5 cmH_2O, reduced forced vital capacity of 15% with positional transition from seated to lied down and reduced peak cough flow of 200 L/min (Fig. 56.1 and Table 56.1). The arterial blood gases test revealed the following values: pH 7.40, pCO_2 44 mmHg, pO_2 77 mmHg, HCO_3-27 mmHg, SaO_2 95%.

Due to her symptoms compatible with nocturnal hypoventilation and signs of respiratory muscle weakness she started bi-level nocturnal non invasive ventilation (NIV). We performed titration of pressures and other ventilatory parameters through therapeutic polysomnography (PSG) to correct hypoventilation. The patient was submitted to bilevel positive airway pressure in a spontaneous time mode through a facial mask, IPAP of 14 cmH_2O, EPAP of 7 cmH_2O, respiratory rate of 12/min and inspiratory time of 1.3 s and complied to home NIV during night with controlled

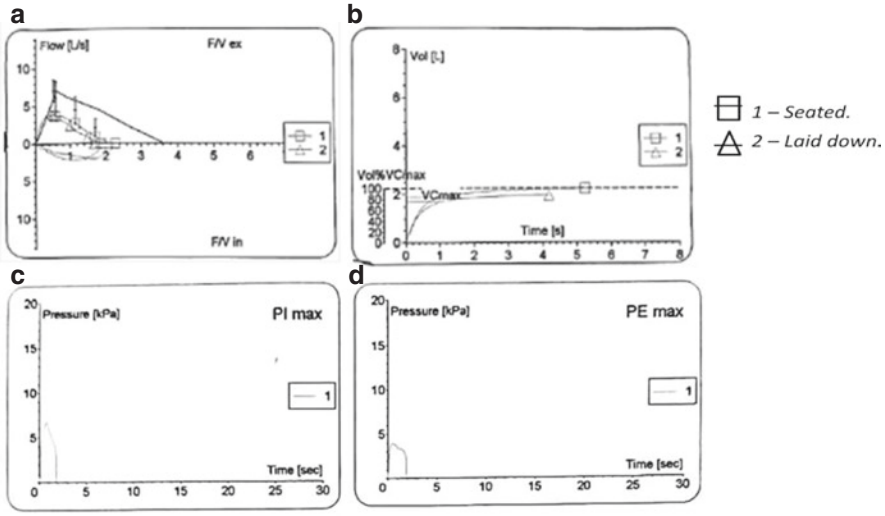

Fig. 56.1 (**a**) Flow-volume curve; (**b**) Vital capacity seated and laid down; (**c**) Maximal inspiratory pressure; (**d**) Maximal expiratory pressure

Table 56.1 Ventilatory parameters

	Unit	Theoretical value	Seated value	%Act./Th.	Laid down value
VC MAX	[L]	3.66	2.27	62.00	1.98
VC IN	[L]	3.66	2.17	59.20	1.83
IC	[L]	2.42			
FVC	[L]	3.61	2.27	62.90	1.98
FEV 1	[L]	3.14	1.87	59.60	1.66
FEV 1% FVC	[%]		82.40		84.18
PEF	[L/s]	7.03	3.71	52.70	4.00
MIP	cmH_2O	113.19		59.41	
MEP	cmH_2O	88.82		40.59	

VC vital capacity, *IC* inspiratory capacity, *FVC* forced vital capacity, *FEV1* forced expiratory volume in the first second, *PEF* peak expiratory flow, *MIP* maximal inspiratory pressure, *MEP* maximal expiratory pressure

leaks and current volume of 500 mL. The patient also started "air-staking" technique with a manual resuscitation bag to support cough. Continued follow-up appointments are required to assess disease progression and need for adjustment of ventilatory parameters. Therefore, it is essential to be aware of the symptoms compatible with hypoventilation and to obtain in the consultations the value of PCF, vital capacity and gasometry. Whenever necessary, nocturnal oximetry helps to rule out episodes of desaturation at night. Currently, the patient has no symptoms and she presents good clinical results during day and night.

56.2 Discussion

Neuromuscular diseases (NMD) are a broadly defined group of disorders that all involve injury or dysfunction of peripheral nerves or muscle. The site of injury can be in the cell bodies, axons, Schwann cells, neuromuscular junction, muscle or any combination of these sites. Moreover, these disorders might affect the respiratory muscles which lead to respiratory failure [4]. WSS is a neurometabolic disease that can progress into muscle weakness, resulting in a similar clinical presentation as some neuromuscular diseases. Depending on the type of NMD, an assessment of muscle weakness and fatigability, change in voice or cough strength, sialorrhea, secretion management problems and recurrent respiratory infections are relevant [2].

The nocturnal hypoventilation most commonly manifests initially in neuromuscular diseases and manifest as daytime hypersomnia, morning headaches, insomnia, nightmares and poor sleep quality. Muscle immobility, contractures, joint pain, muscle cramps, and anxiety may all contribute to sleep disruption [3]. Most neuromuscular diseases are risk factors for the development of obstructive sleep apnea and hypoventilation-hypoxemia syndrome. In REM sleep, there is loss of tonic activity in the muscles of the tongue, pharynx, larynx, and intercostal region and upper airway resistance increases predisposing to upper airway occlusion and obstructive sleep apnea. In fact in REM sleep, the diaphragm is the only functional respiratory muscle. Patients who have weak pharyngeal dilator muscles and a weak diaphragm as a result of a diffuse neuromuscular disorder exhibit the most serious ventilatory compromise in REM sleep [5]. Increased nocturnal CO_2 (capnometry/capnography) is also a hallmark of alveolar hypoventilation during sleep and respiratory muscle weakness. Later signs of muscle weakness manifest as fatigue and dyspnea with respiratory failure (type 2 respiratory insufficiency).

Respiratory function tests are crucial to determine the grade of muscle and diaphragmatic weakness. Both FEV1 and FVC are particularly pertinent in individuals with NMD. They are often reduced in NMD patients compared to healthy controls because they are determined by inspiratory and expiratory muscle strength as well as by chest wall and lung compliance [2]. Total lung capacity itself is reduced because of reduced muscle strength, and as a result, there is a reduction in the exhalation airflow despite structurally normal airways. The volume of FEV1 is reduced in proportion to FVC. Therefore, the FEV1/FVC ratio generally remains in the normal range (i.e., 80–100%) or may even be high. This constellation of spirometry findings is categorized as being consistent with restrictive lung disease [2]. In contrast to FVC, vital capacity (VC) does not require a forceful manoeuvre but still records the maximum amount of air an individual can expel from the lungs after a maximum inhalation. In fact, VC should be measured in all patients with NMD as part of the respiratory assessment. It may be particularly helpful in monitoring disease progression [2].

The MIP reflects the strength of the diaphragm and other inspiratory muscles, while the MEP reflects the strength of the abdominal muscles and other expiratory muscles [6]. Moreover, a decrease in vital capacity more than 25% with positional

transition from seated to lied down, suggests significant diaphragmatic weakness. A different, but complementary test to the MIP is the maximal sniff nasal pressure (SNIP). Sniffing manoeuvres are more reproducible than the sustained efforts used for measuring MIP, and problems related to mouth weakness are avoided. Moreover, cough expiratory airflow can be measured and is known as peak cough flow (PCF). Individuals with weak or impaired inspiratory and/or expiratory muscles, with or without glottis closure issues (bulbar insufficiency, tracheostomy), will have decreased PCF [6]. Coughing weakness (PCF < 270 L/min) indicates the need for the initiation of secretion management. Patients with PCF under 160 L/min should use mechanical insufflation-exsufflation device several sessions during the day.

In addition to secretion management techniques, NIV is crucial for the treatment of respiratory failure due to neuromuscular disease and has been shown to increase overall survival. NIV should be initiated in patients with neuromuscular disease with symptoms (such as fatigue, dyspnea, morning headache) and one of the following physiologic criteria: $PaCO_2 \geq 45$ mmHg (or $TcCO_2$); nocturnal oximetry demonstrating oxygen saturation $\leq 88\%$ for five consecutive minutes; MIP < 60 cmH_2O or FVC < 50% predicted (amyotrophic lateral sclerosis with FVC $\leq 70\%$); reduction of FVC at lied down position >25%; a rapid, significant reduction in VC [7].

Bi-level positive airway pressure (BiPAP ventilator) is the most commonly used device to manage respiratory weakness. These machines are set to deliver a specific inspiratory airway pressure (IPAP) and expiratory airway pressure (EPAP), similar to a pressure-controlled mechanical ventilator. The difference in pressure between IPAP and EPAP represents the level of pressure support. Typically, bi-level PAP has two modes: spontaneous (S) and spontaneous/timed (ST). Some patients may have abnormal central respiratory drive and will benefit from having a set backup respiratory rate. Therefore, it is recommended to use ST mode with high back-up respiratory rates and increase respiratory rate with the progression of the disease. Ventilator settings should be adjusted for optimal patient comfort and improvement of symptoms. NIV should be used pressure cycled during night, however, during the day it is possible to ventilate with pressure or volume-cycled [7]. It is reasonable to begin NIV with 8 cmH_2O IPAP and 4 cmH_2O EPAP and increase the IPAP to alleviate symptoms, or to select the initial pressure based on improvement in daytime arterial blood gases and oximetry/capnography together with patient comfort. When titrating to comfort, increases in IPAP of 2 cmH_2O are reasonable for each adjustment [7].

It is also recommended to use multimodal NIV to prevent skin lesions due to pressure namely mouthpiece during the day, nasal or facial mask at night, and two ventilators (two batteries) when dependence to NIV is above 16–18 h/24 h accepted as “Life sustaining devices”.

In conclusion, it is important to be alert to the signs and symptoms of nocturnal hypoventilation in patients with neuromuscular or neurometabolic diseases. In this clinical case, the patient presented complaints of morning headaches, fatigue, poor sleep and respiratory function test revealed a restrictive respiratory pattern with a decrease of MIP and VC showing a diaphragmatic weakness. Therefore it was necessary to start NIV to correct hypoventilation.

Key Teaching Points

- Patients with NMD at risk of developing respiratory muscle weakness should undergo regular examinations of lung function and blood gases.
- NMD patients should have VC, MIP, and MEP assessed approximately every 2–6 months irrespective of respiratory symptoms. Supine FVC should be considered, as it can detect milder respiratory muscle weakness.
- Polysomnography and $PTcCO_2$-measurement are indicated when VC is <70%.
- The most important criteria for the initiation of NIV are hypercapnia in combination with the characteristic symptoms of ventilatory failure, and a reduction in quality of life.
- The measurement of coughing capacity in NMD patients is obligatory. Coughing weakness (PCF < 270 L/min) indicates the need for the initiation of secretion management.

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Chapter 57
Clinical Case in Noninvasive Ventilation: Clinical Conditions—Respiratory Care of Neuromuscular Disorders—A Rare Case of Charcot-Marie-Tooth Disease (CMT2S)

Richa Kulshrestha, Tracey Willis, and Martin Samuels

Abbreviations

CMT	Charcot Marie Tooth disease
FVC	Forced vital capacity
IGHMBP2	Immunoglobulin-helicase-μ-binding protein 2
LRTI	Lower respiratory tract infection
MEP	Maximal expiratory pressure
MI-E	Mechanical insufflation-exsufflation
MIP	Maximal inspiratory pressure
NIV	Non-invasive ventilation
NMD	Neuromuscular disorder
ODI	Oxygen desaturation index
PCF	Peak cough flow
SMARD1	Spinal muscular atrophy with respiratory distress type 1
VC	Vital capacity

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57.1 Introduction

Over 75 genes are attributed to Charcot-Marie-Tooth disease, an inherited progressive motor and sensory polyneuropathy. Amongst them is the Immunoglobulin-helicase-μ-binding protein 2 (IGHMBP2) gene that causes a spectrum of phenotype with a rare fatal disorder spinal muscular atrophy with respiratory distress type 1 (SMARD1) at one end and progressive neuropathy (CMT2S) at the other. We describe a journey of a young patient with this gene mutation that highlights the principles of management of patients with paediatric neuromuscular disorders.

57.2 Discussion Based on Case Clinic

57.2.1 Development and Progress

A Caucasian male patient, was born healthy. At 6 months he developed bilateral talipes equinovarus deformities of feet. He had distal weakness of lower limbs at presentation and had upper limb involvement at 21 months. He never achieved independent walking but was able to walk at 2 years with K-walker. Weakness was progressive with involvement of proximal muscles of limbs and truncal involvement with poor head control. He was wheelchair dependent at 8 years. He also developed scoliosis and contractures of joints.

He had a weak cough. He struggled to swallow lumpy food from early on but managed soft textures like yoghurt and custard. He had a normal videofluoroscopy. He was supported with a high calorie diet, but weight continued to drop below 0.4th centile. He had a feeding gastrostomy and weight stabilized at second centile.

He started to develop scoliosis around 8 years. It was S-shaped curve that was progressing rapidly. This was affecting his posture, seating and neck control. He was provided with a rigid spinal brace. He had six monthly checks for respiratory status for forced vital capacity (FVC) and yearly cardiorespiratory polygraphy. His FVC was consistently low. At 8½ years his FVC was 0.87 l (51% expected), cardiorespiratory polygraphy showed normal breathing patterns (no apnoea/hypopnoeas), SpO_2 96.0–98.5%, median 97.3%, no study nadir, and 0.1% of sleep spent <95%, Oxygen Desaturation Index (ODI) of 0 dips/hour, and transcutaneous pCO_2 was 5.2–6.0 kPa.

57.2.2 Acute Deterioration of the Patient at 9 Years

At 9 years, this young boy developed chest infection with left sided pleural effusion (Fig. 57.1) drained by video assisted thoracoscopy, haemo-serous fluid was drained and had no growth on culture. He was electively ventilated for 24 h and

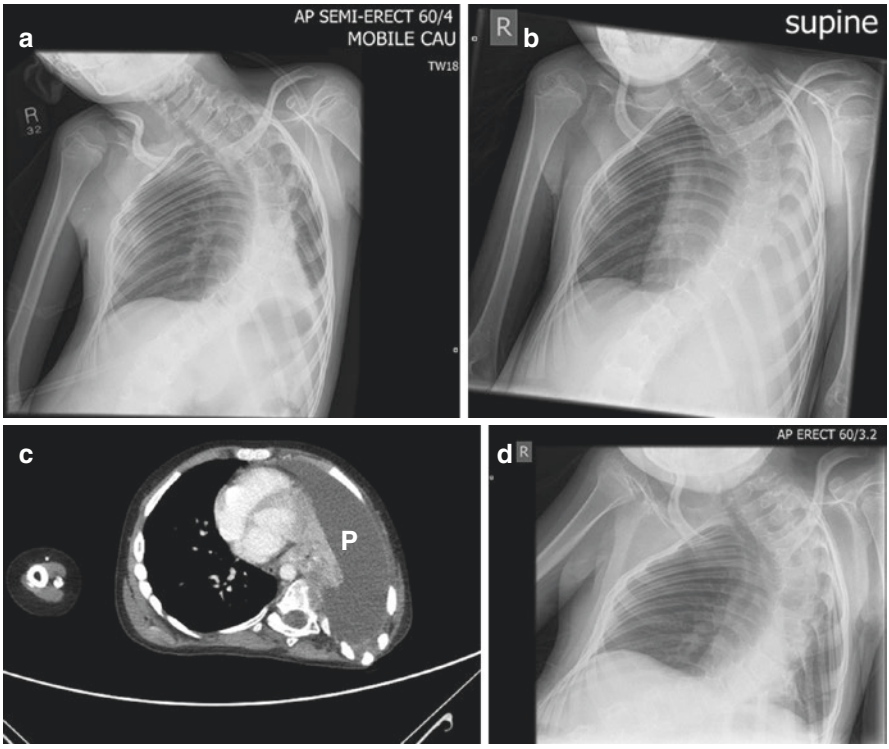

Fig. 57.1 At 9 years. (**a**) Chest X ray at presentation with shortness of breath (SOB) left hemi diaphragm is effaced, with volume loss suggestive of left lower lobe consolidation. There is marked thoracic scoliosis, concave to the right. (**b**) Chest X ray 20 days later. The left lung appearances have worsened with complete white out of the visualised left lung and effacement of the left heart border and the left hemi diaphragm. Trachea appears to be normally positioned, allowing for the scoliosis and the rotation. The right lung is unremarkable. Diagnosis consistent of collapse or consolidation. (**c**) CT thorax confirming left pleural effusion (P). (**d**) Two months post drain: The lungs appear clear and there is no evidence of pleural fluid. Patient still complains of SOB. (Reprinted from Charcot Marie Tooth disease type 2S with late onset diaphragmatic weakness: An atypical case, Vol 28, Richa Kulshrestha, Natalie Forrester, Thalia Antoniadi, Tracey Willis, Sethil Kumar Sethuraman, Martin Samuels, Pages 1016–1021, Copyright (2018), with permission from Elsevier)

then successfully extubated. Left lung expansion confirmed on chest-X ray (Fig. 57.1). After discharge from the hospital he continued to struggle with shortness of breath which was aggravated with the use spinal brace. FVC deteriorated from 0.87 (51% predicted) to 0.35 l (19% predicted). Urgent cardiorespiratory polygraphy showed a marked deterioration, with SpO_2 median 92.5%, 88.3–95.5% (5th, 95th centiles), nadir 77.0% and 89% of sleep spent <95%, and 14% of study spent <90%. He had marked cyclical attenuation of respiratory movements in active sleep resulting in 71 dips/hour (ODI 4%) and ODI 10% of 5 dips/hour (Fig. 57.2), transcutaneous pCO_2 was 7.9–8.7 kPa. He had developed severe respiratory failure, so he was immediately initiated on mask BiPAP and discharged

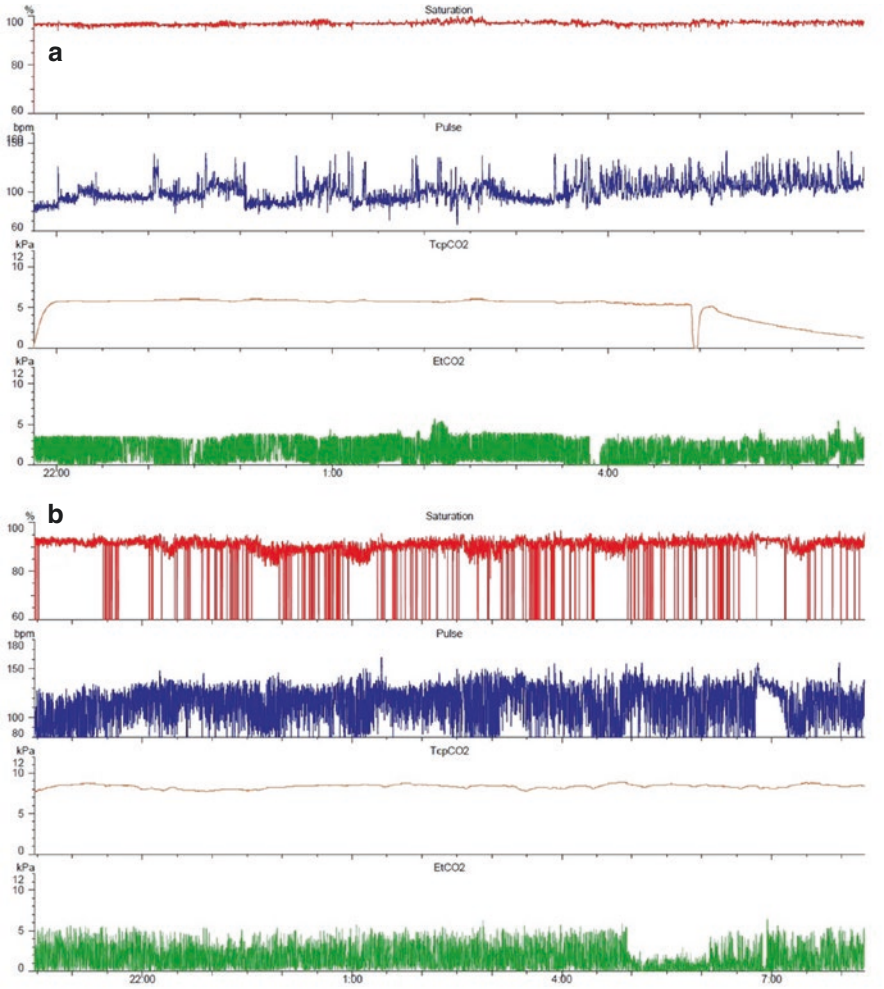

Fig. 57.2 Shows overnight screenshots of two cardiorespiratory polysomnography studies: (**a**) at 8.5 years and (**b**) at 9.3 years. The signals are from top down: SpO_2, pulse rate, transcutaneous pCO_2 and end-tidal CO_2. Study **a** shows normal oxygen and carbon dioxide levels through the night, while study **b** shows abnormally low SpO_2 and raised transcutaneous pCO_2, with poor end-tidal signals. There is a large amount of signal drop-outs on SpO_2 and pulse. (Reprinted from Charcot Marie Tooth disease type 2S with late onset diaphragmatic weakness: An atypical case, Vol 28, Richa Kulshrestha, Natalie Forrester, Thalia Antoniadi, Tracey Willis, Sethil Kumar Sethuraman, Martin Samuels, Pages 1016–1021, Copyright (2018), with permission from Elsevier)

receiving Stellar Resmed ST Mode 14/6 cmH_2O, back-up rate 18 breaths/min, Ti 0.7–1.2 s and 15-min ramp. Six months later, his FVC had improved to 0.4 l, and cardiorespiratory polygraphy showed an excellent response to BiPAP with SpO_2

95.8–98.0%, median 96.8%, study nadir 92.0% and 0.5% of sleep spent <95%. He was synchronizing with the ventilator and an Oxygen Desaturation Index 0.6 dips/hour (ODI 10% was 0). Transcutaneous pCO_2 improved to 6.2–6.9 kPa. In the following months the scoliosis rapidly progressed. Gas exchange had deteriorated and his FVC fell further to 0.28 l (15% predicted). He was on a waiting list for spinal surgery which had to be expedited. Preoperative echocardiography was normal. Following the surgery he resumed to all day BiPAP and was then successfully weaned to night time ventilation. This child's respiratory deterioration was attributed to acute infection, progressive scoliosis and diaphragmatic weakness which was not easily identifiable. At 13 years he is enjoying good quality of life in mainstream education. His latest polygraphy showed SpO_2 96–98.5%, median 97%, study nadir 93.4% and 0.1% of sleep spent <95%. He has good synchrony with the ventilator and an Oxygen Desaturation Index 0.7 dips/hour (ODI 10% was 0). Transcutaneous carbon dioxide is 5.8–6.2 kPa. He is using only night time ventilation and does not need oxygen. He continues with prophylactic co-amoxiclav to prevent infections.

The challenges in this young boy were to maintain adequate growth with nutritional optimisation, monitor and treat respiratory and orthopaedic complications. Standards of care guidelines are available for Duchenne muscular dystrophy [1] and spinal muscular atrophy [2]. Consensus statement for best practice guidance is available for congenital myopathies [3]. There is no specific individual guidance about management of other rare neuromuscular problems but clinical practice involves monitoring and treating for respiratory, cardiac, orthopaedic, nutritional and psychological symptoms and complications.

57.2.3 Best Clinical Practice Statement from the Recommendations of British Thoracic Society Guidelines [4]

57.2.3.1 Respiratory Management

Patients with a neuromuscular disorder (NMD) are at risk of respiratory complications like hypoventilation, airway obstruction, aspiration, lower respiratory tract infection (LRTI), and mechanical effects of scoliosis. Patients need regular respiratory and neuromuscular monitoring to identify sleep disordered breathing and prevent its progression to respiratory failure, a common cause of mortality in neuromuscular diseases [5, 6]. Assessments are needed to ascertain progression of muscle weakness, fatigability, change of strength of voice/cough, problem with clearing secretions, choking with food or chewing difficulties, posture and growth. Symptoms of sleep disordered breathing that develop gradually over a span of weeks and months like disturbed sleep, morning headaches, daytime sleepiness, poor concentration and fatigue are to be noted. Progressive weakness can lead to

day time hypoventilation presenting with signs and symptoms of headache, nausea, dyspnoea, tachycardia, sweating and peripheral vasoconstriction or vasodilatation. Vital capacity (VC) <1.1 l and peak cough flow (PCF) <160 l/min has strong correlation with number of chest infection [7]. Annual monitoring of FVC and six monthly review of FVC, maximal inspiratory and expiratory pressure (MIP/MEP), PCF, are recommended [1]. Standard of care for Duchenne muscular dystrophy also recommends sleep study with capnography for signs and symptoms of obstructive sleep apnoea and sleep disordered breathing [1]. Patients would need non-invasive positive pressure ventilation (NIV) if they are symptomatic, have sleep disordered breathing or respiratory failure. Immunization with pneumococcal and influenza vaccine is recommended and some may need prophylactic oral antibiotics.

57.2.3.2 Airway and Secretion Management

Patients with ineffective cough should have access to manual chest physiotherapy along with mechanical insufflation-exsufflation (MI-E) (Cough Assist® or VitalCough®) [2]. Standard chest therapy involves postural drainage with manual percussion. Glossopharyngeal breathing also known as 'frog breathing' helps to augment cough. It consists of series of 6–10 pumping strokes of lips, tongue, soft pallet, pharynx and larynx while air is held in chest by the valvular function of larynx [8]. Nebulised bronchodilators, saline and mucolytics can be used if secretions are tenacious and may be especially helpful before physiotherapy. Humidification should be considered for patients on NIV with tenacious secretions. For patients with excessive drooling glycopyrrolate or hyoscine patch or soluble tablets (6–8 hourly) are tried. Atropine eye drops can be used for troublesome oral secretions alone, but long term botulinum toxin injections in the salivary glands or surgical procedures can be considered.

57.2.4 Nutrition

Patients with NMD with facial muscle involvement and bulbar weakness frequently have difficulty in chewing and swallowing. Videofluoroscopy and feeding advice from specialist therapist is indicated. They are also prone to gastro-oesophageal reflux requiring antacids, histamine H2-receptor antagonist, proton pump inhibitors and pro-kinetic agents. All these factors can negatively impact the nutrition and growth. Feeding by gastrostomy tube is common amongst these patients. The aim of maintaining good nutrition is to reduce aspiration, enhance the quality of life with positive experience of oral feeding wherever possible.

57.2.5 Orthotics

Scoliosis in NMD impacts respiratory function and stability of neck and pelvic muscles. This affects posture and increases risk of pressure sore particularly in wheelchair dependent patients. Rigid brace from axilla to iliac crest are poorly tolerated and no evidence of its impact in affecting final scoliosis severity. Non-rigid dynamic braces are better tolerated but no evidence about their superiority over the rigid ones. Either of these can reduce the vital capacity and tidal volume hence should be used cautiously in patients with respiratory weakness. Surgical correction of scoliosis corrects the posture but not necessarily the respiratory function. It is indicated for rapid curve progression, uncomfortable sitting, effect on mobility and pain.

57.3 Summary

This case discussion highlights the need of regular respiratory surveillance of neuromuscular patients. In this patient with the current understanding of *IGHMBP2* variants, protein expression and gene modifiers it is hard to explain the reason for rapid diaphragmatic weakness. This could be secondary to environmental factors like chest infections triggering the weakness, and respiratory decline was exacerbated due to additional rapidly progressive scoliosis. Aggressive respiratory and surgical management helped him to achieve good outcome.

Key Teaching Points

- Every medical assessment for patients with NMD should include assessment of respiratory function and weakness.
- Detailed history of symptoms of sleep disordered breathing and obstructive sleep apnoea to be taken.
- Scoliosis evaluation should be part of clinical examination.
- Annual cardiorespiratory polygraphy is good clinical tool to identify deterioration.
- Weaning of ventilation should be slow and cautious after acute deterioration.

Questions and Answers

1. Which statements are true for neuromuscular patients:

   (a) Forced vital capacity (FVC) correlates with survival in patients with muscular dystrophy
   (b) There is considerable drop in FVC with loss of upper limb function.

(c) FVC < 60% and cough peak flow <270 l/min is at risk of chest infection and day time respiratory failure
(d) All of the above

Answer: (d) All of the above

2. Which of the following is not symptoms of sleep disordered breathing in neuromuscular patients:

(a) Tiredness
(b) Early morning or continuous headaches
(c) Seizures
(d) Poor concentration, nausea, hyper somnolence, dyspnoea or nocturnal awakening

Answer: (c) Seizures

3. Choose the right statement for airway clearance and secretion management:

(a) In NMD muscle weakness can cause ineffective coughing and function of mucocilia being hampered by multiple chest infections.
(b) 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}).
(c) Vibrations of chest wall produce oscillatory flow with mobilisation of secretions
(d) All of the above

Answer: (d) All of the above

4. What is the indication for assisted ventilation in neuromuscular patients:

(a) Low SpO_2 < 95% or pCO_2 > 45 mmHg or symptomatic dyspnoea
(b) Cough peak flow of >150 l/min.
(c) Asymptomatic hypoventilation.
(d) Normal polysomnography or cardio-respiratory polygraphy.

Answer: (a) Low SpO_2 < 95% or pCO_2 > 45 mmHg or symptomatic dyspnoea

5. Which of the following is true for ventilating neuromuscular patients:

(a) Consider tracheostomy and invasive ventilation if using >16 h/day of NIV
(b) The ventilation mode of choice is bi-level positive airway pressure which can support inspiration by application of peak inspiratory pressure (PIP)
(c) Continuous positive pressure ventilation (CPAP) 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.
(d) All of the above

Answer: (d) All of the above

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Chapter 58
Clinical Case in Noninvasive Ventilation: Clinical Conditions—Hypercapnic Failure—Neuromuscular Disorders in Amyotrophic Lateral Sclerosis

Joana Barbosa, Sara Salgado, and Paula Esteves

Abbreviations

ALS	Amyotrophic lateral sclerosis
AVAPS	Average volume-assured pressure support
BiPAP	Bilevel positive airway pressure
Bpm	Breaths per minute
EPAP	Expiratory positive airway pressure
FEV1	Forced expiratory volume in the first second
FiO_2	Fraction of inspired oxygen
FVC	Forced vital capacity
Hb	Hemoglobin
HCO_3^-	Bicarbonate
Htc	Hematocrit
IPAP	Inspiratory positive airway pressure
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
NIV	Noninvasive ventilation
NMD	Neuromuscular disease
NT-proBNP	N-terminal pro-brain natriuretic peptide
O_2	Oxygen

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$PaCO_2$	Arterial carbon dioxide partial pressure
PaO_2	Arterial oxygen partial pressure
$PtcCO_2$	Transcutaneous carbon dioxide
RR	Respiratory rate
RV	Residual volume
S/T Mode	Spontaneous/timed mode
SpO_2	Peripheral oxygen saturation
TLC	Total lung capacity
VC	Vital capacity

58.1 Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neuromuscular disease that affects all muscular groups with exception of extrinsic muscles of the eye and sphincters [1]. Respiratory and upper airway muscles weakness can cause insufficient ventilation, ineffective cough and bulbar dysfunction [2]. These complications generally start in late stages of disease [1]. However, dyspnea can be the first symptom in only 1–3% of cases, respiratory failure requiring mechanical ventilation being even more rare [2].

We present a case of a 75 year old man, former smoker (45 pack-year), with a previous history of diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease and repeated respiratory infections. He was sent to the emergency department with fatigue and dyspnea. He also reported hand tremors, imbalance and dry cough which intensified within 2 months. At admission, he presented respiratory failure with respiratory acidemia with progressive worsening of acidosis (Table 58.1). Blood analyses showed Hb 11.7 g/dL, Htc 40.8%, without increased inflammatory parameters and NT-proBNP 616 pg/mL. He started noninvasive ventilation with bilevel positive pressure (BiPAP; Respironics V60; Carlsbad, USA) and the following parameters: IPAP 14 cmH_2O, EPAP 6 cmH_2O, RR 18 bpm, FiO_2 28%, S/T mode, using an oronasal mask. Parameters were adjusted with increased support pressure (IPAP 16 cmH_2O, EPAP 4 cmH_2O, RR 18 bpm) with gasometric improvement, showing good volumes and tolerability; he was then transferred to the pulmonology department. During hospitalization, he maintained NIV during periods of daytime and night, with IPAP 18 cmH_2O, EPAP 4 cmH_2O, RR 14 bpm, showing clinical improvement of symptoms and gasometric values. A weak peak cough was observed. Respiratory function tests showed a MIP 2.19 kPa (28%), MEP 4.65 kPa (37%), with FEV1/FVC 72.77%, FEV1 1.30 L (49%), FVC 1.78 L (51%), RV 3.63 L (138%) and TLC 5.09 L (80%). Chest CT showed bilateral emphysema and atelectasis of the middle lobe and lingula. The echocardiogram was normal. Neurology evaluation was requested and physical examination showed mild fasciculation of the tongue and lower limbs, and increased muscular tonus with amplified deep tendon reflexes, which support a motor neuron disease diagnosis, confirmed by an electromyogram that was suggestive of neuromuscular disease—ALS.

Table 58.1 Gasimetric values and NIV parameters

	D0	D0	D1	D1	D6	D21
FiO_2 (mmHg)	21		24	24	21	21
O_2 (L/min)	–	0.5		1	–	–
pH	7.340	7.328	7.426	7.44	7.43	7.47
paO_2 (mmHg)	53.5	72.7	76.1	60	59	66
$paCO_2$ (mmHg)	61.5	61.9	61.2	62	51	43
HCO_3^- (mmol/L)	28.8	28.2	36.6	42	33.9	31.3
SpO_2 (%)	85.2	93.2	93.9	92	91	94
NIV mode	–	–	**S/T**	–	–	–
Interface	–	–	**Oronasal**	–	–	–
EPAP (cmH_2O)	–	–	**16**	–	–	–
IPAP (cmH_2O)	–	–	**4**	–	–	–
RR (bpm)	–	–	**18**	–	–	–
Obs.	**Admission**	**Started NIV** IPAP 14 cmH_2O EPAP 6 cmH_2O RR 18 bpm		**Pulmonology department admission** **Adjustment of parameters** IPAP 16 cmH_2O EPAP 4 cmH_2O RR 16 bpm periods of daytime and night	**NIV support** IPAP 18 cmH_2O EPAP 4 cmH_2O RR 16 bpm periods of daytime and night	**Discharge Nocturnal NIV** IPAP 18 cmH_2O EPAP 4 cmH_2O RR 16 bpm

The patient was discharged with indication to maintain nocturnal noninvasive ventilation with IPAP 18 cmH_2O, EPAP 4 cmH_2O, RR 16 bpm and FiO_2 21%, with the last gasometric test showing $PaCO_2$ 43 mmHg and PaO_2 66 mmHg.

58.2 Discussion/Main Topic

NIV and pulmonary rehabilitation with airway clearance therapy, such as cough assist, are essential for patients with respiratory failure due to neuromuscular disease [2, 3]. NIV should be initiated as soon as symptomatic nocturnal hypoventilation occurs, before the development of diurnal hypercapnia [4]. Vital capacity (VC) is frequently used to evaluate respiratory muscle weakness in these patients, being a VC less than 50% predicted commonly used as an indication to use NIV [3, 5].

Maximum inspiratory pressure (MIP) can also be used as an indication to start NIV, generally when less than 60 cmH_2O [3, 5]. Other indications to start NIV in symptomatic patients (including fatigue, dyspnea, morning headache) are $PaCO_2 \geq 45$ mmHg, nocturnal oximetry with oxygen saturation $\leq 88\%$ for five consecutive minutes [3, 5, 6]. Additionally, nocturnal $PtcCO_2 \geq 50$ mmHg for over 30 min; diurnal normocapnia with a nocturnal rise in $PtcCO_2$ of $\geq$10 mmHg; and a rapid reduction in FVC > 10% of the initial value within 3 months in ALS or other fast-progressing NMDs, can also be considered [6]. When diurnal clinical symptoms and hypoventilation are lacking, there is no indication for prophylactic mechanical ventilation [6].

When a patient presents with acute hypercapnic respiratory failure, like our patient, NIV should be used when there is tachypnea, signs of high work breathing and hypercapnia [7]. Either pressure or volume control ventilation can be used; however, the first one is preferable.

Generally, we start with low pressures, for example an IPAP of 10 cmH_2O and EPAP of 4 cmH_2O, adjusting then the pressures to reduce $PaCO_2$ and maintain comfort [7]. Then we can increase IPAP by 2–5 cmH_2O according to $PaCO_2$ level and tolerance, and rise EPAP by 1–2 cmH_2O to a maximum of 7 cmH_2O [7]. If such adjustments do not improve arterial blood gases, a volume-assured bilevel device, such as AVAPS, can be used. AVAPS is an alternative mode, defined by an adaptive pressure support that adjusts the pressure to maintain a target tidal volume by automatically controlling the pressure support between the minimum and maximum IPAP settings [3]. IPAP gradually changes over time, depending on the average tidal volume [3]. For example, if the patient's effort decreases, AVAPS will increase IPAP to maintain the target volume [3]. Nicholson and colleagues compared pressure support versus AVAPS in ALS patients, demonstrating that a small difference occurred between the two groups, with a tidal volume significantly lower for pressure support [3]. Figure 58.1 show two different modes in the same patient, demonstrating that in AVAPS we can assure an appropriated tidal volume with lower pressures. See Video 58.1 (S/T Mode) and Video 58.2 (AVAPS Mode). In these patients, a slower rise time may be better tolerated and should be adjusted to maximize patients' comfort [3]. All interfaces can be used, but in acute setting interface covering nose and mouth is preferable [7].

The effects of NIV in these patients are improvements in symptoms and in sleep architecture, enhancement in daytime and nocturnal arterial blood gas tensions [4]. The mechanisms of action of NIV in restrictive disorders are the relief of chronic respiratory muscle fatigue, enhancement in sleep efficiency and quality, improvement in central respiratory drive and in chest wall/lung mechanics and alteration in cardiopulmonary and renal haemodynamics [4]. Without mechanical ventilation the average life expectancy in these patients is 2–5 years from disease onset [6].

In conclusion, NMD should always be suspected in patients who are difficult to wean ventilator support. Respiratory function and sleep study is recommended in these patients. NIV can improve quality of life and survival in NMD patients.

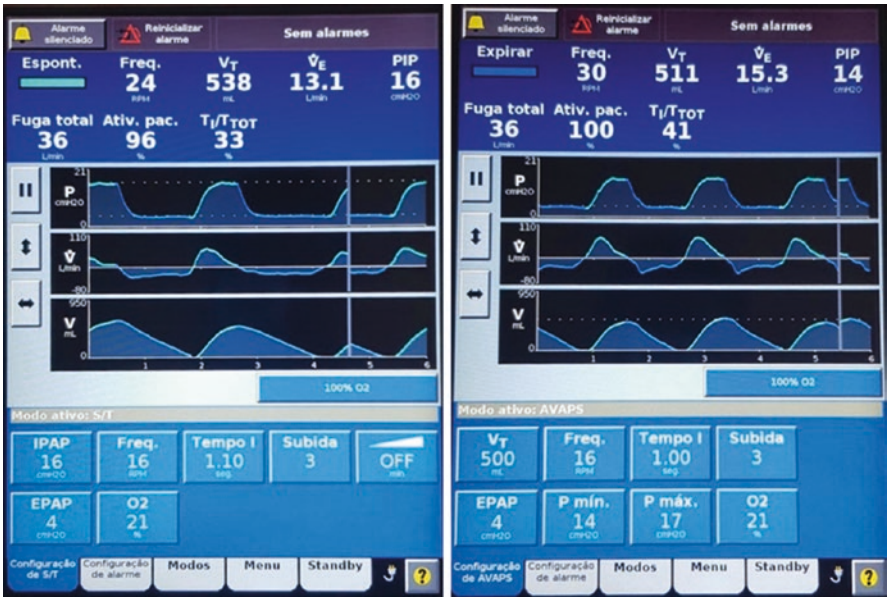

Fig. 58.1 NIV modes that were used in the patient—(**a**) S/T Mode and (**b**) AVAPS Mode. *VT* tidal volume, *Freq*. respiratory rate, *Subida* rise time, *Fuga* air leak

Key Teaching Points

- Respiratory insufficiency can be the first manifestation in neurological diseases.
- It is preferable to use pressure control ventilation and to begin with low pressures.
- All interfaces can be used, but in acute setting interface covering nose and mouth is preferable.
- AVAPS can ensure guaranteed volume and it is better tolerated.
- Noninvasive ventilation in neurological diseases can be used, improving survival and quality of life.

Questions and Answers

1. Regarding Amyotrophic Lateral Sclerosis (ALS), which of the following is correct?

   (a) ALS is a neuromuscular disease (NMD) that affects all muscular groups, including extrinsic muscles of the eye and sphincters.
   (b) Respiratory and upper airway muscles weakness can cause insufficient ventilation, ineffective cough and bulbar dysfunction.
   (c) Those complications generally start in earlier stages of disease.

(d) Dyspnea can be the first symptom in 90% of cases being respiratory failure requiring mechanical ventilation common.

Answer: (b) Respiratory and upper airway muscles weakness can cause insufficient ventilation, ineffective cough and bulbar dysfunction.

2. Which of the following is incorrect?

(a) Respiratory insufficiency can be the first manifestation in neurological diseases.
(b) NMD should always be suspected in patients who are difficult to wean ventilator support.
(c) Noninvasive ventilation in neurological diseases can be used, but improvement of survival and quality of life is not well defined.
(d) NIV and pulmonary rehabilitation with airway clearance therapy, such as cough assist, are essential for patients with respiratory failure due to NMD.

Answer: (c) Noninvasive ventilation in neurological diseases can be used, but improvement of survival and quality of life is not well defined.

3. Indications to start NIV in symptomatic NMD patients are:

(a) $PaCO_2 \geq 45$ mmHg or nocturnal oxygen desaturation ≥88% (5 consecutive minutes).
(b) Progressive disease, MIP > 60 cm/H_2O or FVC < 50% of predicted value.
(c) VC less than 50% predicted is commonly used as an indication to use NIV.
(d) All of the above.

Answer: (c) VC less than 50% predicted is commonly used as an indication to use NIV.

4. When NIV is considered in NMD (select the incorrect):

(a) It is preferable to use pressure control ventilation and to begin with low pressures (IPAP of 10 cmH_2O and EPAP of 4 cmH_2O can be started, adjusting then the pressures to reduce $PaCO_2$ and maintain comfort).
(b) An EPAP superior of 7 cmH_2O is recommended.
(c) All interfaces can be used, but in acute setting interface covering nose and mouth are preferable.
(d) AVAPS can ensure guaranteed volume and it is better tolerated.

Answer: (b) An EPAP superior of 7 cmH_2O is recommended.

5. What are the effects of NIV in NMD patients?

(a) Improvement in symptoms and in sleep architecture.
(b) Enhancement in daytime arterial blood gas tension.
(c) Enhancement in nocturnal arterial blood gas tension.
(d) All of the above.

Answer: (d) All of the above.

6. Which of the following is correct?
   (a) Respiratory function and sleep study is not recommended in these patients.
   (b) When diurnal clinical symptoms and hypoventilation are lacking, there is no indication for prophylactic mechanical ventilation.
   (c) NIV value in NMD is well defined.
   (d) B + C.

   Answer: (d) B + C.

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Chapter 59
Noninvasive Ventilation in Ventilatory Pump Failure: When Is Oxygen Administration Deadly?

C. Matesanz López, C. M. Acosta Gutiérrez, and J. R. Bach

Abbreviations

ARF	Acute respiratory failure
BiPAP	Bi-level positive airway pressure
GPB	Glossopharyngeal breathing
LVR	Lung volume recruitment
MIC	Maximum insufflation capacity
MIE	Mechanical insufflation-exsufflation
NVS	Noninvasive ventilatory support
PEEP	Positive end-expiratory pressure
VC	Vital capacity
VPF	Ventilatory pump failure

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Clinical Case

A 35 year old man with Becker muscular dystrophy, onset of muscle weakness noted at the age of 2 was diagnosed at 8 years of age by DNA gene sequence analysis confirming deletion of exons 5 and 6 of the Xp21 gene. He became wheelchair dependent at 15 years of age and began sleep NVS at full ventilatory support settings of 1100 mL and rate 12 at age 25. By 2014, at age 32, with a vital capacity (VC) of 410 mL and maximum insufflation capacity (MIC) by air stacking to 1880 mL, his daytime end-tidal CO_2 had increased to 57 mmHg but, although refusing to dependent on noninvasive ventilatory support (NVS) around-the-clock, air stacked every several minutes to relieve his dyspnea. However, at one point, he went too long without air stacking, his hypoventilation worsened, and he became obtunded and was brought to a local emergency room. He was immediately placed on fiO_2 100% and a subsequent arterial-blood gas analysis indicated a pH of 6.98, pCO_2 177 mmHg, and pO_2 120 mmHg; his HCO_3 was 41 mEq/L. While instituting manual resuscitation, immediate intubation was suggested but the patient's father insisted that his physician, Dr. John Bach, be called. Bach asked his father where his ventilator was and was told that it was in the trunk of his car whereupon he was told to get it and put it on his son at his usual home care settings. This was done. Thirty minutes later, with normal O_2 sat and $EtCO_2$ less than 45 mmHg he was discharged home.

This patient essentially had no ventilator-free breathing ability except by glossopharyngeal breathing (GPB) which he could use to volumes as high as 1250 mL. However, went he went too long without air stacking or using GPB and was further placed on supplemental O_2, his hypercapnia worsened and CO_2 narcosis developed. Subsequent to the episode of respiratory failure in 2014 he has remained continuous noninvasive ventilatory support (CNVS) dependent but the GPB permits him to take fewer supported breaths via his mouthpiece (Fig. 59.1) than he would otherwise need. He continues to use mouthpiece NVS throughout daytime hours and nasal NVS for sleep on the same settings.

59.1 Clinical Practice

Dependence on up to CNVS and use of mechanical insufflation-exsufflation (MIE) to create effective cough flows to clear airway debris have been permitting patients with ventilatory pump failure (VPF) to prolong survival, in some cases for over 65 years [1], since 1953 [2]. These interventions also permit the safe extubation and tracheostomy tube decannulation of ventilator unweanable patients to maintain quality of life without invasive airway tubes. Volume control modes and active ventilator circuits on portable home care ventilators permit physiological varying of tidal volumes, facilitate communication by varying voice volumes, normalize cough flows, and permit active LVR by air stacking. None of this happens when supplemental O_2 and low span bi-level positive airway pressure are used instead of CNVS and MIE.

Fig. 59.1 Wheelchair dependent patient on CNVS and use of mouthpiece during the day

Morbidity and mortality have decreased in patients with neuromuscular disease due to implementation of therapies to augment cough and normalize alveolar ventilation. The aim of these therapies is to minimize respiratory complications and the acute on chronic respiratory failure that would otherwise be inevitable in these patients as a result of advancing muscle weakness and their inability to compensate during periods of increased respiratory loads. It is a common mistake to administer O_2 which renders the oximeter useless as a gauge of alveolar ventilation (CO_2), airway congestion, and early intrinsic lung disease. It is also a common mistake to administer bi-level PAP at less than ventilatory support settings, that is, 18–20 cmH_2O of pressure support. Full NVS settings can not only provide full ventilatory support and also provide essentially full respiratory muscle rest for sleep. This, in turn, eases symptoms of sleep hypoventilation and normalizes daytime blood gases until respiratory muscle weakness progresses and patients extend sleep NVS into daytime hours. Typically, volume preset ventilation settings of 700–1500 mL is prescribed and home care therapists work with the patient to determine the setting he or she is most comfortable with. Almost invariably patients choose 1100–1200 mL settings.

Another common mistake is to think that patients with VPF require expiratory (E)PAP or positive end-expiratory pressure (PEEP). Crescimanno et al.

demonstrated that all sleep and respiratory parameters are better for bulbar amyotrophic lateral sclerosis patients with no EPAP or PEEP [3]. We have found this to also be true for the over 2000 sleep NVS users in our center as well.

Besides polysomnograms being unnecessary for patients with VPF, pulmonary function testing does not routinely assess VC in the supine position, cough flows, or CO_2 levels (noninvasively). These simple tests, along with oximetry, need to be part of every evaluation of patients with VPF. VC difference greater than 30% between sitting and supine is usually accompanied by orthopnea due to diaphragm dysfunction and indicates need for sleep NVS. Cough peak flows should also be measured via peak flow meter with only flows over 300 L/min indicating relatively low risk of pneumonia. Lower flows indicate need for rapid access to MIE.

The patient described in this clinical case had unassisted cough peak flows less than 160 L/min and used MIE during respiratory tract infections. MIE can be used via oronasal interfaces, simple mouthpieces, and must be used via any invasive airway tubes to clear secretions since routine suctioning via the tubes misses the left main stem bronchus over 90% of the time. MIE settings of 60–70 cmH_2O are used via airway tubes [4]. Need for MIE varies depending on the patient's clinical situation. It can be used three times per day for LVR, or it can be required as often as every 20–30 min around the clock during respiratory infections. In our patient, due to increased respiratory secretions and possible pneumonia, MIE complemented his dependence on CNVS. Manually assisted coughing by air stacking and abdominal thrust has also been reported to increase cough flows from 150 ± 120 L/min to CPF of 255 ± 100 L/min [5]. Active LVR can be achieved by GPB as well as by air stacking of consecutively delivered volumes of air delivered by volume preset ventilator or manual resuscitator.

Although this patient used sleep NVS for years and frequent daytime air stacking, he did not want to think that he was becoming dependent on a ventilator. Thus, his adherence to NVS was erratic for psychological reasons. There is little written about it this in the medical literature, but following his episode of acute respiratory failure (ARF), this is no longer a problem. He has been literally happily using CNVS for the last 6 years. Patients and their caregivers need to be educated about what to expect by using or not using NVS. It should be noted that tracheostomy tubes can almost invariably be avoided by CNVS dependence except for most patients with upper motor neuron disease whose spasticity tends to close the upper airways [6].

In summary, NVS, as opposed to low span (<10 cmH_2O) bi-level PAP and supplemental O_2, is a vital alternative to avoid ARF and prolong life indefinitely without resort to invasive airway tubes. We now have ten patients with spinal muscular atrophy type 1 dependent on nasal CNVS since as young as 4 months of age who are over 20 years old and will never have tracheostomy tubes. Once respiratory muscle dysfunction and symptomatic hypoventilation are documented NVS needs to be introduced and home O_2 therapy avoided for VPF patients [7].

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Chapter 60
Clinical Case in Non Invasive Ventilation: Ethical Aspects of the Palliative Use

Andrea Fabbo, Marilena De Guglielmo, and Nicola Vargas

60.1 Introduction

Recently Non-Invasive Ventilation (NIV) has been found to have a useful application in palliative care because there are many suggestions that this procedure might be a valid alternative to relieve dyspnea in advanced stages of diseases such as cancer, COPD and neurodegenerative disorders [1]. In fact, dyspnea is one of the most distressing symptoms experienced by patients at the end of life and it is a frequent reason for such patients to seek emergency care [2]. This population is potentially a good candidate for NIV, as most of them are patients with a DNI ("do-not-intubate") code although it is controversial that NIV did not provide significant relief of symptoms in some patients who receive it for that reason [3]. While the role of NIV as a palliative strategy against dyspnea in end-of-life neoplastic is well known, the use of NIV in end-stage chronic diseases is unclear [4]. An emerging issue is the management of elderly patients with respiratory failure and dementia although the presence of cognitive impairment and delirium are not a barrier to the administration of

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NIV in some studies that have shown a better management of symptoms in very elderly hospitalized patients in a non-intensive care unit setting followed by a multidisciplinary medical staff conforming to principles of comprehensive geriatric assessment and treatment, the involvement of family caregiver and the attention to quality of life [5–7]. On the other hand the family members of older patients with dementia in critical illness play an essential role in the decision-making process relating to treatment and for the physicians may be difficult to know the patient's wishes and preferences even though that Italian Law on informed consent provided by a supporting administrator and advance directives (DAT) has been approved [8–10].

The publication of the Law of 22 December 2017, n. 219, "Rules on informant consent (CI) and advance dispositions of treatment (DAT)" has filled a regulatory delay in the Italian health scenario. However, crucial questions remain in the application of the Law in the context of people with dementia. To have legal value, in fact, both the CI and the DAT must be issued by a person capable of understanding and of wanting and in case of dementia it can be challenging to determine the level of capacity of the person. In general, at the national level there is a critical situation in the application of the law: poor knowledge, inhomogeneity in the application of the institute of Support Administration (AdS), long time for the appointment of an AdS if no DAT has been arranged, fragmented and inhomogeneous responses from institutions, structures and reference professionals that can disorient the vulnerable person and his family [11]. Clinical ethics implies "the identification, analysis and solution of conflicts of value or uncertainties that emerge in the course of medical care provided in the clinical field" and is a necessary tool particularly in the case of clinical choices involving the sphere of individual values [12–14]. Particularly in the cases of absence of DAT already formulated, an "individual care plan" (PAI) is configured as the only adequate instrument to prepare a shared accompanying path. The PAI identifies the acts of care and assistance that the multidisciplinary team considers ethical and appropriate to pursue and must be understood as a flexible instrument whose objectives are subject to periodic verification and adjustment. The PAI approach to the end of life phase is particularly important. The European Association of Palliative Care (EAPC) has drafted a consensus statement trying to define some practical principles to use along the path of caring for people at the end of life. Great emphasis is given to preventive planning (DAT) as a dynamic process of reflection and dialogue between the individual, his/her family members and health professionals regarding preferences for future care and assistance [15].

We report a case of an elderly patient with exacerbated respiratory failure and dementia handled with NIV in palliative care and managed through an individual care plan (PAI) at the end of life.

An elderly patient with dementia and chronic hypercapnic respiratory failure.

A female of 80 years old with a history of dementia and severe COPD (GOLD IV) lives at home and presents a condition of chronic hypercapnic respiratory failure (blood gas parameters in room air ambient: pH 7.34; pCO_2: 60; pO_2: 47) in the absence of a metabolic cause for the acidosis; she needs to be treated with LTOT (Long Term Oxygen Therapy, FiO_2: 24%) and BiPAP (Bilevel positive airway

pressure) according to the prescription of the pneumologist who follows the patient at home. Due to discomfort associated with the mask she presents severe agitation with aggression, screams and insomnia. Daughter asks doctors to remove the mask and avoid use of sedative according to mom's will and wishes ma at the same time she doesn't accept the idea of a mother's death due to a terminal illness. After a few days the patient is hospitalized in emergency for acute COPD exacerbation with development of severe acidosis due to acute-on-chronic hypercapnic respiratory failure (pH 7.05, pCO_2: 141, pO_2 = 130, HCO_3: 39, FiO_2 = 50%). She is treated with NIV (patient with a DNI order) and after 6 h respiratory parameters improve (pH 7.35, pCO_2: 76, pO_2: 76, HCO_3: 42, FiO_2 = 35%) but a hyperactive delirium appears (hallucinations, restlessness, agitation and aggressive behaviour, reversal of night-day sleep-wake cycle) during the next 24 h. Sedation during NIV can be useful [16] to reduce the rate of treatment failure but knowledge of the pharmacological and hemodynamic characteristics of every single sedative agent is crucial to choose the right drug for every clinical scenario. Delirium assessment by staff and pharmacological intervention has to be considered when persons with delirium are distressed or considered at risk to themselves or others and when non pharmacological approach (environment, light, routine, communication, mobility, integrate food and fluid into daily routine, sensory impairment, sleep disturbances etc.) has been ineffective [17]. Short term (some days) use of appropriate antipsychotic medication, starting at the lowest clinically appropriate dose and increasing cautiously according to symptoms, should be considered [18]. After the use of low doses of haloperidol (0.25–0.50 mg every 4 h), warranty of "patient comfort" and administration of NIV at 6-h intervals there is an improvement of patient's symptoms and blood gas parameter. During the hospital stay the daughter is followed by a psychologist who has the task to prepare her to accept a palliative care at home with support of the palliative team (general practitioner, geriatrician, pneumologist, nurse, psychologist). The team explains and convinces the daughter that NIV should be used to provide palliative care at the end of life and any actions which prolong the dying process should be avoided. So the daughter learns that NIV can only be used to improve symptoms and to avoid hospitalization for a limited time along with a pharmacological (low doses of psychotropic agents, bronchodilators, minimal dose of morphine and O_2 therapy 2 L/min etc.) and non-pharmacological treatments (mobility during the day, nutritional control, environmental stimulation) to provide comfort. Therefore, at time of discharge, an individual care plan (PAI) is drawn up (using a Comprehensive Geriatric Assessment that includes a functional and a behavioural-cognitive evaluation) with indication of care (relief of suffering, control of symptoms, "discomfort reduction"), interventions of health professionals ("when" and "how" on patient and family), preferences and wishes of caregiver in according to patient's needs and Italian law on advance care planning (DAT) [19]. The patient continues the NIV at home in according to ERS guidelines that suggest the application of long-term home non-invasive ventilation to improve quality of life in COPD patients with persistent hypercapnic respiratory failure [20] but, in this case, as a part of a palliative care program. After 1 month the patient died without

suffering and with a control of distress symptoms; the daughter, supported in the making-decision process by the team, no longer asked the doctors to hospitalize her mother.

60.2 Discussion

At the end of life and in elderly with advanced respiratory diseases (persistent hypercapnic respiratory failure) NIV may be effective in alleviating breathlessness and to avoid hospitalization. Although age should be not considered a limiting parameter for NIV use, factors as chronic health status, cognitive impairment and collaboration of family members may influence NIV efficacy. The communication about the goals of NIV treatment in this phase of care and alliance between patients, family members and health professional is crucial. Breathlessness causes distress not only for the patient but also for families and other carers. In every care setting (Hospital, Nursing Home and home care) both patients and their carer need this symptom to be relieved and support strategies (as informations, coping or efficacy communication) should be explained. NIV is increasingly used as a palliative strategy when endotracheal ventilation is inappropriate (patients with "Do Not Intubate Order") although its effectiveness for relieving symptoms in end-of-life care is controversial [3]. Palliative ventilation can be administered to alleviate the symptoms of respiratory distress in advanced stages of diseases and to manage patients with respiratory failure who present suffering from severe dyspnea not respondent to usual pharmacological strategies. For elderly patients with severe illness and dementia treated on long-term NIV at home, the main goal is to optimize their daily quality of life and to obtain a collaboration of family regarding the better "choice" to minimize distress and suffering of patient and to reduce "caregiver burden" consequently [21]. An important pre-requisite before palliative ventilation is to assess the benefits for the patient as well as the skills and experiences of family caregivers; palliative ventilation should not cause patient discomfort and caregiver anxiety (due to concerns about symptom management or difficulty dealing with crises), if it is included (in case of person with cognitive impairment) in shared care plan between health professionals (doctors, nurse) and family member (or legal guardian or surrogate). The plan should address all aspects of care including the reduction of complications (agitation, pain, skin lesions) and monitoring of specific clinical characteristics of these patients (cognitive and behavioral problems, "poor" therapy compliance, atypical presentations of associated diseases, "frailty" and vulnerability to adverse events such as drugs side effects). Any information required for management of care plan may be obtained through comprehensive geriatric assessment [22], family collaboration and a good communication [23]. There is currently a great debate on the opportunity to enter into the issues of end-of-life care from the beginning of a terminally ill diagnostic process (such as neurodegenerative disorders), even if the current legislation establishes its obligation (Italian Law on DAT) [10]. Not all professionals have the necessary communication tools to face a shared information and decision-making process. However, the planning of end-of-life care should take place

soon, when the person has sufficient mental capacity to consider their preferences and make decisions for their future. An approach of this type should be structured in such a way as to involve all reference persons (family member or surrogates) and supported by adequate training initiatives for health professionals.

60.3 Conclusion

NIV as ventilatory support in palliative care should be considered in the management of respiratory failure patients. However the prescription of NIV in this context (palliative care and elderly people with advanced stages of diseases associated with dementia) requires further studies because of these patients have many problems and comorbidities that can complicate the management of acute respiratory failure. The use of NIV to reduce patient discomfort is effective and may improve symptoms of respiratory distress and quality of life of patient and family caregiver especially if it is part of an individual care plan (PAI) drawn up through the collaboration of multidisciplinary team, patient (when it is possible) and caregiver. Assisting a family member with severe chronic condition and dementia is a very burdensome task that affects the entire household. Family members need support and help throughout the care process and especially in the end-of-life phase. Decisions in the terminal phase are even more difficult in cases of disagreement or lack of cohesion within the family unit. In these specific cases it is necessary to make even more explicit the reference legal figures and the definition of clear and easily accessible paths (such as individual care plan) that the health professionals must follow.

Questions and Answers

1. Recently NIV has been found to have a useful application in palliative care. All the following questions are correct, except one. Which of them?

   (a) This procedure might be a valid alternative to relieve dyspnea in advanced stages of diseases
   (b) The use of NIV in end-stage chronic diseases is recommended
   (c) Most people with advanced diseases (cancer, COPD and neurodegenerative disorders) are patients with a DNI ("do-not-intubate") code
   (d) The role of NIV as a palliative strategy against dyspnea in end-of-life neoplastic is well known
   (e) Dyspnea is one of the most distressing symptoms experienced by patients at the end of life

   Answer: (b) The use of NIV in end-stage chronic diseases is recommended

2. In the management of elderly people with respiratory failure and dementia it is important to know that:

   (a) The presence of cognitive impairment and delirium are not a barrier to the administration of NIV
   (b) NIV should not be applied to the elderly with advanced dementia

(c) It can be a problem to apply NIV in the elderly with delirium superimposed to dementia
(d) NIV did not provide significant relief of symptoms in people with dementia
(e) NIV can always be used in the elderly with advanced dementia

Answer: (a) The presence of cognitive impairment and delirium are not a barrier to the administration of NIV

3. In advance dementia, before to use NIV, the involvement of family caregiver and the attention to quality of life is very important; what do you need to know?

(a) The family members of elderly with dementia in critical illness play an essential role in the decision-making process
(b) The physicians may have difficulties to know the patient's wishes and preferences
(c) You should have informed consent from a supporting administrator if available
(d) Advance dispositions of treatments (DAT) should be obtained
(e) All of the above

Answer: (e) All of the above

4. In absence of DAT already formulated, an "individual care plan" (PAI) is configured as the only adequate instrument because:

(a) It is a clinical tool
(b) Does not consider the will of the person
(c) Individual Care Plan identifies the acts of care and assistance that the multidisciplinary team considers ethical and appropriate
(d) It represents a formality only
(e) It's just an agreement between doctor and family member

Answer: (c) Individual Care Plan identifies the acts of care and assistance that the multidisciplinary team considers ethical and appropriate

5. At time of discharge at home of elderly with dementia and severe COPD an individual care plan (PAI) is drawn up with the indications of:

(a) Relief of suffering and control of symptoms
(b) Preferences and wishes of caregiver in according to patient's needs
(c) Use of NIV to improve quality of life and as a part of palliative care program
(d) To avoid inappropriate hospitalization
(e) All of the above

Answer: (e) All of the above

6. The use of NIV at the end of life may be effective in alleviating breathlessness and to avoid hospitalization; all of the following factors may influence the efficacy of NIV except one: which of them?

(a) Chronic health status
(b) Cognitive impairment
(c) Collaboration of family members

(d) Age
(e) None of the above

Answer: (d) Age

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Chapter 61
Clinical Cases in Noninvasive Ventilation in Quality of Life

Toru Oga

Abbreviations

COPD	Chronic obstructive pulmonary disease
CRF	Chronic respiratory failure
HRQL	Health-related quality of life
LTOT	Long-term oxygen therapy
MRF	Maugeri Respiratory Failure Questionnaire
NIV	Noninvasive ventilation
OHS	Obesity hypoventilation syndrome
SF-36	Medical Outcomes Study 36-item short form
SGRQ	St. George's Respiratory Questionnaire
SRI	Severe Respiratory Insufficiency Questionnaire

61.1 Introduction

The improvement of health-related quality of life (HRQL) is an important goal in the management of patients with chronic respiratory failure (CRF) receiving noninvasive ventilation (NIV) and/or long-term oxygen therapy (LTOT). Various pulmonary or extrapulmonary diseases may cause CRF, leading the need for such therapies. However, most of these conditions are at an advanced stage, incurable, and

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progressive. Thus, they damage the physical, psychological and social health of patients. Recently, home NIV is increasingly used in patients with chronic hypercapnic respiratory failure. This method is expected to improve patient-reported outcomes (e.g., dyspnea or HRQL) as well as arterial blood gas, readmission rates, or mortality. Under these conditions, it is necessary to measure HRQL using questionnaires specifically developed for patients receiving treatments, such as NIV and/or LTOT, because they might benefit from using the specific questionnaires.

In general, disease-specific questionnaires are preferred, especially, for the assessment of the effects of medical interventions on HRQL. Disease-specific questionnaires tend to show better responsiveness than generic ones, such as the Medical Outcomes Study 36-item short form (SF-36) [1], which is the most frequently used generic questionnaire in clinical trials associated with NIV [2]. The St. George's Respiratory Questionnaire (SGRQ) [3] is the most widely used respiratory-specific questionnaire, and also utilized in the CRF field. However, it was originally developed for patients with mild-to-severe chronic airflow limitation, such as chronic obstructive pulmonary disease (COPD) or asthma. Therefore, it is not suitable for very severe patients suffering from CRF and are varied underlying diseases. The COPD Assessment Test [4] has been developed i.e. in routine clinical practice in patients with COPD to overcome the 50 questionnaires and complex scoring algorism of the SGRQ. However, on the contrary, its easiness i.e. eight items scored using 6-point Likert scales may limit its use in patients receiving the NIV.

Therefore, condition-specific HRQL measures for CRF patients receiving NIV and/or LTOT are warranted irrespective of the underlying diseases. Firstly, the Maugeri Respiratory Failure Questionnaire (MRF) [5] was developed. Subsequently, a more specific questionnaire for patients with CRF receiving NIV, namely, the Severe Respiratory Insufficiency Questionnaire (SRI) [6] was developed. Recently, in the setting of SRI, the S^3-NIV questionnaire [7] was developed to monitor the effects of NIV in clinical practice rather than to assess HRQL.

61.2 MRF

The MRF was firstly developed as the MRF-28 [5] for use to assess HRQL in patients with CRF. While the MRF is valid in patients receiving NIV and/or LTOT, the MRF-28 was firstly validated for COPD or kyphoscoliosis [5] and validation studies for its application in other disorders are limited. The MRF-28 consists of 28 items which are grouped into three subscales: daily activity, cognitive function, and invalidity. The total score of these subscales is also calculated. The score range from 0 (best HRQL) to 100 (worst HRQL). Later, through Rasch analysis, the MRF-28 was modified to the MRF-26 by removing two items (i.e., 26 items in total) (Table 61.1) [8]. The MRF-26 includes two subscales, namely, activity and perceived invalidity: the total score is also calculated. For each of the 26 items on the MRF-26, the patient provides yes/no responses, rendering the questionnaire easy to

Table 61.1 Questionnaires specifically used in patients receiving noninvasive ventilation

	Items (n)	Answers
Maugeri Respiratory Failure Questionnaire-26 [5, 8]		
Activity (0–100)	13	Yes/no
Perceived invalidity (0–100)	13	Yes/no
Total (0–100)	26	
Severe Respiratory Insufficiency Questionnaire [6, 9, 10]		
Respiratory complaints (0–100)	8	5-point Likert scale
Physical functioning (0–100)	6	5-point Likert scale
Attendant symptoms and sleep (0–100)	7	5-point Likert scale
Social relationships (0–100)	6	5-point Likert scale
Anxiety (0–100)	5	5-point Likert scale
Psychological well-being (0–100)	9	5-point Likert scale
Social functioning (0–100)	8	5-point Likert scale
Summary (0–100)	49	
S^3-NIV questionnaire [7]		
Respiratory symptoms (0–10)	5	5-point Likert scale
Sleep and NIV-related side effects (0–10)	6	5-point Likert scale
Total (0–10)	11	

Numbers in parentheses indicate the theoretical score range. In the Maugeri Respiratory Failure Questionnaire, higher scores indicate worse status. In the Severe Respiratory Insufficiency Questionnaire and the S^3-NIV questionnaire, higher scores indicate better status

complete. Unfortunately, it does not include a psychological domain (i.e., anxiety or depression), which is an important determinant of HRQL.

61.3 SRI

Following the MRF, the Severe Respiratory Insufficiency Questionnaire (SRI) was specifically developed and validated as a multidimensional instrument with high psychometric properties for patients with CRF receiving long-term NIV [6, 9]. Moreover, it was also validated in patients with COPD receiving LTOT [2]. It was originally developed in German, and has been translated into several languages [10].

The SRI structurally measures diversified health impairments multi-dimensionally and discriminatively. The SRI consists of 49 items scored by a 5-point Likert scale (Table 61.1) and divided into seven subscales: Respiratory Complaints, Physical Functioning, Attendant Symptoms and Sleep, Social Relationships, Anxiety, Psychological Well-Being, and Social Functioning, and Summary Score is also calculated, with scores ranging from 0 (worst HRQL) to 100 (best HRQL). Unlike the MRF, the SRI is more widely validated in various disorders such as COPD, restrictive thoracic disorders, neuromuscular disorders, obesity hypoventilation syndrome (OHS) [6, 9]. While the HRQL questionnaire was specifically developed for patients

with various disorders receiving NIV, the SRI is most frequently used in randomized controlled studies to assess the efficacy of NIV [2].

61.4 S³-NIV Questionnaire

The S³-NIV questionnaire, a short questionnaire measuring respiratory symptoms, sleep quality and NIV-related side effects, was recently developed [7]. As mentioned earlier, although the SRI and MRF are most often used to assess HRQL outcomes in daily clinical trials, their length and complex scoring may limit their use in everyday clinical practice. In addition, the treatment-related side effects of NIV are not covered in these questionnaires. Therefore, a simpler and shorter questionnaire has been developed to assess respiratory symptoms, sleep and comfort (discomfort) as a complement to the monitoring of the efficacy of home NIV.

Accordingly, 11 items were retained to assess the psychometric properties of the finalized version of the S³-NIV questionnaire (Table 61.1). It consists of two subscores, namely, "Respiratory symptoms" (five items) and "Sleep & NIV-related side effects" (six items), and total score. Patients score the items using a 5-point scale from "always true (0)" to "completely untrue (4)". The lowest possible score is computed as the average of all answered items multiplied by 2.5; indicating that the lowest possible score (0) corresponds to the lowest impact of the disease and treatment, where as the highest possible score (10) corresponds to the lowest impact of the disease and treatment. The validation study was performed mainly in patients with COPD (21%), OHS (28%) and central breathing disturbances during sleep (34%). Only 12% and 5% of the evaluated population had neuromuscular disorders and restrictive disorders, respectively. Therefore, at present, evaluation in wider groups of patients suffering from such conditions is warranted.

Thus, the S³-NIV questionnaire may be a promising tool for clinicians and patients to assess three important domains related to home NIV, as a complement to the physiological monitoring of home NIV. In contrast, it should be noted that this tool is useful for monitoring and not intended to be a surrogate measure of the general health status or quality of life. Further studies using this questionnaire are expected to acknowledge its features.

61.5 HRQL Scores in Patients Receiving the NIV: Clinical Cases

Considering the severely impaired HRQL of patients with CRF, generic or disease-specific questionnaires may skew to the worse ends of their scores. Thus, CRF-specific questionnaires would be preferable for cross-sectional studies. The relationships of the CRF-specific questionnaires with the currently available

questionnaires (i.e., SF-36 and SGRQ) were modest, indicating that they measure different aspects of HRQL. Therefore, combining the CRF-specific questionnaires with these questionnaires may be complementarily useful. A comparison between the SRI and MRF questionnaires showed that dyspnea and depression were the main determinants. In particular, the SRI was related to the psychological status, where the MRF-28 placed more emphasis on restriction in the degree of activities of daily living.

Usually, HRQL is independently assessed as a patient-reported outcome, because the effects of the medical interventions on HRQL do not mirror changes in physiological measures or survival. The CRF-specific questionnaires of the SRI or the MRF have been used in randomized controlled trials to assess the effects of the NIV on HRQL in patients with CRF, hypercapnic COPD, OHS etc. These questionnaires are usually more representative of medical interventions related to NIV and/or LTOT than other questionnaires. Therefore, they may favorably detect the beneficial effects of medical interventions on HRQL in patients with NIV and/or LTOT, even when generic HRQL questionnaires (e.g., SF-36) and respiratory-specific HRQL questionnaires (e.g., SGRQ) do not. Thus, it is recommended to avoid the use of the SF-36 or even SGRQ alone. However, the minimal clinically important differences between the SRI and MRF, such as the four units on the SGRQ, remain undetermined. These differences should be investigated in the future to better analyze the changes in the scores.

Additionally, improvements in HRQL after therapeutic medical interventions may depend on the underlying disease [2]. For example, in neuromuscular diseases, improvement in HRQL would not be possible after the initiation of NIV, partly due to the progressive nature of such diseases. In that sense, the SRI is the only questionnaire validated for various underlying diseases, including neuromuscular disorders. Moreover, the high applicability and multi-dimensional analytical features of the SRI may be advantageous.

In addition, CRF-specific HRQL measures of the SRI and MRF were recently reported to be significantly associated with mortality [2]. Therefore, these questionnaires may be repeatedly employed in daily practice to identify patients at risk of death.

61.6 Conclusion

Despite the unique features of the CRF-specific questionnaires, they have only been used in clinical trials, and not in daily practice. Improved HRQL is considered to be the most important expected benefit of NIV together with reductions in hospital admissions. However, unfortunately, HRQL is rarely assessed prior to and after initiation of NIV. However, following the wider use of the SRI or MRF in research, the CRF-specific questionnaires have attracted an increasing amount of attention. The novel S^3-NIV questionnaire may be a promising tool for the monitoring of NIV and its safety profile in daily clinical practice.

Questions and Answers

1. What is the main reason to use home NIV in chronic hypercapnic respiratory failure?

   (a) To improve arterial blood gas
   (b) To improve readmission rates
   (c) To improve dyspnea
   (d) To improve health-related quality of life (HRQL)
   (e) All of the above

   Answer: (e) All of the above
2. What is the most frequently used generic HRQL questionnaire in clinical trials associated with NIV?

   (a) Medical Outcomes Study 36-item short form (SF-36)
   (b) St. George's Respiratory Questionnaire (SGRQ)
   (c) Severe Respiratory Insufficiency Questionnaire (SRI)
   (d) Maugeri Respiratory Failure Questionnaire (MRF)
   (e) None of the above

   Answer: (a) Medical Outcomes Study 36-item short form (SF-36)
3. What is the specific HRQL questionnaire for patients with chronic respiratory failure receiving NIV?

   (a) Medical Outcomes Study 36-item short form (SF-36)
   (b) St. George's Respiratory Questionnaire (SGRQ)
   (c) Severe Respiratory Insufficiency Questionnaire (SRI)
   (d) Maugeri Respiratory Failure Questionnaire (MRF)
   (e) None of the above

   Answer: (c) Severe Respiratory Insufficiency Questionnaire (SRI)
4. What is the short questionnaire recently developed in NIV monitoring for use in daily practice?

   (a) St. George's Respiratory Questionnaire (SGRQ)
   (b) Severe Respiratory Insufficiency Questionnaire (SRI)
   (c) Maugeri Respiratory Failure Questionnaire (MRF)
   (d) S^3-NIV questionnaire
   (e) None of the above

   Answer: (d) S^3-NIV questionnaire

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Chapter 62
Pediatric Non-invasive Ventilation: Non-invasive Ventilation Treatment in a Pediatric Patient with Catathrenia

David C. Earl, Steven A. Lopez, and Lee K. Brown

Abbreviations

CPAP Continuous positive airway pressure
CWP Centimeters of water pressure

62.1 Introduction

A 12-year-old boy presented to the University of New Mexico Hospital Sleep Disorders Center with a chief complaint voiced by his mother as "he moans so loudly when sleeping that we are afraid bears will attack us when we're camping, thinking he's a hurt, dying animal." Since age 3, the patient has exhibited periods of groaning and moaning while asleep, lasting for up to about 1 h and occurring several times virtually every night. There does not seem to be a predilection for any particular time of night. His usual bedtime is 8:30 PM but he estimates an initial sleep latency of about 2 h. Once asleep he does not awaken until his usual time of arising at 6:00 AM on weekdays and 6:30 to 7:00 AM on weekends. His mother describes him as a restless sleeper, but she has appreciated no snoring or wheezing. He has no symptoms consistent with restless legs syndrome. Past medical history is

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significant for exercise-induced asthma beginning at age 10, initially severe, but currently well-controlled on inhaled fluticasone propionate/salmeterol xinafoate twice daily and albuterol as needed; and congenital talipes equinovarus (club feet), requiring multiple surgeries between the age of 3 months and 3 years. Family history is positive for snoring and sleep apnea, but not for arousal parasomnias. Physical examination revealed body mass index 18.8 kg/m^2; no grossly dysmorphic features; moderate retrognathia and long tongue. There was no tonsillomegaly, and the remainder of the general and neurological physical examination was unremarkable.

62.2 Video-PSG Sleep Study Data

Overnight polysomnography (PSG) was performed, which included an expanded EEG montage as well as bilateral wrist extensor EMGs and synchronized digital video and audio. Initial sleep latency was 24 min, sleep efficiency 90%, and sleep maintenance 95%. There were 4 REM cycles, and the proportions of the various sleep stages as percent of total sleep time were stage 1, 20%; stage 2, 39%; slow wave sleep, 16%; REM sleep, 20%. Sleep was fragmented by a mean of 27 arousals and 3 awakenings per hour of sleep, with 17 per hour related to respiratory events. Obstructive apnea-hypopnea index (including hypopneas followed by arousal or awakening without desaturation) was 6.9 per hour of sleep, central apnea index was 12.9 per hour of sleep. Oxyhemoglobin saturation nadirs were 83% for central apneas, 85% for hypopneas, and 88% for obstructive apneas. The expanded EEG montage demonstrated no epileptiform activity.

The patient subsequently underwent CPAP titration in the sleep laboratory, and a pressure of 8 cwp successfully treated both the catathrenia as well as the obstructive sleep apnea (Fig. 62.1).

62.3 Discussion

Catathrenia, also referred to as expiratory groaning during sleep, has been described as high-pitched, loud, and/or roaring sounds that occur during sleep. It can be confused with sleep talking or snoring [1]. Catathrenia predominantly occurs during rapid eye movement (REM) sleep, but can also occur during non-rapid eye movement (NREM) sleep [2]. Catathrenia was first described in 1983 by De Roeck [3]. While considered a benign condition by many, there may be social concerns that could arise from the condition. Limited literature has been available regarding the condition and its treatment (Fig. 62.2).

A retrospective analysis published in 2017 was remarkable for describing 38 cases of catathrenia who had polysomnographic evidence of the condition [4]. In that analysis, catathrenia events were found to have a characteristic nature of

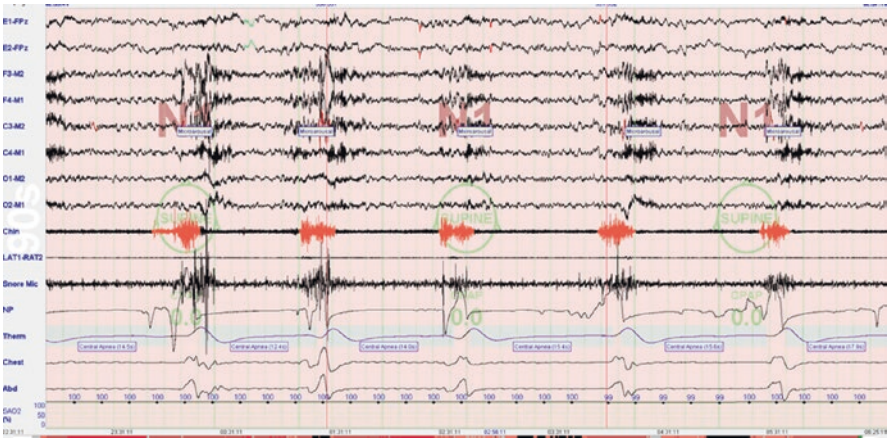

Fig. 62.1 Representative 90 s polysomnographic recording demonstrating episodes of catathrenia associated with central sleep apnea. *E1-FPz, E2-FPz* left and right electrooculograms; *F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1* electroencephalograms with derivations as shown; *CHIN* submental electromyogram (EMG); *LAT1-RAT2* combined left anterior tibialis and right anterior tibialis electromyogram (EMG); *Snore Mic* audio at suprasternal notch (demonstrating catathrenia when respiration resumes after central apneas); *NP* nasal pressure; *Therm* nasal/oral thermometry (demonstrating extended expiratory phase after central apneas); *Chest* respiratory inductance plethysmography; *Abd* respiratory inductance plethysmography; SAO_2 oxyhemoglobin saturation by pulse oximetry

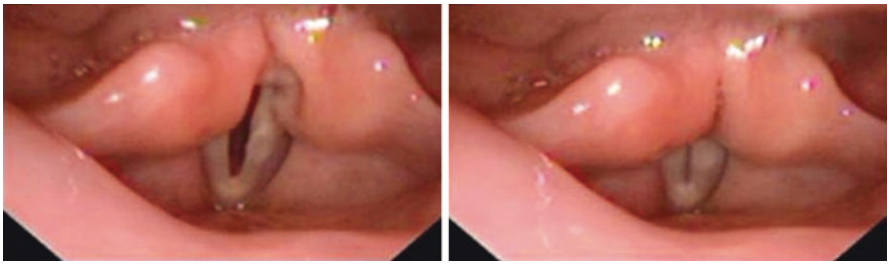

Fig. 62.2 Direct observation of catathrenia by fiberoptic laryngoscopy under deep sedation (propofol). Left: open glottis at inspiration. Right: closure of the glottis associated with audible catathrenia. (From Ott SR, Hamacher J, Seifert E. Bringing light to the sirens of night: laryngoscopy in catathrenia during sleep. Eur Resp J 2011; 37:1288–1289. Reproduced with permission of the © ERS 2020: *European Respiratory Journal 37 (5) 1288 1289;* https://doi.org/10.1183/09031936.00083510 *Published 30 April 2011*)

inspiration followed by an extended expiratory phase, which may be associated with groaning or silent bradypnea followed by deep inspiration [4]. Clusters of catathrenia events were defined as catathrenia periods and 85% of the 427 catathrenia periods described were associated with an arousal [4]. Additionally, 81% of the periods were found to occur during REM sleep, further supporting the predominance of the pattern's occurrence during REM. Drakatos and colleagues' analysis

was also able to further support that transitions between sleep and wake are associated with periods of ventilatory instability.

Not all catathrenia episodes are associated with obstructive sleep apnea (OSA). Limited literature exists regarding the improvement of catathrenia after treatment with CPAP [5]. When catathrenia occurs in a patient with OSA, the use of continuous positive airway pressure (CPAP) appears to muffle the vocalization, but not change the breathing pattern [6]. However, CPAP may still be helpful for resolution of catathrenia symptoms and such treatment may be reasonable.

In a systematic review by Alonso and colleagues, surgical intervention and medications such as, benzodiazepines, antidepressants, and antiepileptics were not found to have evidence supporting their use for treatment of catathrenia [5].

Even less is known about treatment modalities for catathrenia in the pediatric setting. Petitto and colleagues published a small case series of polysomnogram-confirmed catathrenia in three pediatric patients who were 7, 12, and 14 years of age respectively [7]. Two of the three patients were able to obtain CPAP while one patient was not and was eventually lost to follow-up [7]. While all three patients achieved resolution of catathrenia events during titration polysomnogram, the two patients who were available for follow-up also were found to also have experienced continued complete resolution of catathrenia at the 1-year follow-up evaluation [7]. The CPAP pressures in the case series ranged from 4 to 10 cwp and were 8 and 10 cwp for the two patients at the 1 year follow-up [7].

Additionally, home sleep apnea testing (HSAT) has become more prevalent in the field of sleep medicine, although its use in the pediatric age group is controversial with respect to diagnosing OSA [8, 9] and even more so with respect to diagnosing central sleep apnea [9, 10]. HSAT with audio recording signals are preferable when catathrenia is suspected, but type 3 HSAT devices do not usually record audio. Scant literature suggests the catathrenia may be mis-represented as central apneic events on HSAT [11]. While catathrenia is rare, any index of suspicion for catathrenia in the setting of central apneas on HSAT should always be further evaluated in the sleep laboratory.

Catathrenia can exist outside of the context of sleep disordered breathing. Detection of this relatively rare condition can be difficult. CPAP therapy may be beneficial and offering CPAP treatment to adult or pediatric patients may be reasonable. The role of surgical intervention and/or medications is uncertain and limited research to date does not support the use of either. Given that catathrenia is in most situations a benign finding of mainly social importance, a risk-benefit analysis would favor a trial of positive airway pressure therapy rather than surgical or pharmaceutical management. Further research is warranted, particularly in the pediatric population with catathrenia.

Key Teaching Points

- History of prolonged monotone groaning during sleep should raise suspicion for the presence of catathrenia.
- There can be social consequences associated with catathrenia and offering CPAP treatment for catathrenia without otherwise significant sleep disordered breathing may be a reasonable option.
- Catathrenia may be reported as central apneas on home sleep apnea testing and further evaluation may be required if there is an index of suspicion for catathrenia.
- There does not appear to be any evidence supporting the efficacy of surgical intervention or medications for the treatment of catathrenia.

Questions and Answers

1. Catathrenia usually occurs during which the following?

   (a) Inspiration
   (b) Expiration
   (c) Throughout inspiration and expiration
   (d) None of the above

   Answer: (b) Expiration

2. Each of the following are descriptions of sounds that are typically heard during catathrenia episodes **except**?

   (a) Low-pitch monotone sounds
   (b) High-pitch monotone sounds
   (c) Loud sounds
   (d) Roaring sounds

   Answer: (a) Low-pitch monotone sounds

3. Catathrenia can occur during which of the following phases of sleep?

   (a) Rapid Eye Movement sleep (REM)
   (b) Non-Rapid Eye Movement sleep (NREM)
   (c) REM and NREM
   (d) All of the above

   Answer: (d) All of the above

4. In a patient that has catathrenia and obstructive sleep apnea (OSA), continuous positive airway pressure therapy (CPAP) can be expected to:

   (a) Amplify catathrenia sounds
   (b) Muffle catathrenia sounds

(c) Have no effect on catathrenia sounds
(d) Significantly worsen catathrenia

Answer: (b) Muffle catathrenia sounds

5. A home sleep apnea test (HSAT) may report catathrenia as:

(a) An obstructive apnea
(b) A central apnea
(c) REM sleep without atonia
(d) A periodic leg movement

Answer: (b) A central apnea

6. Catathrenia is typically a:
(a) Benign condition requiring no treatment
(b) Serious condition requiring medication treatment
(c) Serious condition requiring surgical treatment
(d) Sign of impending respiratory failure

Answer: (a) Benign condition requiring no treatment

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